INNOVATION AND PATENT LAW REFORM

HEARINGS

BEFORE THE

SUBCOMMITTEE ON COURTS, CIVIL LIBERTIES, AND THE ADMINISTRATION OF JUSTICE

OF THE

COMMITTEE ON THE JUDICIARY HOUSE OF REPRESENTATIVES

NINETY-EIGHTH CONGRESS

SECOND SESSION

ON

H.R. 3285, H.R. 3286, and H.R. 3605

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MARCH 28, APRIL 26, AND JUNE 6, 27, 1984

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July 16, 1984

David Beier
House Judiciary Committee
Subcommittee on Courts, Civil Liberties
& Administration of Justice
2137 Rayburn Office Building
Washington, D.C. 20515

Dear Dave:

Enclosed please find a copy of Al Engelberg's constitutional law memo on §202 of H.R. 3605. I suggest that it be used as an insert to Bill Haddad's testimony at the appropriate point with an introduction that "we will provide for the record a response to Professor Dorsen's testimony."

Sincerely,

James F. Flug

Enclosure

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COUNSELORS AT LAW
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July 11, 1984

Honorable Robert W. Kastenmeier
Chairman, Subcommittee on Courts, Civil Liberties
and the Administration of Justice
Committee on the Judiciary
House of Representatives
Washington, D.C. 20515

Re: H.R. 3605 - Drug Price Competition and Patent Term Restoration Act of 1984

Dear Mr. Chairman:

I am patent counsel to the Generic Pharmeceutical Industry Association (GPIA) and am submitting this letter in response to the June 27, 1984 testimony of Gerald J. Mossinghoff, Assistant Secretary and Commissioner of Patents and Trademarks, on HR 3605.

In his testimony, the Commissioner suggested sweeping changes in the patent term extension provisions of the bill which would clearly upset the delicate balance on which the compromise embodied in H.R. 3605 is based. The Commissioner claims that these changes are necessary because HR 3605, is too complicated and would create an undue administrative burden on the Patent Office; and that the eligibility requirements for patent extension are too arbitrary and undermine principles of patent law which have existed for over 200 years. None of these arguments can withstand scrutiny.

At the hearing, the Commissioner used a chart of frightening dimensions to illustrate his allegation that HR 3605 would impose an inordinate administrative burden on the Patent Office. The appearance of this chart was so intimidating that it seemed on its face to prove the Commissioner's point and there was no opportunity at the hearing to examine its actual content. In fact, the chart is nothing more than a piece of advocacy which contains an overly complicated "computer age" breakdown of the provisions of HR 3605. It is not representative of the manner in which

applications for extensions would actually be processed despite its title. In actual practice, the Patent Office would most certainly require the use of a standardized form of Application for Extension. Similar forms are a normal part of current Patent Office practice. Such a form would obligate the patent holder to provide the necessary information to establish both the eligibility for and duration of a patent extension. I have prepared a model for such a form and it is attached to this letter. This simple, one page form contains the essence of the Commissioner's useless chart in a practical and usable manner and demonstrates that the "administrative burden" amounts to a few minutes of clerical time for each extension application.

HR 3605, expressly permits the Commissioner to rely upon representations made by the applicant for extension in determining whether or not the applicant meets the eligibility requirements for an extension. The proposed form takes advantage of that provision in a manner which is analogous to the manner in which the Commissioner now relies upon representations of an applicant for an original patent with respect to such matters as prior public use, prior publication or prior sale of an invention. Full disclosure by the applicant for an extension is assured by criminal penalties (18 U.S.C. Section 1001) as well as the possible loss of any patent extension. In addition, HR 3605 provides that the validity of an extension can be challenged in any patent infringement litigation just as the validity of an issued patent may now be challenged.

In view of the foregoing, it is hard to escape the conclusion that the Commissioner has unfairly characterized the administrative burden actually imposed by HR 3605.

HR 3605 would not make every patent eligible for extension and would limit the length of extensions. The Commissioner claims that these limitations are arbitrary, unduly restrictive and violate principles of patent law which are as old as the patent system. This is a meaningless and unfair criticism since the idea of patent extension itself is a radical departure from the basic principles of the patent system. As the Commissioner certainly knows, the issuance of a patent carries with it only the right to exclude others from the practice of an invention and was never intended to provide any guaranteed period of commercial exploitation to the patent owner. In fact, the patent owner's ability to derive profit from a patented invention has always depended on a variety of factors which are not relevant to the date on which a patent is granted. These include federal and state laws which might restrict or prohibit the use of a patented invention on safety, moral or

other grounds; the existence of an earlier-issued blocking patent; the time and money needed to commercialize an invention; the existence of a market; etc.

About 20 years ago, when the safety and efficacy requirements of the current food and drug law were first enacted, the Commissioner of Patents took the position that a patent covering a drug should not be granted unless and until the FDA had ruled that the drug was safe and efficacious. At that time, the highest patent court ruled to the contrary based, in part, on the argument made by research intensive drug companies that the issuance of patents for non-commercialized products would spur the investment necessary to develop these products. See Application of Anthony 414 F.2d 1383 (CCPA 1969). The issuance of a patent on a drug product at an embryonic stage of its development, is inconsistent with the argument that a patent should guarantee its owner 17 years of commercial exploitation. Yet, that has been the practice in recent years and it accounts for far more of the loss in commercial patent life than regulatory delay.

It is well-known that the impetus for patent term extension legislation came from the research intensive drug companies through the lobbying activities of the Pharmaceutical Manufacturers Association. PMA produced a mass of questionable statistics which were designed to support a claim that commercial patent life had shrunk to as low as 7 or 8 years. It heavily relied on that data to argue for legislation which would have extended the life of every patent for up to 7 years. In the course of legislative hearings on earlier versions of patent extension, it became apparent that the PMA statistics were misleading and that pre-marketing regulatory review was only one of many factors which had an effect on the length of a commerical monopoly. A large number of other significant factors, all of which are largely under the discretion and control of the patent owner, were identified. These factors include when a patent application is filed in relation to the actual state of development of the invention; how long the patent application remains pending in the Patent Office; the scope of the patent in relation to the commercial product which it seeks to dominate; the number and type of patents which may ultimately be granted to cover different aspects of the commercial development; the time at which clinical investigations are commenced in relation to the patent application and issue date; and the pace of development.

At the time HR 6444 was under active consideration by the House, PMA was still managing to successfully resist Congressman Gore's demand for the production of sufficient information with respect to NDA application and approval dates and the identification of all relevant patents so that an independent determination could be made with respect to the extent of the alleged problem of shrinking patent life.

Congressman Synar was finally able to pry that data loose from PMA in the latter part of 1983. It revealed that the arguments for shrinking patent life were based on the first patent to issue which covered a new chemical entity that had never before been used as a drug. When full consideration was given to the existence of other (later) patents and to the regulatory delays encountered by generic drug makers in bringing products to the market, the effective commercial monopoly life for the 50 top selling drugs turned out to be 15.5 years and for the 100 top selling drugs it was almost 14 years. Although the Commissioner continues to deny the existence of "evergreening", the data presented to Congressman Synar and analyzed by Congressman Waxman's staff established that there are numerous instances in which more than one patent must expire before there can be any competition. The most typical situation involves an early issued product patent followed by a later issued therapeutic use patent claiming the only FDA approved use.

HR 3605,incorporates the knowledge gleaned from the foregoing data and is therefore more restrictive than earlier versions of patent term extension legislation such as S. 255 and H.R. 6444. More specifically, the bill is based on the simple principle that only the earliest issued patent which either claims or fully discloses an approved drug product can be extended one time. That extension is for a maximum period of five years or for 14 years following the drug approval date whichever is shorter. These rules do not, prevent the research-intensive drug companies from continuing to apply for large numbers of related patents or to control the filing or issue dates of those patents in relation to the commercial development. Rather, they provide a reasonable period of extension for the only problem which the PMA companies have even alleged to exist -- shortened patent life for the first patent covering a new chemical entity -- while discouraging the use of patent extensions to slow down new developments or as a new tool for manipulating the patent system so as to unfairly lengthen patent monopolies.

The ultimate test of the fairness of the patent term extension provisions of HR 3605 is the endorsement of the bill by a 2 to 1 majority of PMA members. If PMA did not believe that the bill fairly addresses and solves the problem of shortened patent life it would not have endorsed this compromise. In view of that fact, it simply makes no sense for the Commissioner to attack those provisions as being too arbitrary or restrictive or to argue in favor of a more liberal patent extension policy.

The Commissioner's lack of appreciation for the problem which HR 3605 addresses and equitably solves is highlighted by his testimony with respect to the Bolar decision. GPIA and PMA were able to reach a compromise only because patent owners were assured of a longer commercial

monopoly period and generic drug manufacturers were assured of obtaining the necessary approval to engage in competition immediately after that well-defined monopoly period ended. The parties recognized that it was essential to this compromise that generic companies engage in the necessary steps required to obtain ANDA approval prior to the patent expiration date so that they could commence marketing immediately after the patent expired rather than 2 or 3 years later. The agreement to accomplish that result was reached without controversy because it was consistent with common industry practice extending back over many years and therefore did not infringe on any vested economic interest of drug patent owners. The Commissioner's disregard for the fairness of the compromise is demonstrated by the fact that he is anxious to provide patent owners with relief (in the form of patent extension) for the time which they lose in getting to market because of regulatory delay but is unwilling to give generic companies the same relief from the same problem at the end of the patent monopoly period.

Finally, it should be noted that throughout the course of the many hearings which have been held on the subject of patent term extension, the Commissioner has not come forward with any data whatsoever which would suggest that the commercial life of patented inventions in any field remotely approaches 17 years; that the commercial life of drug patents is materially shorter than the commercial life of patents in other fields; or that extending patent life in any field for any reason would stimulate investment in research or development. Rather, the Commissioner has consistently supported whatever proposal would lead to longer patents without regard for any demonstrated need for such a change in the patent law or the impact of such a change on the competitive environment or on consumers. Such an institutional bias is not surprising but it is disappointing that the Patent Office is unable to make a more constructive contribution to this compromise effort.

Respectfully submitted,

AMSTER, ROTHSTEIN & ENGELBERG

Alfred B. Engelberg

ABE:llk

APPLICATION FOR PATENT EXTENSION
(DRUG PRODUCT OR USE PATENT)

Extension Application Date: _____

Patent No. _____ Issue Date: _____ Expiration Date: _____

Patent Holder: _____ Assignment Recorded: Reel _____ Frame _____

NDA Approval Date: _____ NDA Submission Date: _____ IND Filing Date: _____

Active Ingredient(s) in Approved Product: _____

_____

Approved Uses: _____

Patent Claims Covering Approved Product or Use(s): _____

_____ declares that (s)he is the _____ [title] of the above-identified patent holder and is authorized to submit this application for extension of the above-identified patent pursuant to 35 U.S.C. §156. A copy of the patent for which extension is sought is enclosed.

I hereby declare the following with respect to this application:

1. The patent for which this extension is sought claims a product (method of using a product) which was subject to a regulatory review period under the Food, Drug and Cosmetic Act prior to its commercial marketing. The relevant dates of that regulatory review period are set forth above.

2. The patent for which this extension is sought has never been extended.

3. The patent for which this extension is sought does not claim a product (method of using a product) which received permission for commercial marketing under the Food, Drug and Cosmetic Act before the NDA Approval Date set forth above.

4. The active ingredient(s) in the approved product, including any salt or ester thereof, as a single entity or in combination with another active ingredient has never received permission for commercial marketing under the Food, Drug and Cosmetic Act before the NDA Approval Date set forth above.

5. The following patents have been identified in the application under Section 505(b) of the Food, Drug and Cosmetic Act for the above-identified approved product as patents for which a claim of patent infringement might reasonably be asserted in the event of the unlicensed manufacture, use or sale of the approved product:

   _____.

   _____

   _____

6a. To the best of my knowledge, the approved product (method of using the product) is not claimed in another patent having an earlier issuance date or which was previously extended.

6b. The approved product is claimed in U.S. Patent No. _____ but it is not identically disclosed or described therein. U.S. Patent No. _____ has never been and will never be held by the patent holder herein and the patent for which extension is sought has never been and will never be held by the holder of U.S. Patent No. _____.

7. To the best of my knowledge, the approved product and the use approved for the approved product are not identically disclosed or described in another patent having an earlier issuance date or which was previously extended.

An extension of _____ years, _____ months and _____ days until _____ [Date] is sought based upon the following calculation:

1/2 (NDA Submission Date - IND Filing Date) = _____ yrs. _____ mos. _____ days

(NDA Approval Date - NDA Submission Date) = _____ yrs. _____ mos. _____ days

Total = _____ yrs. _____ mos. _____ days

The extension does not exceed five years and will not extend the expiration date of the patent for more than fourteen years from the NDA Approval Date.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent extension issued thereon.

_____ _____

APPLICANT'S SIGNATURE DATE

_____

POST OFFICE ADDRESS

_____

AMSTER, ROTHSTEIN & ENGELBERG
COUNSELORS AT LAW
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July 20, 1984

Honorable Robert W. Kastenmeier
Chairman, Subcommittee on Courts, Civil Liberties
and the Administration of Justice
Committee on the Judiciary
House of Representatives
Washington, D.C. 20515

Re: H.R. 3605 - Drug Price Competition and
Patent Term Restoration Act of 1984

Dear Mr. Chairman:

I am patent counsel to the Generic Pharmeceutical Industry Association (GPIA) and am writing this letter to provide the Committee with important new information bearing on the alleged constitutional law issue which the dissident pharmeceutical companies have raised. This new information establishes, that the decision in Roche v. Bolar made completely new law and was contrary to industry practices and expectations. Accordingly, Section 202 cannot possibly upset any reasonable investment-back expectations.

On December 23, 1975, Hoffman-LaRoche Inc. commenced a Civil Action (Civil Action No. 75-2221) in the United States District Court for the District of New Jersey charging Zenith Laboratories, a generic manufacturer, with infringement of Roche's patent covering valium. In an Answer (copy enclosed) filed by Zenith on March 26, 1976, Zenith asserted that it was not liable for patent infringement because the only activity in which it had engaged was experimental studies for the purpose of seeking F.D.A. approval. Accordingly, Zenith filed a counterclaim seeking a declaratory judgment that experimental use did not constitute patent infringement.

In early June 1976, Roche sought to have Zenith's counterclaim dismissed on the ground that there was no case or controversy. In support of that motion, Roche made the following statement:

> "It has been clear from the outset of this case that Roche does not seek to interfere with Zenith's legitimate activities in seeking F.D.A. approval of a New Drug Application (NDA)

> for diazepam. Nor has Roche done anything to interfere with Zenith's bidding for U.S. Government contracts. Roche's brief in opposition to Zenith's Rule 12 motion expressly states:
> "Roche does not seek to enjoin Zenith from doing the experimental work necessary for it to secure F.D.A. approval or from bidding for U.S. Government contracts.""

On June 14, 1976, a hearing was held on Roche's motion before the Honorable Frederick B. Lacey. At that hearing, Roche's attorney stated:

> "We have indicated -- we've taken the position that attempts to secure NDAs in the proper manner do not constitute patent infringement."

On August 2, 1979, Zenith and Roche entered into an Agreement which led to a Consent Judgment in the foregoing Civil Action. A copy of that Consent Judgment is enclosed. The Consent Judgment clearly states that Zenith was engaged in PDA related experimental activities and wished to continue with such activities. Paragraph 9 of the Consent Judgment permitted Zenith to retain 5 kilograms of diazepam so that it could engage in such experimentation.

It is respectfully submitted that the foregoing facts establish beyond question that until the recent decision in Roche v. Bolar, no one in the industry believed that F.D.A. experimental activity constituted patent infringement. Certainly, there is no other reasonable explanation for Roche's statements with regard to experimental activity involving the most important drug in Roche's recent history.

The foregoing facts cast serious doubt on the testimony of both Professor Dorsen and Commissioner Mossinghoff in stating that the decision in Roche v. Bolar was a mere reaffirmation of a 200 year old principle of patent law. In actual fact, the decision is a total departure from past industry practice. Accordingly, the enactment of Section 202 will clearly not upset any reasonable investment-backed expectations and is not unconstitutional.

Respectfully submitted,

AMSTER, ROTHSTEIN & ENGELBERG

Alfred B. Engelberg

ABE/jm
Encs.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HOFFMANN-LA ROCHE INC., a corporation,

Plaintiff,

vs.

ZENITH LABORATORIES, INC., a corporation,

Defendant.

Civil Action No. 75-2221

ANSWER, COUNTERCLAIM AND DEMAND FOR TRIAL BY JURY

3-26-76

Defendant, Zenith Laboratories, Inc., with offices at 140 LeGrand Avenue, Northvale, New Jersey, by way of Answer to the Complaint herein, says:

AS TO COUNT ONE

1. Defendant denies that this Court has jurisdiction under the Patent Laws of the United States or under 28 U.S.C. Sec. 1338 in that no case or controversy is stated sufficient to invoke the jurisdiction of this Court either under the above-listed sections or under 28 U.S.C. Sec. 2201 (the Declaratory Judgment Act).

2. Defendant admits the allegations of Paragraph 2.

3. Defendant admits the allegations of Paragraph 3.

4. Defendant, Zenith Laboratories, Inc., denies knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 4.

5. Defendant denies knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 5.

6. Defendant denies knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 6.

7. Defendant denies each and every allegation contained in Paragraph 7, except to admit that it has imported into the State of New Jersey approximately 5 kilograms of diazepam in its raw state.

8. Defendant denies each and every allegation contained in Paragraph 8, except to admit that it has undertaken, as part of the experimentation required for a new drug application to the Food and Drug Administration to reduce part of its diazepam supply into tablet form by mixing the active ingredient with the excipients created by the employees of defendant.

9. Defendant denies each and every allegation contained in Paragraph 9, except to admit that it has applied for approval to market the diazepam in tablet form.

10. Defendant denies each and every allegation contained in Paragraph 10.

11. Defendant denies each and every allegation contained in Paragraph 11, except to admit that it does not possess any assignment of or license under plaintiff's patent rights, if any, in diazepam.

12. Defendant denies each and every allegation contained in Paragraph 12.

AS TO COUNT TWO

13. Defendant denies each and every allegation contained in Paragraph 13.

14. Defendant repeats and realleges each and every of its answers to Paragraphs 1-9 and 11 of the First Count of this Complaint as if set forth at length herein.

15. Defendant denies each and every allegation contained in Paragraph 15.

WHEREFORE, defendant, Zenith Laboratories, Inc. demands

judgment dismissing the within Complaint, with costs.

AS AND FOR AFFIRMATIVE DEFENSES
TO ALL COUNTS

FIRST AFFIRMATIVE DEFENSE

The judicial power of the United States District Court is limited to adjudicating actual cases or controversies arising under its laws or constitution and no act or factual instance of present infringement is charged or shown within the Complaint of the plaintiff herein.

SECOND AFFIRMATIVE DEFENSE

This Court ought not to exercise the discretionary authority vested in it by the Declaratory Judgment Act to adjudicate the validity of plaintiff's patent for the threat of infringement is, at best, speculative and abstract where none of the activities undertaken by defendant, Zenith, with reference to the importation of and experimentation with diazepam constitute infringements in and of themselves but, rather, are susceptible to a multitude of innocent possibilities, most of which would not ever constitute infringement for which a patentee may sue in this Court.

THIRD AFFIRMATIVE DEFENSE

The filing of a new drug application for approval to market and distribute diazepam is privileged under the statutory scheme creating the Food and Drug Administration and that application may be neither interfered with nor restrained, though that drug be then the subject of a previous patent grant, by or on behalf of the patentee.

FOURTH AFFIRMATIVE DEFENSE

Plaintiff is barred from obtaining any remedy in this Court for actions taken by defendant, Zenith, in preparation for or anticipation of gaining eligibility to bid for government contracts for the supply of diazepam

by reason of 28 U.S.C. Sec. 1498(a) by which the United States has authorized the manufacture by private companies of products arguably subject to a patent grant that are needed for the government's use.

FIFTH AFFIRMATIVE DEFENSE

Upon information and belief, plaintiff is precluded from enforcing the patent issued to it because said patent grant is invalid and void for failure to comply with the statutory requirements for issuance thereof, for misuse of the patent by attempting to widen the temporal and physical scope of the patent monopoly granted by statute, and for leveraging the patent monopoly in violation of the Anti-Trust laws in the United States.

COUNTERCLAIMS OF DEFENDANT
ZENITH LABORATORIES, INC.

FIRST COUNT

1. This Court has jurisdiction over the within Counterclaim under Sec. 4 of the Clayton Act, 38 Stat. 731, 15 U.S.C. Sec. 15 and by reason of pendant jurisdiction under the common law of the State of New Jersey for damages suffered and to be suffered by defendant as a result of the actions alleged infra. undertaken by the plaintiff.

2. Zenith Laboratories, Inc. is a generic drug house involved in the manufacture, distribution and sale of drugs under their chemical name.

3. Hoffmann-La Roche Inc. is a major name brand drug company which manufactures, distributes and sells, among others, a drug under the trademark name of Valium. Valium is the name for and is chemically identical with diazepam.

4. Within the drug market, and especially the market in minor tranquillizers, plaintiff and defendant operate as competitors and as potential competitors.

5. The filing of the within litigation by plaintiff, Hoffmann-La Roche Inc., is part and parcel of a malicious course of conduct embarked

upon by plaintiff to harass defendant, Zenith Laboratories, Inc., at every turn and to thwart defendant from competing fairly with Roche with the effect that restraints of trade have been and will continue to occur in the minor tranquillizer field, specifically diazepam, beyond the bounds of the patent grant heretofore issued to plaintiff under 35 U.S.C. Sec. 154.

6. Plaintiff is aware of, well knows and fully intends that continuous litigation with defendant will have the effect of delaying and frustrating defendant's legitimate plans to gain an F.D.A. approval for the marketing of diazepam thereafter to bid in competition with Roche for the sale of diazepam to federal government agencies.

7. The relatively small size of the assets and income flow of Zenith Laboratories, Inc. in comparison with the assets possessed and income generated by the business activities of Roche, is such that Roche well knows that it can and does seek to wear down and deter by the process of litigative attrition, the attempt of Zenith to engage in activities which Roche knows are ones in which Zenith is entitled to engage under law.

8. The plaintiff is fully aware of, well knows and fully intends by this litigation to create an effective economic barrier (composed of legal fees, Court costs and expenses of litigation) in the path of Zenith's business relationship into which it has or is about to enter with the various governmental agencies before which it would be eligible to bid to be their suppliers of diazepam.

9. Plaintiff's complaint in the instant action is part of a tortious campaign and illegal course of conduct designed to obstruct, by means of vexatious litigation, defendant's right of access to the Food and Drug

Administration and to those governmental agencies which, pursuant to bid, allow each and every eligible contractor to compete for the supply of its needs for diazepam.

10. No ordinarily prudent man or company, with the proper advice of counsel, could believe, after reasonable inquiry, that a probable basis for the institution of this civil action was presented by the circumstances from which plaintiff's allegations and charges arise.

11. Plaintiff pursues this litigation for reasons and purposes having nothing whatever to do with the merits or issues which are the ostensible objective of their action and plaintiff well knows that no reasonable chance exists that their claims, on the merits, will be found to be valid.

12. The real purpose and hoped for effect of the within litigation, so far as plaintiff is concerned, is to coerce the defendant to remove its application for F.D.A. approval on diazepam, which plaintiff well knows defendant is entitled to process, and to frustrate defendant's legitimate plans, pursuant to 28 U.S.C. 1498(a) to bid, in competition, with the plaintiff, for government contracts to supply diazepam. Plaintiff's conduct in harassing and attempting to thwart legitimate competitive activities of Zenith Laboratories, Inc. constitutes unfair competition with and restraint of trade against Zenith Laboratories, Inc. in violation of the Anti-Trust laws of the United States and the common law of the State of New Jersey.

WHEREFORE, defendant, Zenith Laboratories, Inc., demands judgment against the plaintiff for:

(a) Treble damages, pursuant to 15 U.S.C. Sec. 15;

(b) Compensatory and punitive damages for unfair competition in violation of the common law of the State of New Jersey;

(c) A reasonable attorney's fee;

(d) Costs of suit;

(e) Such other and different relief as this Court, in its discretion, may deem just and equitable.

SECOND COUNT

1. Defendant, Zenith Laboratories, Inc., repeats and realleges each and every of its allegations contained in Paragraphs 1 through 12 of the First Count of its Counterclaim, as if set forth at length herein.

2. This Court has jurisdiction over the within Counterclaim under 28 U.S.C. 1338 and under 28 U.S.C. 2201.

3. During 1975, Zenith, pursuant to 21 U.S.C. Sec. 355, submitted a new drug application to the Food and Drug Administration to gain approval for marketing and distribution of a drug known generically as diazepam. In 1968, plaintiff, Hoffmann-La Roche Inc., was the recipient of a patent grant issued for a drug whose only active ingredient was and is diazepam.

4. To gain approval of a new drug application from the F.D.A., applicant, here Zenith, is required to submit experimental studies performed on the drug in question to demonstrate, to the satisfaction of the F.D.A., that the drug is "safe and effective". As part of that experimentation process, Zenith imported approximately 5 kilograms of diazepam in its raw bulk state into New Jersey from another country and reduced part of that bulk supply into tablet form by mixing the raw diazepam with excipients prepared by employees of defendant.

5. Upon approval of its application of diazepam by the F.D.A., defendant, Zenith, may bid, as an eligible contractor, in competition with Roche to supply agencies of the federal government with their needs for that drug.

6. By its complaint in the within action, plaintiff has charged that application to the F.D.A., as described above, importation of diazepam from abroad, and reduction of part of that imported supply to tablet form constitute infringements of the patent previously issued to it in 1968. Defendant, Zenith Laboratories, Inc., believes that all of its activities with relation to diazepam are lawful and actions which, even assuming the validity of the patent grant, are ones with which it is entitled to undertake. The initiation of the within complaint has caused apprehension that defendant may be acting at its peril and it desires adjudication as to the validity of the activities which it has undertaken and which it may undertake in the future with reference to sale and distribution of diazepam to the U.S. Government and to none other.

WHEREFORE, defendant, Zenith Laboratories, Inc., demands judgment against the plaintiff for:

(a) A Declaratory Judgment that its acts undertaken with relation to importation, F.D.A. application, and sale to the government of diazepam do not and shall not constitute an infringement of the patent previously issued to plaintiff;

(b) Compensatory damages;

(c) A reasonable attorney's fee;

(d) Costs of suit; and

(e) Such other and different relief as this Court, in its discretion, may deem just and equitable.

JURY DEMAND

Defendant, Zenith Laboratories, Inc., hereby demands trial

by jury as to all issues cognizable by such body in both the Complaint and Counterclaims in the within litigation.

SILLS, BECK, CUMMIS, RADIN & TISCHMAN
A Professional Corporation
Attorneys for Defendant, Zenith Laboratories, Inc.

BY: _____
STEVEN S. RADIN

CERTIFICATION

I hereby certify that the within Answer and Counterclaims has been served within time, as extended by stipulation and Rule.

SILLS, BECK, CUMMIS, RADIN & TISCHMAN
A Professional Corporation
Attorneys for Defendant, Zenith Laboratories, Inc.

BY: _____
STEVEN S. RADIN

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HOFFMANN-LA ROCHE INC., a corporation,	:	(Hon. Frederick B. Lacey)
Plaintiff,	:	Civil Action No. 75-2221
-vs-	:	CONSENT JUDGMENT
ZENITH LABORATORIES, INC., a corporation,	:	
Defendant	:	

WHEREAS, the above entitled action was brought by Hoffmann-La Roche Inc. (hereinafter "Roche"), as plaintiff, against Zenith Laboratories, Inc. (hereinafter "Zenith"), as defendant, charging Zenith with having taken steps and made arrangements and preparations to infringe United States Letters Patent No. 3,371,085, owned by Roche, and with infringement thereof; and

WHEREAS, Zenith has answered the complaint, denying the aforesaid allegations, and has asserted affirmative defenses including absence of a case or controversy, that the Court ought not to exercise its discretionary jurisdiction because the threat of infringement by Zenith is too speculative and abstract, that Zenith's application to the United States Food and Drug Administration for approval to market and distribute diazepam is privileged, that Roche is barred from obtaining any remedy in this Court for Zenith's actions by reason of 28 U.S.C. § 1498 (a), and that Roche is precluded from enforcing said patent because the same is invalid and void for failure to meet the statutory requirements for issuance thereof, for misuse of the patent and for violation of the antitrust laws of the United States; and

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ANGELO W. LOCASCIO, CLERK
Entered on 8-1-79 on Docket.

WHEREAS, Zenith has asserted counterclaims against Roche alleging a malicious course of conduct to harass Zenith, unfair competition and restraint of trade in violation of the antitrust laws of the United States and of the common law of the State of New Jersey, and has sought relief including treble damages and judgment that Zenith's activities in connection with its importation of diazepam, its FDA application and sale to the United States Government do not constitute patent infringement; and

WHEREAS, Zenith has acknowledged, and by its consent hereto does hereby acknowledge, that upon entry of this Judgment, it will deliver up to Roche from the United States, its territories and possessions, all diazepam in its possession, custody or control, in bulk form for which it shall be reimbursed by Roche in the amount of twenty-five thousand dollars ($25,000); and F.O.B. our plant in the Virgin Islands

WHEREAS, Roche has replied to Zenith's counterclaims, denying all allegations of illegality, impropriety, inequitable conduct and liability contained therein, and has asserted affirmative defenses including that the Court lacks jurisdiction over the second counterclaim; and

WHEREAS, discovery has been conducted on the issues framed by the complaint, answer, affirmative defenses, counterclaims and replies thereto, and the parties have additionally had the benefit of prior discovery of each other in Civil Action No. 75-96 in this Court; and

WHEREAS, Zenith has acknowledged, and by its consent hereto does hereby acknowledge, that said United States Letters Patent No. 3,371,085 are good, valid and enforceable; that diazepam is disclosed and claimed in said Letters Patent; and that Roche is the owner of said Letters Patent and is solely entitled to recover for infringement of said Letters Patent; and

WHEREAS, Zenith has acknowledged, and by its consent hereto does hereby acknowledge, that Zenith has imported into the United States, its territories or possessions, a quantity of diazepam in excess of 500 kilograms (more than half a ton); that Zenith has manufactured, from a part thereof, pharmaceutical dosage form units suitable for administration to humans, including some 100,000 tablets each containing two milligrams of diazepam as the active ingredient, some 100,000 tablets each containing five milligrams of diazepam as the active ingredient, and some 100,000 tablets each containing ten milligrams of diazepam as the active ingredient; that Zenith has used several thousand of said tablets for the purpose of obtaining data and information demonstrating the pharmacological efficacy and suitability for administration of such tablets to humans, the portion so used amounting to approximately 0.19 kilogram of diazepam (less than 0.04% of the amount imported); that Zenith's remaining stock of diazepam is sufficient for it to manufacture more than 250,000,000 tablets each containing two milligrams of diazepam as the active ingredient; that Zenith has made application to the United States Food and Drug Administration for approval to market and distribute diazepam in dosage unit form of tablets containing two milligrams, five milligrams, or ten milligrams of diazepam as the active ingredient, and has pursued said application by, inter alia, submitting data and information, including that described above, in support thereof; that Zenith's aforesaid acts have all been without leave or license of Roche; and that Zenith has never received the authorization or consent of the United States Government to use or manufacture diazepam in dosage unit form or otherwise; and

WHEREAS, new management has assumed responsibility for the decision making process in Zenith and that management has chosen not to continue with the litigation or contest the validity of Roche patents, the subject of this litigation and desires to settle this litigation; and

WHEREAS, Zenith has acknowledged, and by its consent hereto does hereby acknowledge, that the invention disclosed and claimed in said Letters Patent No. 3,371,085 is the invention of Earl Reeder and Dr. Leo Henryk Sternbach, that it was made by them in this country and that said invention is a pioneer invention; and

WHEREAS, Zenith desires to continue in its experimentation with diazepam as hereinafter provided, and will retain in its possession for such use only five (5) kilograms of diazepam; and

WHEREAS, Zenith has represented, and by its consent hereto does hereby represent, that it will not make, use or sell diazepam, either alone or in conjunction with others, and will not assist, aid or abet others to make, use or sell diazepam, in bulk or dosage unit form, either pure or in admixture with other compounds, including excipients, without leave and license of Roche, on or after the date of this Judgment and until expiration of said Letters Patent on February 27, 1985; and

WHEREAS, Zenith has acknowledged, and by its consent hereto does hereby acknowledge, that it consents to entry of this Judgment as its free act and deed, without coercion or duress, and that there are no agreements or understandings between the parties, except as part of this Judgment;

IT IS HEREBY ORDERED, ADJUDGED AND DECREED:

1. That this Court has jurisdiction over the parties and the subject matter of this action.

2. That United States Letters Patent No. 3,371,085, issued to Roche on February 27, 1968, are good, valid and enforceable, and that Roche is the owner of said Letters Patent and solely entitled to recover for any infringement thereof.

3. That Zenith, each and every subsidiary thereof and each and every company under its direct or indirect control, their officers, agents, servants, employees, successors and assigns, be, and each of them hereby is, enjoined and restrained, for the duration of said Letters Patent No. 3,371,085 through and including February 27, 1985, from

(a) infringing United States Letters Patent No. 3,371,085 or aiding, assisting or abetting others to infringe said Letters Patent;

(b) inducing or contributing to the infringement by others of United States Letters Patent No. 3,371,085;

(c) making, using, selling, offering for sale, delivering, formulating, encapsulating, tableting, advertising, importing or otherwise obtaining diazepam, or any other substance covered by any claim or claims of United States Letters Patent No. 3,371,085, without leave and license of Roche;

(d) making, using, selling, offering for sale, delivering, formulating, encapsulating, tableting, advertising, importing or otherwise obtaining any product containing diazepam or any other substance covered by any claim or claims of United States Letters Patent No. 3,371,085 as an active ingredient, without leave and license of Roche; and

(e) making, using or selling diazepam, or any other substance covered by any claim or claims of said Letters Patent No. 3,371,085, either alone or in conjunction with others, and will not assist, aid or abet others to make arrangements or preparations for, or take steps, to make, use or sell diazepam, or any other substance covered by any claim or claims of said Letters Patent No. 3,371,085, without leave and license of Roche.

4. That nothing herein shall be construed as limiting, expanding or otherwise affecting any applicability of Title 28, United States Code, Section 1498(a), to Zenith's past or future activities.

5. That nothing herein shall be taken as a waiver or limitation of Roche's right to seek remedy for any sales by Zenith to the United States Government, or others; and nothing herein shall be taken as the grant of a license, or as the grant or waiver of any rights by Roche.

6. That the answer, affirmative defenses and counterclaims filed by Zenith be dismissed with prejudice in all respects.

7. That no costs, disbursements, attorneys' fees or damages be awarded.

8. That all terms and conditions of this Judgment shall apply to Zenith and each and every subsidiary thereof and each and every company under its direct or indirect control.

9. Zenith may retain in its possession five (5) kilograms of diazepam for the limited purpose of such experimentation as fairly falls within permissible experimentation under the patent laws of the United States. Nothing herein shall prejudice Zenith from taking advantage of its rights, if any, under Title 28 U.S.C. § 1498(a). Nothing contained herein [and in particular by way of illustration and not limitation, Paragraphs 3(c), 3(d) and 3(e)] shall be construed as limiting, expanding or otherwise affecting the provisions of this Paragraph 9.

ENTERED as of this 2nd day of August, 1979,

United States District Judge

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
Civil Action No. 75-2221

Plaintiff,

HOFFMANN-LaROCHE INC.,
a corporation, :

vs. :

Defendant, :

ZENITH LABORATORIES, INC.,
a corporation. :

PLAINTIFF ROCHE'S MEMORANDUM IN SUPPORT OF ITS MOTION UNDER RULE 12 DIRECTED TO ZENITH'S ANSWER AND COUNTERCLAIMS

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No Cites

II. THE MISUSE AND ANTITRUST ALLEGATIONS OF THE FIFTH AFFIRMATIVE DEFENSE SHOULD BE STRICKEN

Rule 12(f), F.R.Civ.P. provides in part that "the court may order stricken from any pleading any insufficient defense or any redundant, immaterial, impertinent, or scandalous matter." Zenith's fifth affirmative defense alleges, in part, misuse of the '085 patent and violation of the antitrust laws, which allegations, as shown above, were asserted and resolved in C.A. 75-96. The prior dismissal with prejudice of those allegations as being without merit is a bar to relitigating those same issues here irrespective of the pleading device employed.

Prior to discovery

Although cast in vague and imprecise terms*, the allegations of the fifth affirmative defense are nevertheless plainly within the ambit of the misuse and antitrust issues determined in the prior litigation. Accordingly, they constitute insufficient defenses and, in addition they are couched in inflammatory language, are prejudicial to Roche, particularly since a jury has been demanded. Those allegations should, therefore, be stricken.

III. THE SECOND COUNTERCLAIM SHOULD BE DISMISSED FOR LACK OF SUBJECT MATTER JURISDICTION

Roche has moved, under subdivisions (1) and (6) of Rule 12(b), to dismiss Zenith's second counterclaim for lack of subject matter jurisdiction and for failure to state a claim upon

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* The specific language we are asking the Court to strike reads: "for misuse of the patent by attempting to widen the temporal and physical scope of the patent monopoly granted by statute, and for leveraging the patent monopoly in violation f the Anti-Trust laws in the United States."

which relief can be granted. That pleading fails to present a case or controversy for adjudication in that the counterclaim (which is brought under the declaratory judgment act) seeks an advisory opinion "as to the validity of the activities which [Zenith] has undertaken and which it may undertake in the future...."

It has been clear from the outset of this case that Roche does not seek to interfere with Zenith's legitimate activities in seeking F.D.A. approval of a New Drug Application (NDA) for diazepam. Nor has Roche done anything to interfere with Zenith's bidding for U. S. government contracts. Roche's brief in opposition to Zenith's Rule 12 motion expressly states:

> "Roche does not seek to enjoin Zenith from doing the experimental work necessary for it to secure F.D.A. approval or from bidding for U.S. government contracts." (p.5)

Yet these are the only activities to which the second counterclaim is addressed.

Since Roche does not seek to interfere with Zenith's doing that which is required for it to secure F.D.A. approval of its diazepam NDA, or to interfere with Zenith's subsequent bidding for U. S. government contracts, as to the matters raised in the second counterclaim there simply is no dispute. There is therefore no claim to be adjudicated and no controversy to which this Court's jurisdiction can attach.

While the second counterclaim asserts that the filing of the complaint herein has caused Zenith to be apprehensive about its F.D.A. activities, no reasonable basis exists for any such apprehensions. Since the complaint does not seek to prevent Zenith's legitimate activities in connection with pursuing F.D.A. approval for Zenith's U. S. governmental sales, if there was any reasonable basis for apprehension, it could only have been because Zenith's conduct and intentions have not been as limited as the second counterclaim would lead one to believe.

The second counterclaim should also be dismissed because it seeks an advisory opinion sanctioning acts "which [Zenith] may undertake in the future...." There is, however, no indication (much less assurance) of what those acts may be. Even Zenith admits it does not know. Mr. Rooney, Zenith's Vice-President, has stated under oath in his February 9, 1976 affidavit:

> "We had sought FDA approval to market and distribute Diazepam and, upon obtaining such approval, would make a further judgment, only at that point, as to what, if any, additional steps to take prior to the expiration of the seventeen year patent period." (¶10)

He went on to say that in light of the recent F.D.A. rejection of Zenith's application:

> "Senior management at Zenith has made no determination, at this time, whether to re-apply." (¶10)

That even Zenith does not know what it may do in the future is further confirmed in Zenith's "Memorandum Of Law In Support of Motion To Dismiss Complaint," filed on or about February 9, 1976:

> "The problem, of course, is that no one - neither the plaintiff nor even the defendant - knows what Zenith will actually do once FDA approval is given." (p.13)

That Article III courts are not empowered to adjudicate hypothetical disputes or render advisory opinions scarcely needs to be stated or supported by citation of authority. This most basic precept of the judicial function under the Constitution is as applicable to declaratory judgment actions as to others. Golden v. Zwickler, 394 U.S. 103,108 (1969).

Zenith's second counterclaim is a classic example of a pleading which seeks an advisory opinion from this Court: as to past activities, because there is no dispute between the parties, and as to future activities because those activities are unknown and impossible to predict. The second counterclaim should, therefore, be dismissed for lack of subject matter jurisdiction as well as for failure to state a claim upon which relief can be granted.

It is further submitted that as a matter of discretion the Court should decline to exercise any jurisdiction it might contendedably have, in view of the circumstances set forth above.

CONCLUSION

For the foregoing reasons, Roche's motion should be granted, Zenith's first and second counterclaims should be dismissed and the last three lines of the fifth affirmative defense should be stricken.

Respectfully submitted,

CRUMMY, DEL DEO, DOLAN & PURCELL

By_____
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February 15, 1984

Mr. David Beier
Committee on the Judiciary
2137 B, Rayburn Building
Washington, D.C. 20515

Re: Patent Legislation - Experimental Drug Use Exception

Dear Mr. Beier:

Pursuant to our telephone conversation, I am enclosing the following:

1. A copy of the October 11, 1983 decision of Judge Wexler in Roche v. Bolar.

2. A copy of our Amicus Brief on behalf of the Generic Pharmaceutical Industry Association on the appeal from Judge Wexler's opinion.

The Roche v. Bolar case was argued before the Federal Circuit on February 9, 1984. As I indicated during our telephone conversation, you may also wish to look at Pfizer v. IRC, 217 U.S.P.Q. 157, which is a Central District of California decision involving a somewhat similar issue, but a vastly different set of facts.

It is our belief that the experimental exception language which we proposed to you during our telephone conversation (copy enclosed) represents a fair solution to this problem. It would ensure that the patent owner obtains the full exclusivity from a patent for 17 years but could not receive a monopoly which would extend beyond that time period. The proposed experimental use exception is entirely consistent with the principles embodied within the "fair use" exception to copyright infringement. In that regard, we direct your attention to the following langugage of the Supreme Court in its recent Betamax decision:

> "The purpose of copyright is to create incentives for creative effort. Even copying for noncommercial purposes may impair the copyright holder's ability to obtain the rewards that Congress intended him to have. But a use that has no demonstrable effect upon the potential market for, or the value of, the copyrighted work need not be prohibited in order to protect the author's incentive to create."

The philosophy embodied in the foregoing language would appear to be equally applicable to the patent law which is derived from the same constitutional provision.

Please let me know if we can be of further assistance with respect to this matter.

Cordially,

AMSTER, ROTHSTEIN & ENGELBERG

Alfred B. Engelberg

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Encs.

cc: James Flug, Esq.
Mr. William Haddad

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July 25, 1984

Chairman Robert W. Kastenmeier
Subcommittee on Courts, Civil
Liberties and the Administration
of Justice
2232 Rayburn House Office Building
Washington, D. C. 20515

Dear Mr. Chairman:

We have been requested by David Beier, Assistant Counsel of the Subcommittee, to comment on Mr. Engelberg's letter to you dated July 20, 1984.

Two contentions are made in Mr. Engelberg's letter: first, that the decision in Roche v. Bolar made "completely new law" and, second: that the Court of Appeals' decision "was contrary to industry practices and expectations." We believe that neither of these two points are supportable. Bolar is a continuation of pre-existing law, and we are aware of no industry practice which condones open testing of patented drugs for submission of data to the FDA for clearance preparatory to post-expiration marketing.

Commissioner of Patents and Trademarks Mossinghoff, himself, testified that the Bolar decision was the correct application of hornbook patent law. It should be recalled that in the Bolar litigation, it was the defendant, Bolar, which sought to change the established law by having the Court add a new category to the "experimental use" exception. The Court of Appeals rejected that attempt. It upheld the patent law's grant to the patentee of the exclusive right to use the patented substance. It reiterated that the doctrine of experimental use did not encompass pre-expiration testing when it was done for plainly commercial purposes. In this respect, the Court's analysis was consistent with the way the experimental use

doctrine has been applied since it was introduced almost 200 years ago. See Roche v. Bolar, 733 F.2d 858, 862-63 (Fed. Cir. 1984). Bolar reaffirmed the law. It did not change it.

In support of the assertion that "industry practices" have permitted the testing of patented substances for FDA approval, Mr. Engelberg's letter contains selective excerpts from the record in one patent infringement action between Roche and Zenith. His analyses of the facts are incorrect. Roche is not aware of any such "industry practice." If some generic manufacturers engaged covertly in pre-expiration tests for later business use, that practice could hardly result in depriving a patentee of his rights. For to do so would be to reward deception.

As to the specific allegations concerning the Zenith litigation, Mr. Engelberg's letter fails to mention that Roche's 1975 complaint specifically alleged that Zenith's infringing activities included steps that had been taken by Zenith "to secure approval from the United States Food & Drug Administration for [Zenith] . . . to market and distribute . . . diazepam." Complaint, Hoffmann-La Roche Inc. v. Zenith Laboratories, Inc., Civil Action No. 75-2221, para. 9. */ This is

*/ In full text, paragraph 9 of Roche's complaint stated:

> "On information and belief, steps have been taken to secure approval from the United States Food & Drug Administration for defendant (and/or its subsidiaries or those with whom it is in concert or controls) to market and distribute for use in this country diazepam and/or pharmaceutical preparations containing diazepam as an active ingredient, and to sell to others and enable them to market diazepam and preparations containing diazepam as an active ingredient; or, alternatively,

[Footnote continued on next page]

conclusive evidence of Roche's understanding -- years before the Bolar case was decided -- that such activity was unauthorized and that it amounted to infringement.

The quotation in Mr. Engelberg's letter of one sentence from a 20 page transcript of an argument in the Zenith case on June 14, 1976 is taken out of context. One of the issues in that litigation was the effect of 28 U.S.C. § 1498(a), a statute which provides that when a patented invention is used by or for the United States, the patentee's only remedy is to bring an action against the government in the Claims Court. Since this statutory protection extends to contractors and subcontractors of the government, Zenith claimed its protection, by alleging that it was engaged in steps necessary to supply diazepam under a government contract, asserting that 28 U.S.C. § 1498(a) barred Roche's suit. Answer, Fourth Affirmative Defense. (Zenith's assertion that its activities fell within the protection of § 1498(a) is quoted in the margin in full.) */

[Footnote continued from last page]

> defendant has actively taken steps and made arrangements to procure (and/or to have its subsidiaries or those with whom it is in concert or controls procure) diazepam and/or pharmaceutical preparations containing diazepam as the active ingredient from a source (other than plaintiff) which has or expects to obtain such approval from the Food & Drug Administration."

*/ Zenith's Fourth Affirmative Defense said:

> "Plaintiff is barred from obtaining any remedy in this Court for actions taken by defendant, Zenith, in preparation for or anticipation of gaining eligibility to bid for government contracts for the supply of diazepam by reason of 28 U.S.C. Sec. 1498(a) by which the United States has authorized the manufacture by private companies of products arguably subject to a patented grant that are needed for the government's use."

As Zenith's then-counsel argued to the court, "We will sell only . . . to the government," and "We have admitted that we intend to apply to the FDA for approval for purposes of selling to the government. . . ." Transcript, pp. 6, 8. (Emphasis supplied). Although Roche does not concede the legal soundness of Zenith's theory that Section 1498(a) shields such activity, the sentence quoted by Mr. Engelberg in his letter was intended to make the point that Roche was not engaged in challenging activities that were within the legitimate scope of 28 U.S.C. § 1498(a). References in the transcript to 28 U.S.C. § 1498(a) and to Roche's desire not to enjoin Zenith from doing work for "bidding for United States government contracts" makes it clear that Roche desired to avoid any possible conflict with that statute.

The Zenith case was terminated by a Consent Judgment in 1979 which did not sanction continued testing to obtain FDA approval for the marketing of diazepam products commercially. Paragraph 9 of the Consent Judgment allowed Zenith to use diazepam "for the limited purpose of such experimentation as fairly falls within permissible experimentation under the patent laws of the United States." But, here too, the intent was to avoid any possible conflict with Section 1498(a), and to allow the traditional types of experimental use under the established doctrine. As the very next sentence in that paragraph recites, "Nothing herein shall prejudice Zenith from taking advantage of those rights, if any, under Title 28 U.S.C. § 1498(a)." */

Roche certainly did not understand the Consent Judgment to permit unlimited testing of its patented product for FDA approval. It is doubtful that Zenith ever understood it differently since, as Zenith conceded in open court this week, Zenith did not proceed with experimentation for the purpose of gaining FDA premarketing approval in the years immediately following entry of that Judgment.

*/ In the same vein, the Consent Judgment also states in paragraph 4:

> "That nothing herein shall be construed as limiting, expanding or otherwise affecting any applicability of Title 28, United States Code, Section 1498(a), to Zenith's past or future activities."

In 1984, it came to the attention of Roche Products, Inc. that Zenith was conducting infringing tests of diazepam to obtain data for FDA premarketing clearance. Accordingly, Roche Products filed a new infringement suit in the Northern District of New Jersey on July 13, 1984. The case has been assigned to Judge Lacey, the same judge who had responsibility over the earlier Zenith case. Last week Zenith moved to vacate Judge Lacey's order granting Roche the right to expedited discovery. In support of its motion, Zenith relied on the same quotation from the 1976 transcript that appears in Mr. Engelberg's letter to you. In essence, Zenith argued that Roche Products had conceded (through its predecessor in interest, Hoffmann-La Roche Inc.) that Zenith could engage in such testing. We are informed that on July 23, 1984, Judge Lacey denied Zenith's motion after hearing argument in open court. The same argument is entitled to no greater weight when it is made to the Subcommittee.

In conclusion, we submit that none of the arguments in Mr. Engelberg's letter displaces the rationale of Roche v. Bolar. In effect, his letter seeks to relitigate Bolar by having this Subcommittee displace the Court of Appeals. However, the law which the court applied is well established and, as Commissioner Mossinghoff testified, the doctrine is a sound one. The "new information" in his letter is not at all "new." More importantly, they establish that Roche has long relied on the doctrine expounded in the Bolar decision to enforce its patent rights.

Sincerely,

Jack Lipson

cc: Subcommittee Members
David Beier
Assistant Counsel
Thomas Mooney, Minority Counsel

AMERICAN HOME PRODUCTS CORPORATION
685 THIRD AVENUE
NEW YORK, N.Y. 10017

JOHN R. STAFFORD
PRESIDENT

June 22, 1984

The Honorable Robert W. Kastenmeier
Rayburn House Office Building
Room 2232
Independence and S. Capitol Street, S.W.
Washington, D.C. 20515

Dear Mr. Kastenmeier:

Thank you for meeting with us yesterday concerning the Patent Term/ANDA bill (H.R.3605) which will be before your subcommittee next week. As I mentioned, we have serious concerns with some provisions of this measure. Your willingness to hear from constitutional, law and patent experts is encouraging to our research coalition as we continue to press for changes in H.R.3605.

Time constraints prevented me from elaborating on all our concerns so I am enclosing for you and your staff additional copies of our position paper, the comments of the Food and Drug Administration listing that agency's concerns and a summary and memorandum regarding constitutional problems we see with the current bill.

Finally, on a more personal note, enclosed is a copy of our annual report. I thought you might be interested in reviewing the total operations of our company.

We look forward to working with you and your staff on this important piece of legislation.

If you have any questions, feel free to contact me or my associates, Jack Wood or Duke Reid at (202) 659-8320.

Very truly yours,

John R. Stafford
President

Enclosures (5)

June 16, 1984 ..

POSITION PAPER

on

S 2748 and HR 3605

DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT OF 1984.

The undersigned are among the nation's leading research-based pharmaceutical companies and contribute approximately 50% of the pharmaceutical research dollars spent in the United States by private industry. We favor a patent term restoration -- abbreviated new drug application bill which: (1) Restores patent life lost to regulatory review for innovative drug products; and (2) Accelerates the availability of safe and effective generic drug products.

We are prepared to support a bill that addresses the following issues:

LIMITS ON FDA AUTHORITY TO ASSURE SAFETY AND EFFICACY

Background

Unlike current ANDA regulations for drugs approved before 1962, the bill precludes FDA from requesting information

from an ANDA applicant concerning its drug product beyond the limited information specifically set forth in the bill. For most drugs, this does not permit FDA to request safety and effectiveness data other than bioequivalence data. In addition, the bill does not authorize rejection of an ANDA for most drugs on grounds of lack of safety or effectiveness. We believe that failure to include simple clear authority in the bill will (1) raise questions about the scope of FDA's authority; (2) probably result in litigation; and (3) perhaps create a separate class of products subject to premarket approval requirements -- post-1962 ANDAs -- for which FDA will be unable to obtain adequate safety and efficacy data.

Recommendations

The FDA, which is charged by statute with protecting public health, should have the same authority for all products it approves to properly protect consumers. Simply stated: Congress should maintain FDA's explicit discretionary authority: (1) to require safety and effectiveness information from an ANDA applicant when needed to protect the public health; and (2) in such instances, to disapprove any ANDA if the applicant is unable to demonstrate that its drug product is safe and effective.

ENCOURAGEMENT OF PATENT LITIGATION

Background

A prior concern of the research-based pharmaceutical companies was that the notice provisions allowed an ANDA applicant to force the patent holder to litigate the validity of a patent well before ANDA filing at a time when the applicant had incurred only minimal expense. It allowed the ANDA applicant easily to challenge patent validity beyond those circumstances permitted under current law. The provisions for providing notice to the patent holder have now been changed to require notice on the ANDA submission date. While this is an improvement, it is only partial. In order to trigger the notice provision, the ANDA "submission" need not be complete or acceptable for filing. This would permit sham ANDA applications to be submitted solely for the purpose of precipitating litigation.

Recommendations

The bill should provide that the trigger mechanism can occur only upon the "filing" of a complete ANDA. As used in the context of the current Federal Food, Drug and Cosmetic Act, this

means acceptance for "filing" by FDA of a complete application.

ENCOURAGEMENT OF PATENT INFRINGEMENT

Background

Under present law, a patent has a statutory presumption of validity. Under the bill, an ANDA applicant automatically will be allowed to market a drug after the expiration of an eighteen month period following notice to the patent holder*. This is unfair because final adjudication of the validity of a patent normally will not be reached within the eighteen month time period. Additionally, in some jurisdictions there may be a judicial backlog which could result in many years of delay. Since a patent is presumed valid, an ANDA applicant should not be allowed to market the drug until adjudication of the patent by the trial court.

Recommendations

An ANDA applicant should not be allowed to market a drug until a trial court has ruled that a patent is not valid or has not been infringed. However, if the pioneer fails to exercise

* This has been reduced from two years in the June 2, 1984 draft.

due diligence in prosecuting an infringement action, the court should have discretion to make effective the second-comer's ANDA, if FDA has approved the ANDA. Should a district court's ruling in favor of a patent challenger be reversed on appeal, an injunction against marketing of the infringing product should be mandatory.

REVERSAL OF THE BOLAR DECISION

Background

In the Bolar case, the United States Court of Appeals for the Federal Circuit reaffirmed the rights of the pharmaceutical innovator to prevent others from using its patented products during the patent term. The Court ruled that the use of a patented pharmaceutical compound for the purpose of testing or investigating it in order to obtain FDA approval constitutes patent infringement.

Under the provisions of the bill, Bolar is now completely reversed so that infringement may not be alleged prior to ANDA filing. This portion of the bill raises serious constitutional questions as it relates to the elimination of rights on patents that have already issued. In particular, it abridges the patentees' rights by permitting the manufacture, use or sale of the patented product during the patent term.

Recommendations

Bolar should be reversed only for drugs covered by patents issued after enactment of the bill and which are eligible for patent term restoration.

PATENT TERMS NOT SUBJECT TO RESTORATION

Background

The bill contains limitations on the patent terms which can be restored. Under present law, a patent can be obtained containing a broad claim (genus) covering many compounds. It is possible subsequently to obtain a patent for specific claims (species) on a few specific compounds encompassed within the genus. Under the bill, should a patent holder obtain a patent with species claims covered by a previously issued genus patent, the patent holder could not obtain restoration of the term of the species patent. The bill, differing from an earlier draft, only partially addressed this issue by providing for patent restoration if the earlier issued genus patent belonged to a third party and there was no exclusive license between the parties.

In addition, under present law, the Patent Office can require that the claims in a patent application be divided and prosecuted in separate patents. Under the bill, the first issued patent of the series would be the only patent term entitled to restoration, and subsequently issued patents of the series would be precluded from restoration. Accordingly, unless an FDA approved product is claimed within the first issued patent of the series, restoration of a patent term covering the product would not be available. During the patent application process, it is impossible to know which drug or drugs will ultimately be successfully tested and marketed. Therefore, a patent holder is being denied the benefit of patent term restoration due to circumstances beyond its control.

Another exception to patent term restoration would occur where one patent covers two FDA approved drugs. Any claims in the patent covering the second FDA approved drug could not be restored. Accordingly, only one restoration is available per patent even though a company has expended considerable resources in developing each FDA approved product.

The bill also limits availability of patent term restoration for method of manufacturing patents (not using DNA technology), including the limitation that no other type of

patent has been or "may be issued for any known therapeutic purposes" claiming the method of using the product.

Recommendations

Eliminate these exceptions to the extent necessary to encourage innovation and further research of new drugs through patent term restoration.

DISCLOSURE OF TRADE SECRETS

Background

The bill would permit FDA to release all safety and effectiveness data and information submitted in an NDA at the time the first ANDA is approved or could be approved. Those data and information may retain proprietary value in the United States and could be used by competitors to obtain product registration in foreign countries. Also, it is not clear in the bill that the term "information" is limited to safety and effectiveness information, as distinguished from other confidential data in NDAs such as manufacturing methods and processes.

Recommendations

The bill should require FDA to make available a detailed summary of safety and effectiveness data, but not the complete raw data. Also, it should be clarified that the term "information" relates only to information on safety and effectiveness.

INADEQUATE TRANSITION PROVISIONS

Background

The bill would permit marketing exclusivity for 10 years only for active ingredients first approved between January 1, 1982 and the date of enactment of the bill. It would also provide 4 year marketing exclusivity for non-patentable active ingredients first approved after the date of enactment of the bill. The bill discriminates against those companies that invested in research in areas such as new indications, new dosage forms, new delivery systems and innovative formulations. The current bill penalizes those companies by excluding those products from the transition provisions.

Recommendations

The periods of exclusivity provided by the transition provisions should apply to new salts or esters, new dosage forms, new release mechanisms, new dosages, and, importantly, new indications for which FDA has required a submission of safety and efficacy data.

American Home Products Corporation

Bristol-Myers Company

Carter-Wallace, Inc.

Hoffmann-La Roche, Inc.

Johnson & Johnson

Merck, Sharp & Dohme

Norwich Eaton Pharmaceuticals, Inc.
A Procter and Gamble Company

Schering-Plough Corporation

Squibb Corporation

Stuart Pharmaceuticals
Division of ICI Americas Inc.

TECHNICAL COMMENTS ON JUNE 2 DISCUSSION DRAFT
ANDA/PATENT TERM RESTORATION LEGISLATION

Comments are keyed to page and line number of the June 2 draft.

GENERAL COMMENT

1. The June 2 draft fails to include a transition provision. We have pointed out in previous comments that a transition provision is needed to protect the agency from a substantial increase in workload during the first few years immediately following enactment. As currently drafted, the bill would immediately open to ANDA eligibility all drug products approved from 1962 through 1981 other than those that are subject to patent protection. FDA's analysis of resource requirements associated with a possible post-1962 ANDA procedure established that the immediate eligibility for ANDA approval for drug products approved between 1962 and 1972 would produce unacceptable backlogs of ANDAs (reaching a peak of about 1,300 applications more than 180 days old). However, the agency found that by taking an initial 5-year group, allowing three years for processing, then adding the next 5-year group for a second three year period, it could handle the workload with the addition to staff of only four persons. If the agency were to timely process an initial 10 year period of applications, its analysis showed that it would need 21 additional ANDA reviewers, and these extra reviewers would need to be relocated after the initial submissions had been processed, because FDA estimated that the increased level of staffing would not be needed beyond the first three years.

To prevent unacceptable backlogs of pending applications and to avoid substantial resource increases that would be needed for only a relatively short period of years, a transition provision should be incorporated in the bill. As we have pointed out, a transition provision that opened only the 1962-67 period to ANDA approvals for the first three years after enactment would alleviate the immediate resource impact of the legislation but would still make immediately available for ANDA approval most of the drugs that would be available under the bill as currently drafted, including six of the drugs that are among the top selling prescription drug products.

ANDA PROVISIONS

2. The definition of the term "therapeutic alternative" has been deleted from the June 2 draft, but the bill still includes the concept (page 3, lines 24-27; page 4, lines 1-3) and the associated petition procedure for combination drugs (page 6, line 24; page 7, line 9). The petition procedure would permit prospective applicants to seek permission to file for ANDA approval of combination drugs that have not been previously approved. These new combinations would be required to include at least one ingredient that is the same as an ingredient in a listed (previously approved) drug. Because ANDA approval would appear to be authorized for a combination of active ingredients that had not been previously approved, the petition procedure and its associated "therapeutic alternative" concept are plainly inconsistent with the medical and scientific rationale that supports FDA's current ANDA procedure.

In addition, the petition procedure appears to be inconsistent with FDA's combination policy, 21 CFR 300.50, which generally requires a showing through appropriate studies comparing the combination with its individual active ingredients that each ingredient contributes to the safety or effectiveness of the combination drug. A number of provisions in the June 2 draft would appear to restrict FDA to consideration only of the safety and effectiveness of the different active ingredient in the new combination rather than to the new combination as a whole:

- o ANDAs for new combinations would be required to include information showing that the <u>different active ingredient</u> had been previously approved (apparently either as a single ingredient or as part of another combination), or that the <u>different ingredient</u> was no longer a new drug, and any other information with respect to the <u>different active ingredient</u> with respect to which a petition was filed as the Secretary may require (page 3, lines 1-8).

- o The petition procedure (page 6, line 24 -- page 7, line 9) requires that a petition for ANDA eligibility for a new combination be approved unless the Secretary finds that investigations are needed to show the safety or effectiveness of the active ingredients in the new drug <u>which differ from the listed drug</u>.

- Approval of an ANDA authorized through the petition procedure may be denied if the ANDA fails to contain information required by the Secretary respecting the active ingredient in the new drug which is not the same as in a previously approved drug (page 9, lines 6-11).

- Approval of an ANDA authorized through a petition may be denied if the application fails to show that the new drug can be expected to have the same therapeutic effect as the listed drug (page 9, lines 12-24).

Under FDA's current policy, approval of combination drugs that have not been previously approved would require data showing that the new drug (not just one of its ingredients) will have its intended effect. Consistent with the agency's current policy, the abbreviated procedure should be limited to drugs with the same active ingredients. Combinations of drugs with active ingredients different from previously approved drugs should be the subject of investigations to establish whether they are safe and effective.

For these reasons, the petition procedure that would authorize ANDA approval for combination drugs that have not been previously approved should be removed from the bill. The statutory ANDA procedure should be limited to duplicate versions of previously approved drugs under previously approved conditions of use.

3. Page 6, line 24. If a petition procedure consistent with FDA's current policy for ANDA approval and the approval requirements for new combination drugs were to be incorporated in the bill, it should eliminate consideration of ANDAs for drugs with different "active ingredients." The procedure should be limited to minor differences in route of administration, dosage form, or strength. Under FDA's current ANDA policy, different "active ingredients" as therapeutic alternatives are not permitted. There may be circumstances in which route of administration, dosage form or strength may differ slightly from those for a previously approved drug product. However, it should be stressed that even minor changes would not routinely be subject to implementation through ANDAs without clinical data.

4. Page 10, lines 6-14. The June 2 draft provides for denial of ANDA approval if the information submitted in the application or other information available to the Secretary shows that the inactive ingredients of the drug are unsafe or the composition of the drug is unsafe due to the type or quantity of inactive ingredients or the manner in which the inactive ingredients are included in the new drug. We had suggested such a revision, but our suggested revision also included, as a ground of denial, the failure of the information submitted to provide sufficient information to establish the safety of the inactive components or the composition of the new drug for its intended uses. Because it is the applicant's obligation to provide the information needed to support ANDA approval, the provision should be revised to provide for denial of ANDA approval if the information submitted is insufficient to show the safety of the inactive ingredients or composition of the product for its intended use. The following revision is suggested:

> (H) information submitted in the application is insufficient to show that (i) the inactive ingredients of the drug are safe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is safe under such conditions because of the type of quantity of inactive ingredients included or the manner in which the inactive ingredients are included, or (iii) such information or any other information available to the Secretary shows that the inactive ingredients are unsafe or the composition of the drug is unsafe under such conditions.

5. Page 11, lines 1-5. The June 2 draft continues to provide that the 180 day period for ANDA approval or disapproval runs from the initial receipt of the application. Consistent with the statutory provision for full NDAs, the period should run from the filing of the application, rather than the time of submission. There should be no implication that FDA may not refuse for filing an ANDA that is facially deficient nor should the agency be required to develop different procedures to deal with such problems than those already established for full NDAs. The provision should be revised to read as follows:

(4)(A) Within 180 days of the filing of an application under paragraph (2), or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall approve or disapprove the application.

6. Page 11, line 6 et. seq. The June 2 draft continues to condition the effective date of ANDA approval on the patent information filed for pioneer drugs and on the patent status of pioneer drugs. FDA would continue to be required to consider whether an ANDA is the "first application which contains" a certification, to hold application approvals pending applications for preliminary injunction to district courts, to hold the approval of applications pending a request for a reexamination of patentability to the Patent Office, and to hold the approval of subsequent applications until the first application involved in a patent dispute has been marketed for 180 days.

As pointed out previously, the provisions which key the effective date of ANDA approval to the patent status of the pioneer product would impose burdensome requirements upon the agency. Although the requirements are not intended to require judgmental determinations by the agency with respect to patent status, the complexity of the recordkeeping requirements and effective date of ANDA approval provisions will be burdensome and will be inconsistent with the kind of recordkeeping for which the agency is currently responsible. From a practical viewpoint, moreover, a successful litigant in a patent suit would learn of a court decision before FDA could be officially notified and could attempt to pressure the agency to issue an approval prior to the official notification.

As also pointed out previously, the patent status of the pioneer product would be adequately protected through a notice provision like that already incorporated in the revised bill. See page 5, lines 10-22 (ANDA applicant required to notify patent owner of application which applicant believes does not infringe a valid patent). Notification of the pioneer firm by the applicant, which would precede ANDA approval in every case by six months or more, would enable the pioneer manufacturer to protect its patent rights through judicial remedies and would not require FDA to divert its limited resources to issues that are peripheral to its primary public health protection responsibilities.

The complex effective date provisions, which would impose burdensome requirements on FDA, obviously are intended to prevent duplicate product marketing before issues concerning the pioneer's patent status are resolved. Those provisions should be replaced by a provision which prohibits the duplicate applicant from marketing the duplicate product -- even if it has received ANDA approval -- until the patent issues are resolved. Since the patent issues will already be involved in litigation before the courts, a statutory prohibition on marketing could be easily enforced as part of the litigation. Note that the patent term extension provisions already authorize a court to establish by order the effective date of approval for a duplicate product involved in a patent infringement suit (page 44, line 25 et. seq.). Under such an approach, FDA would be relieved of complex administrative responsibilities and it would be permitted -- as it is now -- to act on ANDAs without regard to patent controversies.

7. Page 20, lines 2-6. The June 2 draft continues to provide for the amendment of section 505(e) to authorize the withdrawal of pioneer NDA approval if the patent information for the pioneer product was not filed "within 30 days after the receipt of written notice from the Secretary specifying the failure to file such information." The agency continues to be concerned that the provision may impose additional burdens on the agency if it contemplates that FDA would be expected to take affirmative action to require pioneer manufacturers to supply information to the agency concerning the patent status of their products.

8. Page 23, line 9 et. seq. The June 2 draft continues to establish effective dates for the approval of paper NDAs based on the applicant's certification of the patent status of the pioneer drug product. Although paper NDAs may be less attractive to generic manufacturers if a post-1962 ANDA procedure were available, the new provisions would impose additional burdens on the agency that could be resolved by a less burdensome procedure, discussed above, which would require notification by the paper NDA applicant to the pioneer NDA holder and a statutory prohibition on market introduction pending the resolution of the pioneer product's patent status.

Patent Extension Provisions

9. Page 34, line 17. The June 2 draft continues to require the applicant to submit to the Commissioner of

Patents a brief description of the applicant's activities during the regulatory review period and the significant dates applicable to such activities. The Commissioner of Patents would be required to send a copy of the application containing the information to the Secretary who would be required within 30 days to determine the applicable regulatory review period. See page 35, lines 9-19. These burdens could be eliminated if the applicant were required to determine the regulatory review period in its application to the Commissioner of Patents. The applications could be made available to the FDA for inspection or audit at FDA's discretion, on the same enforcement basis that other reports, such as income tax filings, are regulated. Since the patent term extension is tacked on to the end of the patent term, FDA continues to believe that there is no public health reason to require the agency to determine the regulatory review period under a restrictive 30-day time schedule. The validity of the regulatory review period may be adequately addressed through applicant determination and a discretionary enforcement approach.

10. Page 35, line 20 et. seq. The June 2 draft continues to provide for a due diligence determination to be made by the Secretary if petitioned to do so within 180 days after the publication of the patent extension determination. The June 2 draft, despite our earlier comment, also continues to provide that the authority to make the due diligence determination may not be delegated to an office below the Commissioner of Food and Drugs. FDA had objected that the agency did not have an adequate perspective to make a due diligence determination. This objection was raised with respect to the first draft, which would have permitted the due diligence determination to be made by the FDA organizational component directly responsible for the application. As pointed out previously, the due diligence determination will be even more difficult if the determination may be made only by the Office of the Commissioner. In effect, the revised bill would require a de novo review by personnel who have not had any prior familiarity with the application or with the problems associated with the development of the product or its investigation and approval. Since patent term extension is subject to a 14 year cap, counts only 1/2 of the investigational period, and is limited to a 5 year extension in any event, it continues to be FDA's view that a requirement for a de novo due diligence determination would clearly impose burdensome resource requirements on the agency with

little, if any, public benefit in the earlier availability of generic drug products. In FDA's experience, based on the latest year for which calculations were made, the average new chemical entity gaining NDA approval would have been entitled, under the proposed formula, to the maximum 5 years of patent term restoration (based only on review time). Assuming that the average application was pursued with diligence, it would seem unlikely that the 5 year maximum extension would ever be reduced for lack of due diligence. Nonetheless, FDA will have been required to promulgate regulations, review petitions, and prepare due diligence determinations. As a practical matter, therefore, it appears that a complex system is being established that will require FDA resources to implement and maintain for no public benefit.

11. Page 36, line 8 et. seq. The due diligence determination is required to be published in the FEDERAL REGISTER with a statement of the factual and legal basis for the determination. The June 2 draft still provides that any interested person may require the Secretary to hold an informal hearing on the determination. The owner of the patent involved is entitled to notice and may participate in the hearing. The Secretary is provided only 30 days after the completion of the hearing to affirm or revise the determination of due diligence. There is no provision that would limit judicial review. See page 36, line 20 et. seq.

The FDA continues to regard the due diligence provision as imposing unnecessary and burdensome requirements on the agency. While the petition requirement may limit the number of determinations, the procedural restrictions imposed on the agency would provide no public health benefit and may divert scarce resources from more important matters, especially the review of other new drugs. In view of the limitations associated with patent term restoration, as noted above, the due diligence provision should be deleted on the ground that it will provide no public health benefit.

Substantial Constitutional Questions Raised By Section 202 of the Proposed Abbreviated New Drug Application and Patent Term Restoration Act

As set forth in the attached Memorandum of Law, Section 202 of the above-noted legislation raises serious Constitutional issues that have not yet been addressed by the Congress. These issues are in addition to the other public policy issues raised by the proposed legislation.

Proposed Section 202 permits parties other than the patent owner to use a drug subject to an existing patent to develop data to submit to the FDA for purposes of obtaining an Approved New Drug Application, without permission of the patentee and without infringement of the patent.

The courts expressly recognize that this right to develop data is an exclusive right granted by the patent to the patentee. Accordingly, as proposed Section 202 retrospectively deprives the patent holder of valuable rights in contravention of the Constitution.

-- Patent rights are recognized as property rights. The retroactive deprivation of one of these rights, i.e., the exclusive right to develop information for FDA submissioons, constitutes an uncompensated "taking" in violation of the Fifth Amendment of the Constitution, as well as a violation of the Due Process Clause of that Amendment.

-- Section 202 also violates the Constitutional principles concerning the Separation of Powers, in that it would reverse the decision of the Federal Circuit Court of Appeals in Roche Products Inc. v. Bolar Pharmaceutical Company, Inc., even though that case is still pending. Section 202 intrudes Congress into the District Court proceedings where that case has been remanded to deny the relief to the patentee to which the Federal Circuit has ruled it is entitled.

In view of such Constitutional problems, as well as the unfairness involved, Congress has traditionally made changes in patent legislation which withdraw rights of the patentee only on a prospective basis.

MEMORANDUM OF LAW

Constitutional Issues Presented by Section 202 of the Proposed Abbreviated New Drug Application and Patent Term Restoration Act

This Memorandum addresses the significant constitutional deficiencies raised by Section 202 of the proposed legislation concerning abbreviated new drug applications and patent term restoration for pharmaceuticals.

Summary

As currently devised, proposed Section 202 would permit parties other than the patent owner to use at any time during the term of the patent a patented drug to develop data for purposes of obtaining approval by the Food and Drug Administration of New Drug Applications. This could be done without permission of the patentee and without infringement of the patent. Most particularly, Section 202 would not just apply to patents issued after passage of the bill, but would impair existing rights of owners of patents that have already been issued. Such a retroactive taking of patent rights not only is unfair but involves substantial constitutional flaws for the following reasons:

To provide incentives for innovation, the patent law gives the patentee exclusive rights to make, use and sell his invention during the 17-year period of the patent. As recognized by the courts (Roche Products, Inc. v. Bolar Pharmaceutical Company, Inc.; Pfizer, Inc. v. International Rectifier Corp.), the patent grant includes the exclusive right to use the patented invention to develop data on a patented product for Food and Drug Administration submissions. Section 202, which extinguishes this right of existing patent holders would implicate two constitutional principles:

First: Patent rights are property rights. The retroactive deprivation of one of these rights, i.e., the exclusive right to develop information for FDA submissions, constitutes an uncompensated "taking" in violation of the Fifth Amendment of the Constitution. Cf. Hawaii Housing Authority v. Midkiff, 52 U.S.L.W. 4673 (U.S. May 30, 1984). Even if a taking could be justified as having a public purpose, an uncompensated taking is not justified as a matter of the state's police power. Here, the Constitution requires the payment of just compensation, and Section 202 makes no provision for this.

Second: Section 202 also contravenes the constitutional principle concerning the Separation of Powers. Section 202 would reverse the holding of the Court of Appeals for the Federal Circuit, the basic arbiter of patent rights, in a pending case, Roche Products v. Bolar Pharmaceutical Company, Inc. That case has been remanded to the district court for further proceedings to give the patentee relief to which this Court has ruled it is entitled. Section 202 would now deny such relief.

Nature of Preexisting
Property Rights that Will Be
Affected by the Proposed Legislation

The patent statute gives the owner of a patent the exclusive right to make, use and sell the patented invention 35 U.S.C. §§ 154 and 271(a). Section 202 of the proposed legislation would take away that right retroactively. It would allow a third party to make, use or sell a patented invention for purposes "reasonably related" to the submission of information to obtain premarketing approval under the Food, Drug and Cosmetic Act in order to engage in the commercial manufacture, use or sale of the drug after patent expiration. Section 202 would directly contravene the substance of existing patent rights as they have been declared to exist by judicial authority.

In Roche Products, Inc. v. Bolar Pharmaceutical Co., Inc., ___ F.2d ___ (Slip op. April 23, 1984), the Court of Appeals for the Federal Circuit held that Bolar, a generic drug manufacturer, unlawfully infringed a patent owned by Roche when, during the patent term, Bolar used the patented substance to prepare submissions to the Food and Drug Administration for eventual marketing after the Roche patent expired. The Court of Appeals agreed with Roche that such "use" by Bolar of Roche's patented drug during the term of the patent grant for the purpose of engaging in federally mandated premarketing tests was part of the exclusive patent grant reserved to the patent owner. Having determined that Bolar's unauthorized use infringed Roche's patent, the Court of Appeals then held that "Roche is entitled to a remedy," in the form of an injunction or damages. Bolar, supra, at 16. It ordered that specific relief was to be fashioned in the first instance by the District Court to which the case was then remanded and before which it is now pending. In directing that remand, the Court of Appeals recognized that although the infringement involved a small amount of material, "the economic injury to Roche is, or is threatened to be, substantial . . . ." Bolar, supra at 19.

The Bolar decision is consistent with a long history of patent law cases that give effect to the exclusivity provisions of the patent statute. See also Pfizer Inc. v. International Rectifier Corp., 217 USPQ 157 (C.D. Cal. 1982). It is justified by the same considerations of public policy that are the foundation of the patent system, to create an incentive to invention that will promote the progress of science and useful arts. Constitution, Art. I, Sec. 8.

Section 202 of the proposed legislation would reverse the Bolar decision in its entirety, not just for the patent involved in that particular case, but for all existing drug patents. It would do so by making it lawful for an infringer to make, use or sell the patented substance during the period of the patent grant, if done for the purposes indicated. It would also reverse existing patent law by prohibiting courts from issuing an injunction against making, using or selling the substance for that purpose, and it would withdraw from the patentee his current right to collect damages for such infringement.

Section 202 Constitutes a Taking of Property Without Just Compensation

Existing patent law declares that a patent is a property right. Title 35 U.S.C. § 261 states in relevant part: ". . . patents shall have the attributes of personal property." Indeed, a patent has all the attributes one normally associates with property; it can be bought, sold, licensed or pledged. In essence the concept of property is the equivalent of a bundle of rights, and ownership of a patent gives the owner the basic right one normally associates with property -- the right to exclude others from trespassing on the owner's rights.

Proposed Section 202 takes substantially from the value of that existing property right. The bill's retroactive impairment of rights is most apparent when viewed in light of the facts of the Bolar case itself -- although the effect of the bill goes far beyond Bolar and applies to every existing drug patent. In Bolar the Court of Appeals found that infringement had occurred, and that Roche was entitled to damages. Those issues have been decided. All that is now pending is the determination of adequate relief. By this legislation, however, the infringer would be exonerated and Roche's

entitlement to injunctive relief and damages would be utterly defeated. The patentee's right to an injunction against unauthorized infringement and his right to damages to compensate for past infringement are also property rights deserving of Fifth Amendment protection. Under Section 202, an act which was wrongful when done, and which gave rise to civil liability at the time, would be declared retroactively lawful, and the injured victim will be deprived of its present right to an injunction or damages.

If Section 202 applied only to patents granted after its enactment, Congress could address the serious issues of public policy with respect to the effect of such legislation on the patent system generally, but at least the present constitutional problems would not exist. Under the present text, considerations of fundamental fairness are involved because the legislation purports to act retroactively to withdraw existing rights.[1]

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[1] Although retroactivity is not itself a bar to federal legislation, it does raise serious questions of constitutional policy that must be addressed by the Congress and not merely left to the courts to decide. In Pension Benefit Guaranty Corp. v. R. A. Gray & Co., 52 U.S.L.W. ___ (June 18, 1984), the Supreme Court deferred to the Congress and upheld an amendment to the ERISA statute which created retroactive obligations on employers who terminated their pension plans within five months of the statute's enactment. The object of that short period of retroactivity was to prevent

[Footnote continued on following page]

The effect of Section 202 would be to transfer part of a patent owner's exclusive right to make, use and sell to a third person. It is essentially a forced taking of a valuable asset from one party and a gift of it to another. Under the Fifth Amendment that sort of transfer would be allowed only if it meets two standards: First, for such a taking to be legitimate it must qualify as a "public use." However, even if that point could be overcome, the Fifth Amendment still requires that there must be "just compensation" for which the bill makes no provision.

[Footnote 1 continued from preceding page]
employers from withdrawing their plans while the legislation was pending in Congress. However, in United States Trust Co. v. New Jersey, 431 U.S. 1, 21-22 (1977), the Court invalidated a retroactive state statute that impaired preexisting contract rights when less drastic alternatives were available to the legislature. Compare also Lynch v. United States, 292 U.S. 571 (1934) (federal government prohibited from impairing its own contract obligations by legislation that cancelled war risk life insurance policies), and Allied Structural Steel v. Spannaus, 438 U.S. 234 (1978) (declaring invalid a state statute which materially altered the terms of a preexisting pension plan causing a severe permanent and immediate change in the expectations of the parties), with Home Building & Loan Ass'n v. Blaisdell, 290 U.S. 398 (1934) and Energy Reserves Group, Inc. v. Kansas Power & Light Co., 103 S. Ct. 697, 706-08 (1983) (permitting state legislation that impaired preexisting contracts).

This is not a case where the requirement for just compensation may be excused by invoking the government's police power on the theory that the property which is to be taken is akin to a nuisance which needs to be extinguished or removed. On the contrary, the patents which are most likely to be affected by Section 202 will be those which are of considerable social and economic value. Those patents are the object of Section 202 because of their intrinsic desirability. Nor is this the case where the patentee can be said to have received some reciprocal benefits by way of compensation.

A frequently cited case exemplifying the state's police power is Miller v. Schoene, 276 U.S. 272 (1928), where the Supreme Court upheld a state's uncompensated cutting down of diseased cedar trees in order to protect neighboring apple orchards from infestation. Here, however, no other property interest is threatened which would require the state to expend one class of property to save another. Instead, the issue here is whether the owner of a valuable property right shall be forced to share those economic benefits with others, without receiving any compensation.

In another well known case, Penn Central Transportation Co. v. United States, 438 U.S. 104 (1978), the Supreme Court held that New York could designate the Grand Central Terminal as a landmark and thereby block the construction of a multi-story office building over it. It held that the application of the New York Landmarks Law did not constitute a taking within the meaning of the Fifth Amendment. However, it is notable that the owners were granted development rights above the Terminal which were made transferable to other sites in the vicinity and which provided significant compensation for their loss.

Today, a patent owner has the right to sue for injunctive relief and damages under Bolar if his patent was infringed in any way, even if the purpose of the infringement was to secure government approvals for marketing the substance later on. Under Section 202, that right will be lost without any compensation. As the Supreme Court observed this term in Hawaii Housing Authority v. Midkiff, 52 U.S.L.W. 4673 (U.S. May 30, 1984), even where property is taken for a public use, there must be a provision for just compensation, citing Thompson v. Consolidated Gas Crop., 300 U.S. 55 (1973). See also United States Trust Co. v. New Jersey, supra,

431 U.S. 19 n.16 (a "taking" of contract rights for a public purpose is taking of property and requires just compensation). In short, the bill suffers from a basic infirmity under the Fifth Amendment.

Finally, as a matter of Fifth Amendment Due Process guarantees, the retroactive application of patent legislation to the prejudice of the property rights of holders of existing patents has long been regarded as constitutionally prohibited. See McClurg v. Kingsland, 42 U.S. (1 How.) 202, 206 (1873) (new patent legislation "can have no effect to impair the right of property then existing in a patentee"); Diebold, Inc. v. Record Files, Inc., 114 F. Supp. 375, 376 (N.D. Ohio 1953) ("The constitutional principle of due process prohibits the retroactive application of the new statute and a resultant invalidation of the plaintiffs patent claims").

To avoid the constitutional difficulties inherent in retroactive legislation, Congress has been careful to limit the effect of new statutes on existing patent rights. This was most evident in the Patent Act of 1952, which revised and codified the patent laws and repealed prior laws. There, Congress specifically provided that "any rights or liabilities now existing under such [repealed] sections or parts thereof shall

not be affected by this repeal." Act of July 19, 1952, c. 950, § 5, 66 Stat. 815. (A current patent bill under consideration, H.R. 4526, does not raise such considerations since it does not impair existing rights of patent holders.)

Section 202 Violates the Separation of Powers

Section 202 has been drafted with the Bolar facts in mind, and it is equally clear that its retrospective reach would reverse the rule of decision in that still pending litigation. By substituting a legislative fiat for the present judicial determination of the Court of Appeals, the bill would violate the policy of Congress to refrain from legislating in pending cases and would contravene the fundamental separation between the judicial and legislative branches that the framers wrote into the Constitution. As Chief Justice Marshall stated in Marbury v. Madison, 5 U.S. (1 Cranch) 137, 177 (1803), "It is emphatically the province and duty of the judicial department to say what the law is." See Ogden v. Blackledge, 6 U.S. (2 Cranch) 272 (1804).

This very issue was conclusively decided more than a century ago in United States v. Klein, 80 U.S. (13 Wall) 128 (1871). In that case, plantiff claimed

a right to the proceeds of property that had been seized and sold by federal authorities during the Civil War. Plaintiff sued in the Court of Claims and recovered on making proof of his loyalty as a result of a presidential pardon, a procedure which had been upheld by the Supreme Court. However, while the case was on appeal, the Congress passed an act which altered that rule, and which provided that a pardon would not be admissible to prove loyalty. In questioning the constitutionality of that Act the Supreme Court asked:

> "What is this but to prescribe a rule for the decision of a cause in a particular way? . . . Can we [dismiss the appeal] without allowing that the legislature may prescribe rules of decision to the Judicial Department of the government in cases pending before it?" Supra at 146.

The Court answered these questions with a resounding negative. It declined to enforce the legislation, and observed:

> "We must think that Congress has inadvertently passed the limit which separates the legislative from the judicial power.
>
> "It is of vital importance that these powers be kept distinct." Supra at 147.

The Klein decision remains an authoritative guide in upholding the separation of powers principle. Pacemaker Diagnostic Clinic of America v. Instromedix, Inc., 725 F.2d 537, 544 (9th Cir. 1984).

This limit against congressional intrusion on judicial power is plainly applicable here because Section 202 would repudiate the Court of Appeals' holding of infringement and would deny Roche the very relief to which the court said it was entitled.

CONCLUSION

We have focused attention to the constitutional issues in this memorandum. In this document we do not address the additional and serious patent law and public policy issues raised by Section 202, including its possible adverse impact on future incentives to innovation. These issues raised by Section 202 are significant. However, they can be cured by giving the Section prospective effect only.

QUESTIONS AND ANSWERS ABOUT
DRUG PRICE COMPETITION/PATENT TERM EXTENSION ACT

A coalition of the nation's leading research-based pharmaceutical companies is seeking amendments to H.R. 3605 and S. 2748, the Drug Price Competition/Patent Term Extension Act, which will maintain incentives for continuing research and help ensure the safety of generic drugs.

The coalition supports the goals of the legislation but favors seven specific amendments that, if enacted, would help encourage pharmaceutical research in the U.S. as well as accelerate the marketing of safe generic drugs.

Following are questions and answers about the legislation:

Q. What are the bill's purposes?

A. There are two:

1. To restore patent rights to drugs approved by FDA, to compensate for time lost during the mandatory testing phase and the regulatory review process.

2. To make it easier for generic versions of drugs whose patents have expired to be marketed.

Q. What is the status of the legislation?

A. H.R. 3605 was reported by the Energy & Commerce Committee June 12, the same day it was introduced and without any opportunity for review or for the public, federal agencies or industry to present their views on this complex legislation.

Q. What committees have jurisdiction?

A. Because the bill combines health issues and patents, the Senate and House Judiciary Committees and the Senate Labor and Human Resources Committee have jurisdiction, in addition to the House Energy and Commerce Committee.

Q. What companies form the coalition?

A. American Home Products, Bristol-Myers, Hoffmann-La Roche, Johnson & Johnson, Merck & Co., Procter & Gamble, Schering-Plough, Squibb Corp., and Carter-Wallace. These companies sponsor a significant percentage of U.S. pharmaceutical research. ICI/Stuart has just joined the coalition and other companies are opposing the legislation and considering joining the coalition.

Q. Why do these companies favor amending the bill, when other PMA firms favor it as is?

A. The bill combines two concepts, on patent restoration and on generic drug approvals. The companies believe that the combined legislation fails to achieve a proper balance between the two issues and would not adequately accomplish either of its stated objectives.

Q. What would be accomplished by the coalition's proposed amendments?

A. They would provide appropriate incentives for pharmaceutical innovation. They would provide FDA added authority to assure the safety and effectiveness of generic drugs. They would protect certain trade secret data of commercial value to foreign competitors.

The coalition also favors changes in the patent section of the bill. As drafted, the current bill in effect encourages patent litigation as well as patent infringement.

It also raises serious constitutional questions about elimination of patent rights for already-patented products.

Q. Does the coalition oppose the entire legislation?

A. It supports the legislation with the seven amendments that would stimulate continued research investment.

Q. Has the coalition established priorities among its seven amendments?

A. No. The coalition believes that all are critical for the legislation to accomplish its stated objectives.

Q. Have the coalition's views been expressed at Congressional hearings?

A. No. There have been no hearings, in either the House or Senate, on the current bill. A hearing was held in July 1983 on a one-page bill; the current bill is 52 pages long and deals with many other issues.

Q. How was the legislation developed?

A. It was developed by staffs from three groups: the House Health Subcommittee, the Pharmaceutical Manufacturers Association and the Generic Pharmaceutical Industry Association. The companies in the coalition oppose PMA support of the bill.

Q. Where do the Administration, or the FDA and Patent and Trademarks Office, stand on the legislation?

A. Although they have not publicly expressed their views, since there have been no hearings, we understand they have raised concerns and questions about sections of the bill.

Q. Since generic competition lowers drug prices, would the amendments sought by the coalition lead to higher prices, especially for the elderly?

A. No. The coalition is not seeking changes in the provisions making it possible for low-cost generics to come on the market more quickly. The coalition's amendments would help stimulate more research into new drugs, many of which would benefit the elderly and would help ensure the safety of the generic drugs.

# # #

6/19/84

MEMORANDUM OF LAW

Constitutional Issues Presented by Section 202 of the Proposed Abbreviated New Drug Application and Patent Term Restoration Act

This Memorandum addresses the significant constitutional deficiencies raised by Section 202 of the proposed legislation concerning abbreviated new drug applications and patent term restoration for pharmaceuticals.

Summary

As currently devised, proposed Section 202 would permit parties other than the patent owner to use at any time during the term of the patent a patented drug to develop data for purposes of obtaining approval by the Food and Drug Administration of New Drug Applications. This could be done without permission of the patentee and without infringement of the patent. Most particularly, Section 202 would not just apply to patents issued after passage of the bill, but would affect patents that have already been issued. Such retroactive application involves substantial constitutional flaws for the following reasons:

1. To provide incentives for innovation, the patent law gives the patentee exclusive rights to make,

use and sell his invention during the 17-year period of the patent. As recognized by the courts (Roche Products, Inc. v. Bolar Pharmaceutical Company, Inc.; Pfizer, Inc. v. International Rectifier Corp.), the patent grant includes the exclusive right to use the patented invention to develop data on a patented product for Food and Drug Administration submissions. Section 202, which extinguishes this right in existing patent holders would violate two provisions of the Constitution:

A. The patent grant constitutes a contract between the patentee and the United States Government under which in exchange for disclosures of the invention, the Government has granted the patentee exclusive rights for the prescribed period in the statute. Article I, Section 10 of the Constitution, bars the United States Government (through the Fifth Amendment) from passing any law which impairs the obligation of contract, as reflected by the teaching of United States Trust Company v. New Jersey, 431 U.S. 1 (1977) and other cases noted herein. Section 202 would also impair contracts between patentees and licensees relating to the use of the patented drug in the development of such data, also in violation of the Contract Clause.

B. Patent rights are property rights. The retroactive deprivation of one of these rights, i.e., the exclusive right to develop information of FDA submissions, constitutes an uncompensated "taking" in violation of the Fifth Amendment of the Constitutions." Cf. Hawaii Housing Authority v. Midkiff, 52 U.S.L.W. 4673 (U.S. May 30, 1984). Even if a taking could be justified as having a public purpose, the Constitution requires the payment of just compensation, and Section 202 makes no provision for this.

2. Beyond these issues, Section 202 also violates the constitutional principles concerning the Separation of Powers. Section 202 would reverse the holding of the Court of Appeals for the Federal Circuit, the basic arbiter of patent rights, in a pending case, Roche Products v. Bolar Pharmaceutical Company, Inc. That case has been remanded to the district court for further proceedings to give the patentee relief to which this Court has ruled it is entitled. Section 202 would now deny such relief.

Nature of Preexisting Contract
and Property Rights that Will Be
Affected by the Proposed Legislation

The patent statute gives the owner of a patent the exclusive right to make, use and sell the patented invention 35 U.S.C. §§ 154 and 271(a). Section 202 of the proposed legislation would take away that right retroactively. It would allow a third party to make, use or sell a patented invention for purposes "reasonably related" to the submission of information to obtain premarketing approval under the Food, Drug and Cosmetic Act in order to engage in the commercial manufacture, use or sale of the drug after patent expiration. Section 202 would directly contravene the substance of existing patent rights as they have been declared to exist by judicial authority.

In Roche Products, Inc. v. Bolar Pharmaceutical Co., Inc., ___ F.2d ___ (Slip op. April 23, 1984), the Court of Appeals for the Federal Circuit held that Bolar, a generic drug manufacturer, unlawfully infringed a patent owned by Roche when, during the patent term, Bolar used the patented substance to prepare submissions to the Food and Drug Administration for eventual marketing after the Roche patent expired. The Court of Appeals

agreed with Roche that "use" by Bolar of Roche's patented drug during the term of the patent grant for the purpose of engaging in federally mandated premarketing tests was part of the exclusive patent grant reserved to the patent owner. Having determined that Bolar's unauthorized use infringed Roche's patent, the Court of Appeals then held that "Roche is entitled to a remedy," in the form of an injunction or damages. Bolar, supra, at 16. It ordered that specific relief was to be fashioned in the first instance by the District Court to which the case was then remanded and before which it is now pending. In directing that remand, the Court of Appeals recognized that although the infringement involved a small amount of material, "the economic injury to Roche is, or is threatened to be, substantial . . . ." Bolar, supra at 19.

The Bolar decision is consistent with a long history of patent law cases that give effect to the exclusivity provisions of the patent statute. See also Pfizer Inc. v. International Rectifier Corp., 217 USPQ 157 (C.D. Cal. 1982). It is justified by the same considerations of public policy that are the foundation of the patent system, to create an incentive to invention that will promote the progress of science and useful arts. Constitution, Art. I, Sec. 8.

Section 202 of the proposed legislation would reverse the Bolar decision in its entirety, not just for the patent involved in that particular case, but for all existing drug patents. It would do so by making it lawful for an infringer to make, use or sell the patented substance during the period of the patent grant, if done for the purposes indicated. It would also reverse existing patent law by prohibiting courts from issuing an injunction against making, using or selling the substance for that purpose, and it would withdraw from the patentee his current right to collect damages for such infringement.

Section 202 Contravenes the Constitutional Restrictions Against Impairing Contract Rights and Constitutes a Taking of Property Without Just Compensation

Existing patent law declares that a patent is a property right. Title 35 U.S.C. § 261 states in relevant part: ". . . patents shall have the attributes of personal property." Indeed, a patent has all the attributes one normally associates with property; it can be bought, sold, licensed or pledged. Ownership of a patent gives the owner the basic right one normally associates with property -- the right to prevent others from trespassing on his rights.

At the same time the patent grant bears the attributes of a contract. In exchange for the exclusive right to make, use or sell his invention for a limited duration, the inventor has made a public disclosure of his secret. The patent which has been granted to him represents a bargained-for exchange, which gives the patent holder legal rights against the government and third persons. As the Supreme Court said in United States Trust Co. v. New Jersey, 431 U.S. 1, 17 n.14 (1977), "In general, a statute is itself treated as a contract when the language and circumstances evince a legislative intent to create private rights of a contractual nature enforceable against the State."

Proposed Section 202 takes substantially from the value of those existing contractual and property rights. The bill's retroactive impairment of rights is most apparent when viewed in light of the facts of the Bolar case itself -- although the effect of the bill goes far beyond Bolar and applies to every existing drug patent. In Bolar the Court of Appeals found that infringement had occurred, and that Roche was entitled to damages. Those issues have been decided. All that is now pending is the determination of adequate relief. By this legislation, however, the infringer would be

exonerated and Roche's entitlement to injunctive relief and damages would be utterly defeated. Under Section 202, an act which was wrongful when done, and which gave rise to civil liability at the time, would be declared lawful, retroactively and the injured victim will be deprived of its present right to an injunction or damages.

If Section 202 applied only to patents granted after its enactment, serious issues of public policy would still exist with respect to the effect of such legislation on the patent system generally, but at least the present constitutional impediments would not then be a problem. The constitutional issues arise under the present text because considerations of fundamental fairness are necessarily involved whenever legislation purports to act retroactively. The strong policy against retroactive legislation which impairs preexisting contract rights grows out of the Contract Clause of the Constitution, the vitality of which was reaffirmed in United States Trust Co. v. New Jersey, 431 U.S. 1, 21-22 (1977). In that case, the Supreme Court reviewed New York and New Jersey legislation which retroactively repealed a statutory covenant that had protected New York Port Authority bond holders from diversion of Port Authority funds available for bond repayment in order

to subsidize commuter railroads. In striking down the legislation as a violation of the Contract Clause, the Court emphasized that the retroactive impairment of the rights of the bond holders was unnecessary, since there were reasonable, "less drastic" alternatives to achieve the states' goal of developing mass transportation. Id. at 30-31. The Court expressly noted that the Due Process Clause also bars retroactive application of civil legislation whose consequences would be "harsh and oppressive." Id. at 17 n.13.

Similarly, in Lynch v. United States, 292 U.S. 571 (1934), the federal government was prohibited from impairing its own contract obligations by legislation that canceled government war risk life insurance policies. In an opinion by Justice Brandeis, the Court held that such destruction of preexisting rights granted by the government was unconstitutional.

The leading case which allowed retrospective legislation that impaired preexisting rights is Home Building & Loan Association v. Blaisdell, 290 U.S. 398 (1934), a case arising under the Contract Clause, but followed in applying the Due Process Clause as well as to federal statutes. In Blaisdell, the Supreme Court upheld state mortgage relief legislation enacted during

the depths of the depression; the law authorized the state courts to allow a debtor in default to defer foreclosure and remain in possession for as long as two years, so long as he paid a reasonable rent to the mortgagee.

In sustaining the legislation, the Court identified five extraordiary factors justifying its retrospective application to vested rights and liabilities:

(1) a national emergency existed;

(2) the legislation was no broader than that required to meet the emergency;

(3) the legislation did not destroy the mortgagee's interest, but merely postponed the realization of his rights under the mortgage agreement;

(4) the legislation was temporary; and

(5) the legislation was not designed to advantage particular individuals but was to protect a basic interest of society.

Id. at 444-47.

Measured by the standard articulated in Blaisdell, the retroactive application of the proposed legislation would be fatally defective. Most crucial is the fact that no emergency exists requiring retroactive application of the bill, nor is there a basis for Congress to declare the existence of an emergency. Thus, Blaisdell factors one and two are not present. The third Blaisdell factor is absent because the patentee's right to recovery is not merely delayed, it is withdrawn entirely. The fourth Blaisdell factor is also lacking because the legislation is not offered as a temporary measure. Only the fifth Blaisdell factor may be implicated, but that interest could be safeguarded by giving the bill only prospective effect.[1]

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[1] A less rigorous application of Blaisdell has been allowed "in a heavily regulated industry" where the history of governmental supervision has been both "extensive and intrusive," Energy Reserves Group, Inc. v. Kansas Power & Light Co., 103 S. Ct. 697, 706 (1983). In that case the Court permitted Kansas ceiling price legislation to stand despite a Contract Clause challenge even though the law was enacted after the contract to purchase wellhead gas was entered. As the Court explained, however, the "significant fact" was the background of extensive federal price regulation of the natural gas industry and a 75-year history of regulation by the State of Kansas of the production, transportation, distribution and sale of natural gas. As the Court held: "Thus, at the time of the execution of the contracts, ERG did not expect to receive deregulated prices. The very existence of the governmental price escalator clause and the price

[Footnote continued on following page]

Moreover, it is not just contract rights between the patentee and the government which may be impaired by Section 202. Retroactive legislation may impact the rights of third-party licensees under existing patents where the licensees contracted in good faith for patent licenses under the reasonable -- and lawful -- assumption that they were getting an exclusive license.

Legislation which deprives one group of its pre-existing contractual rights against a second has been stricken by the Supreme Court. In Allied Structural Steel v. Spannaus, 438 U.S. 234 (1978), the Court declared

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[Footnote 1 continued from preceding page] redetermination clause indicates that the contracts were structured against the background of regulated gas prices," supra at 707. And, ". . . ERG knew its contractual rights were subject to alteration by state price regulation. Price regulation existed [at the time of contracting] and was foreseeable as the type of law that would alter contract obligations." Supra at 708.

Unlike such pervasive public utility-type regulation, the patent statute does not establish a regulatory framework by which governmental agencies control the day-to-day business of how patents are to be exploited; nor does it purport to regulate what, if any, licenses are to be granted, or what prices may be charged, etc. These matters are left largely to the marketplace and remain subject to the general law. It would be contrary to the facts for Congress to imply that a patentee who received his patent grant did so with any reason to anticipate the the enactment of Section 202 or any similar legislation.

invalid a Minnesota statute which provided that pension rights would automatically become vested when a company closed its plant in that State. Allied Steel had a preexisting pension plan which, at the time the company closed its plant, had not yet vested. (Under its existing plan, the company's obligation was merely to distribute assets of the fund at the time it was terminated.) The legislation in issue which vested those pension rights on plant closings was deemed invalid under the Contract Clause because it affected a severe permanent and immediate change in the expectations of the parties. For that legislation to survive, the Supreme Court held that it would have to meet the five criteria found in Blaisdell, supra.

Section 202 works both an impairment of contract and constitutes a taking of part of a patentee's property. Its true effect would be to transfer part of a patent owner's exclusive right to make, use and sell to a third party generic drug manufacturer. It is essentially a forced taking of an asset from one party and a gift of it to another. Whether that sort of transfer could qualify as a "public use" under the terms of the Fifth Amendment so that it may constitute a legitimate "taking" presents a difficult question that cannot be resolved

on the record of this legislation. However, even if such a transfer could be construed to constitute a public use, the Fifth Amendment still requires that there must be "just compensation" for which the bill makes no provision. Today, a patent owner has the right to sue for injunctive relief and damages under Bolar if his patent was infringed in any way, even if the purpose of the infringement was to secure government approvals for marketing the substance later on. Under Section 202, that right will be lost without compensation. As the Supreme Court observed this term in Hawaii Housing Authority v. Midkiff, 52 U.S.L.W. 4673 (U.S. May 30, 1984), even where property is taken for a public use, there must be a provision for just compensation, citing Thompson v. Consolidated Gas Crop., 300 U.S. 55 (1973). See also United States Trust Co. v. New Jersey, supra, 431 U.S. 19 n.16 (a "taking" of contract rights for a public purpose is taking of property and requires just compensation). In short, the bill suffers from a basic infirmity under the Fifth Amendment.

Section 202 Violates the Separation of Powers

Section 202 has been drafted with the Bolar facts in mind, and it is equally clear that its retrospective

reach would reverse the rule of decision in that still pending litigation. By substituting a legislative fiat for the present judicial determination of the Court of Appeals, the bill would violate the policy of Congress to refrain from legislating in pending cases and would contravene the fundamental separation between the judicial and legislative branches that the framers wrote into the Constitution. As Chief Justice Marshall stated in Marbury v. Madison, 5 U.S. (1 Cranch) 137, 177 (1803), "It is emphatically the province and duty of the judicial department to say what the law is." See Ogden v. Blackledge, 6 U.S. (2 Cranch) 272 (1804).

This very issue was conclusively decided more than a century ago in United States v. Klein, 80 U.S. (13 Wall) 128 (1871). In that case, plantiff claimed a right to the proceeds of property that had been seized and sold by federal authorities during the Civil War. Plaintiff sued in the Court of Claims and recovered on making proof of his loyalty as a result of a presidential pardon, a procedure which had been upheld by the Supreme Court. However, while the case was on appeal, the Congress passed an act which altered that rule, and which provided that a pardon would not be admissible to prove loyalty. In questioning the constitutionality of that Act the Supreme Court asked:

> "What is this but to prescribe a rule for the decision of a cause in a particular way? . . . Can we [dismiss the appeal] without allowing that the legislature may prescribe rules of decision to the Judicial Department of the government in cases pending before it?" Supra at 146.

The Court answered these questions with a resounding negative. It declined to enforce the legislation, and observed:

> "We must think that Congress has inadvertently passed the limit which separates the legislative from the judicial power.
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The Klein decision remains an authoritative guide in upholding the separation of powers principle. Pacemaker Diagnostic Clinic of America v. Instromedix, Inc., 725 F.2d 537, 544 (9th Cir. 1984).

This limit against congressional intrusion on judicial power is plainly applicable here because Section 202 would repudiate the Court of Appeals' holding of infringement and would deny Roche the very relief to which the court said it was entitled.

CONCLUSION

The constitutional issues raised by Section 202 are significant. All of them stem from the retroactive nature of Section 202, on which we have focused our attention in this memorandum. In this document we do not address the additional and serious patent law and public policy issues raised by Section 202, including its possible adverse impact on future incentives to innovation.

Substantial Constitutional Questions Raised
By Section 202 of the Proposed Abbreviated New
Drug Application and Patent Term Restoration Act

As set forth in the attached Memorandum of Law, Section 202 of the above-noted legislation raises serious Constitutional issues that have not yet been addressed by the Congress. These issues are in addition to the other public policy issues raised by the proposed legislation.

Proposed Section 202 permits parties other than the patent owner to use a drug subject to an existing patent to develop data to submit to the FDA for purposes of obtaining an Approved New Drug Application, without permission of the patentee and without infringement of the patent.

The courts expressly recognize that this right to develop data is an exclusive right granted by the patent to the patentee. Accordingly, as proposed Section 202 retrospectively deprives the patent holder of valuable rights in violation of the Constitution.

-- A patent grant is recognized as a contract between the patentee and the U.S. Government, under which in exchange for the public disclosure of the invention, the Government grants the patentee exclusive rights provided by the patent law. Under the Contracts Clause

of the Constitution, the Government is barred from passing laws which impair such rights of contract.

-- Patent rights are also recognized as property rights. The retroactive deprivation of one of these rights, i.e., the exclusive right to develop information for FDA submissions, constitutes an uncompensated "taking" in violation of the Fifth Amendment of the Constitution, as well as a violation of the Due Process Clause of that Amendment.

-- Section 202 also violates the Constitutional principles concerning the Separation of Powers, in that it would reverse the decision of the Federal Circuit Court of Appeals in Roche Products Inc. v. Bolar Pharmaceutical Company, Inc., even though that case is still pending. Section 202 intrudes Congress into the District Court proceedings where that case has been remanded to deny the relief to the patentee to which the Federal Circuit has ruled it is entitled.

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June 13, 1984

Alan A. Parker, Esq.
General Counsel
Committee on the Judiciary
U.S. House of Representatives
2137 Rayburn Building
Washington, D.C. 20515

Dear Alan:

As we discussed earlier today, we are working with a number of the drug companies that are concerned about certain provisions of H.R. 3605 dealing with patent term extension and new drug applications. This bill contains some of the most significant changes in patent law that one has seen in the last few years; it also attempts to overrule certain very important judicial interpretations of existing law.

An example of the variety of patent law issues that are raised by this bill is presented in Section 202 which reverses a decision of the Federal Court of Appeals. This provision would, surprisingly, apply both prospectively and retroactively; it thereby would extinguish significant rights under the present patent law which adhere in existing patents. This legislative deprivation of the existing rights of patent holders raises significant constitutional questions under the taking clause of the Fifth Amendment and the Contract Clause of the Constitution, as well as posing important separation of powers questions since the bill as drafted attempts to reverse a specific judicial decision. A memorandum on those issues is attached.

This is only one of many issues that require thorough hearings and independent judgment by the Judiciary Committee. A fuller discussion of the patent law issues which the bill proposes to resolve in a manner inconsistent with established patent policy is provided in the second memorandum I am attaching to this letter.

For these reasons, we think it would be appropriate for the Judiciary Committee to ask for a period through the end of July in which to study the bill and, once received, to ask Chairman Kastenmeier's Subcommittee to promptly commence an appropriate set of hearings. I am sure that all the parties concerned with these issues will be prepared to present witnesses at the hearings.

In this regard, it is significant, as you know, that no hearings at all have been held before the Judiciary Committee on these important issues. Indeed, representatives of the Pharmaceutical Manufacturers Association and the Generic Pharmaceutical Industry Association were scheduled to testify last week on these very issues before Chairman Kastenmeier's Subcommittee, but at the last moment declined to testify.

We think it is imperative that a record be made on these important Judiciary Committee issues and, as I said, that your Committee make an independent call on these troubling provisions of the proposed legislation.

Thanks so much for your consideration. I hope you will share these concerns with Chairman Rodino.

Best wishes.

Sincerely,

James F. Fitzpatrick

Enclosures

bcc: David Beier
Michael Remington

POSITION PAPER

The companies, which are among the nation's leading research-based pharmaceutical companies, favor a patent term restoration -- abbreviated new drug application bill which: (1) Restores patent life lost to regulatory review for innovative drug products; and (2) Accelerates the availability of safe and effective generic drug products.

The companies are prepared to support a bill that addresses the following issues:

LIMITS ON FDA AUTHORITY TO ASSURE SAFETY AND EFFICACY

Background

Unlike current ANDA regulations for drugs approved before 1962, the June 2 discussion draft precludes FDA from requesting information from an ANDA applicant concerning its drug product beyond the limited information specifically set forth in the draft. This does not permit FDA to request safety and effectiveness data other than bioequivalence data. In addition, the draft does not authorize rejection of an ANDA for most drugs on grounds of lack of safety or effectiveness.

Recommendations

Congress should maintain FDA's explicit discretionary authority: (1) to require safety and effectiveness information from an ANDA applicant when needed to protect the public health; and (2) in such instances, to disapprove any ANDA if the applicant is unable to demonstrate that its drug product is safe and effective.

We believe that failure to include simple clear authority in the bill will: (1) raise questions about the scope of FDA's authority; (2) probably result in litigation; and (3) perhaps create a separate class of products subject to premarket approval requirements -- post-1962 ANDAs -- for which FDA will be unable to obtain adequate safety and efficacy data. Simply stated: The FDA, which is charged by statute with protecting public health, should have the same authority for all products it approves to properly protect consumers.

ENCOURAGEMENT OF PATENT LITIGATION

Background

Under the discussion draft, an ANDA applicant can force the patent holder to litigate the validity of the patent well before the ANDA filing date and at a time when the applicant has incurred only minimal investment. The bill permits the ANDA applicant, in effect, to compel the patent owner to commence litigation on the validity of a patent within 45 days of receiving notice of formulation of dosage form or initiation of bioequivalence studies.

Recommendations

The bill should provide that the trigger mechanism can occur only upon the "filing" of a complete ANDA. As used in the

context of the current Federal Food, Drug, and Cosmetic Act, this means acceptance for "filing" by FDA of a complete application.

ENCOURAGEMENT OF PATENT INFRINGEMENT

Background

Under present law, a patent has a statutory presumption of validity. Under the draft, an ANDA applicant will be allowed to market a drug after the expiration of a two year period following notice to the patent holder. This is unfair because final adjudication of the validity of a patent normally will not be reached within the two year time period. Since a patent is presumed valid, an ANDA applicant should not be allowed to market the drug until adjudication of the patent by the trial court.

Recommendation

An ANDA applicant should not be allowed to market a drug until a trial court has ruled that a patent is not valid or has not been infringed. However, if the pioneer fails to exercise due diligence in prosecuting an infringement action, the court should have discretion to make effective the second-comer's ANDA, if FDA has approved the ANDA. Should that occur, and be reversed on appeal, an injunction against marketing of the infringing product should be mandatory.

REVERSAL OF THE BOLAR DECISION

Background

In the Bolar case, the United States Court of Appeals for the Federal Circuit reaffirmed the rights of the pharmaceutical

innovator to prevent others from using its patented products during the patent term. The Court ruled that the use of a patented pharmaceutical compound for the purpose of testing or investigating it for drug approval constitutes patent infringement.

Under the provisions of the draft, Bolar would be substantially reversed. This portion of the bill raises serious constitutional questions as it relates to the elimination of rights on patents that have already issued. In particular, it abridges the patentees' rights by permitting the manufacture, use or sale of the patented product during the patent term.

Recommendations

Bolar should be reversed only for drugs which are eligible for patent term restoration.

PATENT TERMS NOT SUBJECT TO RESTORATION

Background

The draft contains limitations on the patent terms which can be restored. Under present law, a patent can be obtained containing a broad claim (genus) covering many compounds. It is possible subsequently to obtain a patent for specific claims (species) on a few specific compounds encompassed within the genus. Under the draft, should a patent holder obtain a patent with species claims covered by a previously issued genus patent, the patent holder could not

obtain restoration of the term of the species patent. This provision applies even if the earlier issued genus patent belonged to a third party.

In addition, under present law, the Patent Office can require that the claims in a patent application be divided and prosecuted in separate patents. Under the draft, the first issued patent of the series would be the only patent term entitled to restoration, and subsequently issued patents of the series would be precluded from restoration. Accordingly, unless an FDA approved product is claimed within the first issued patent of the series, restoration of a patent term covering the product would not be available. During the patent application process, it is impossible to know which drug or drugs will ultimately be successfully tested and marketed. Therefore, a patent holder is being denied the benefit of patent term restoration due to circumstances beyond its control.

Another exception to patent term restoration would occur where one patent covers two FDA approved drugs. Any claims in the patent covering the second FDA approved drug could not be restored. Accordingly, only one restoration is available per patent even though a company has expended considerable resources in developing each FDA approved product.

The draft also limits availability of patent term restoration for method of manufacturing patents (not using DNA technology), including the limitation that no other

type of patent has been "or may be" issued claiming the product or a method of using it.

Recommendations

Eliminate these exceptions to encourage innovation and further research of new drugs through patent term restoration.

DISCLOSURE OF TRADE SECRETS

Background

The draft would permit FDA to release all safety and effectiveness data and information submitted in an NDA. Those data and information may retain proprietary value in the United States and could be used by competitors to obtain product registration in foreign countries. Also, it is not clear in the draft that the term "information" is limited to safety and effectiveness information, as distinguished from other confidential data in NDAs such as manufacturing methods and processes.

Recommendation

The draft should require FDA to make available a detailed summary of safety and effectiveness data, but not the complete raw data. Also, it should be clarified that the term "information" relates only to information on safety and effectiveness.

INADEQUATE TRANSITION PROVISIONS

Background

The draft would permit marketing exclusivity for 10 years only for active moieties approved between January 1, 1982 and

the date of enactment of the bill. It would also provide 4 year marketing exclusivity for non-patentable active moieties approved after the date of enactment of the bill. The discussion draft discriminates against those companies that invested in research in areas such as new dosage forms, new delivery systems and innovative formulations. The current draft penalizes those companies by excluding those products from the transition provisions.

Recommendation

The periods of exclusivity provided by the transition provisions should apply to new salts or esters, new dosage forms, new release mechanisms, new dosages, and, importantly, new indications, for which FDA has required a submission of safety and efficacy data.

* * *

STATEMENT

ON BEHALF OF

American Home Products Corporation
Bristol-Myers Company
Carter-Wallace, Inc.
Hoffmann-La Roche Inc.
Johnson & Johnson
Merck & Co., Inc.
Norwich Eaton Pharmaceuticals, Inc.
(A Procter and Gamble Company)
Schering-Plough Corporation
Squibb Corporation
Stuart Pharmaceuticals
(Div. of ICI Americas Inc.)

BEFORE THE SUBCOMMITTEE
ON COURTS, CIVIL LIBERTIES, AND THE
ADMINISTRATION OF JUSTICE
OF THE COMMITTEE ON THE JUDICIARY
UNITED STATES HOUSE OF REPRESENTATIVES

HEARING ON H.R. 3605

June 27, 1984

INTRODUCTORY REMARKS

Mr. Chairman and Members of the Committee:

My name is Jack Stafford and I am the President of American Home Products Corporation. We are here today to speak on behalf of 10 of the nation's leading research-based pharmaceutical companies: American Home Products Corporation; Bristol-Myers Company; Carter-Wallace, Inc.; Hoffmann-La Roche Inc.; Johnson & Johnson; Merck & Co., Inc.; Norwich Eaton Pharmaceuticals, Inc., a Procter and Gamble Company; Schering-Plough Corporation; Squibb Corporation; and Stuart Pharmaceuticals, a Division of ICI Americas Inc.

Together our companies account for approximately 50% of the pharmaceutical research dollars spent in the United States by private industry. Let there be no mistake about the public benefit of this pioneering work. Our companies have been responsible for some of the most significant pharmaceutical breakthroughs of the last several decades. Not only have we developed new drug therapies for many previously untreatable conditions, but drug innovations often provide the least expensive, most cost-effective form of medical therapy. Several recent studies establish that pharmaceuticals can lead the way in the effort to curtail health-care costs by cutting back the need for more expensive surgery and hospitalization. (Appendix A.) Moreover, the pharmaceutical industry is undeniably important to our national economy. Our group of com-

panies employ approximately three-quarters of a million workers in the United States. In 1983, the U.S. exported over $2.5 billion worth of pharmaceutical products that accounted for a net favorable trade surplus in excess of $1.2 billion. These health and economic benefits make it imperative for Congress to encourage adequate future research by restoring the effectiveness of America's patent system while maintaining our commitment to providing the world's safest and most dependable drug products.

Therefore, at the outset Mr. Chairman, we would like to commend the Congress for considering this important piece of legislation. We support its objectives. Specifically, our group favors legislation which would (1) restore some of the patent life lost to the regulatory review process for innovative drug products, and (2) accelerate the availability of safe and effective generic drug products. Although we support the goals and purposes of H.R. 3605, we believe that certain changes are essential in order to produce a bill which achieves its objectives fairly and equitably. This complex legislation must receive careful and thorough consideration.

We applaud your efforts, and those of the entire Committee to tackle these problems and we appreciate the opportunity to appear before the Subcommittee today.

As you know, this bill raises many difficult patent issues including serious constitutional questions about the elimination of patent rights for already-patented products.

In the past Representative Henry Waxman, who introduced this legislation, has said, "On first glance the proposal to restore patent term appears to be a simple and straight-forward issue of equity. But, ... it is really a complex and difficult public policy decision which requires a careful balancing of the need for incentives for pharmaceutical innovation and the societal impact of those incentives." H.R. 3605 is by far the most intricate measure of its type ever introduced, and some of its effects of pharmaceutical patent issues are not immediately clear. On careful examination, though, several flaws relating to the patent provisions become clear.

Most important, it would limit unduly the kinds of drugs and patents that would benefit from patent term restoration under the bill: products with multiple patents, significant improvements to existing products, and other worthwhile uses of the pharmaceutical research dollar all would be ineligible for restoration under H.R. 3605. The bill will encourage needless patent infringement and premature patent litigation. H.R. 3605 would also provide for the retroactive taking of important patent ownership rights without just compensation and would require the FDA to disclose valuable proprietary data to competitors both here and abroad. The bill's proposed restrictions on existing patent rights and the lengthy litany of the types of patents not eligible for patent term restoration could have far ranging adverse effects on the development of new technology in this country, including serious implica-

tions for the future of university-based research and the emerging and vitally important field of biotechnology. In addition, the bill contains narrow transition provisions that would penalize companies that invested in research in areas such as new indications, new dosage forms, and new delivery systems. We hope to be able to assist the Committee in understanding the impact this bill will have on innovation in our industry.

H.R. 3605 also raises significant public health concerns which need to be addressed before final consideration of this legislation. Our group believes and the FDA agrees that the bill restricts FDA's authority to insure that all drugs are safe and effective.

The FDA, in fact, raises a number of additional points that our group has not asserted. The FDA's "Technical Comments" on the legislation identify several of the health and safety problems which could arise if this legislation is enacted in its present form. For example, the bill would impose a number of severe administrative burdens on the FDA which could have the unintended consequence of actually thwarting the statutory objective of speedy approval of safe and effective innovative drugs. (Technical Comments, Appendix D.)

Some may have represented to you that our group, by seeking careful consideration of this legislation and its complex issues, is really trying to defeat the bill. I assure

you that this is not the case. We believe that the issues embodied in the bill deserve far more consideration than they received before the House Energy and Commerce Committee where this complex 45-page bill was entered as an amendment to a 1 1/2-page bill, and the amended bill was reported out of the Committee on the very same day it was introduced.

Today, in keeping with the Committee's expertise and jurisdiction over patent issues, we would like to use our limited time to focus the Committee's attention on several issues affecting patent rights and innovation which are raised by the legislation.

I. THE NEED FOR REAL PATENT TERM RESTORATION IS COMPELLING

The 98th Congress must deal with many difficult and controversial problems, but none are more challenging nor more crucial than the need to reverse the decline in U.S. innovation and productivity. Congress must not only be concerned with how to reverse this trend, but also must avoid unintentionally stifling U.S. technology.

- The U.S. share of world pharmaceutical R&D expenditures has fallen from greater than 60 percent during the 1950s to less than 30 percent now.
- The U.S. share of world pharmaceutical exports has fallen from greater than 30 percent before 1960 to less than 15 percent today.
- The number of new drugs entering clinical trials and owned by U.S. firms has steadily dropped from a yearly average of 60 in the mid-1960s to about 25 a year now. In contrast, the number of compa-

rable foreign-owned new drugs has remained almost constant at about 20 a year.

- The percentage of world pharmaceutical production occurring in the United States has fallen from 50 percent in 1962, to 38 percent in 1968, to 27 percent in 1978.

- Smaller U.S. pharmaceutical firms self-originate fewer new drugs than before 1960 and are increasingly dependent on foreign firms for licensing new products, though licensed products still make up less than half of drug introductions by small firms.

By any measure the pace of America's drug innovation is slowing. Unless Congress and the public are willing to provide meaningful incentives for pioneering research while insuring the safety and effectiveness of all drug products, then investment in private pharmaceutical research is likely to decline and will no longer provide the kind of products that have brought such an improvement in public health over the past 30 years.

One big step in the right direction would be to restore the diminishing effectiveness of the U.S. patent system for certain products, such as pharmaceuticals, that are subject to elaborate pre-market approval requirements by the Federal Government. Under current law, the Government grants a 17-year patent and then prohibits the pharmaceuticals from being marketed until all FDA-required tests are completed, reviewed, and approval is obtained. During this time, the life of the patent is ticking away, often for many years. For example, FDA reported that of 205 drug products approved between

1962 and 1978, 51, or 25%, had no or comparatively little, effective patent life at the time of approval. (Appendix B.)

Gradually, the time needed to complete and clear the regulatory review process has grown longer, as products and tests have become more sophisticated and the regulatory resources of agencies like the FDA have become stretched to their limit. In 1962, for example, it took approximately 2 years and $6 million to bring a new medicine from the laboratory to the marketplace. It now takes an average 7 to 10 years and about $70-85 million to complete this testing period. Thus, it is not uncommon for a drug product to have lost up to one-half of its patent life without having yet been marketed. (Appendix B.)

This phenomenon, coupled with the inability of many new products to recover their investment, discourages innovation. For example, from 1955 through 1962, an average of 46 drugs were introduced annually in the United States; today, undoubtedly for a variety of reasons, that average is only 17 drugs a year, a decline of 63 percent.

This reduction in the number of drug innovations strongly indicates that the public is being deprived of new therapies. A decline in pharmaceutical patent lives -- the result of inadvertence rather than Congressional intent -- could erode the investment research incentive provided by the traditional 17 year statutory patent term. No one could have anticipated that a testing and approval process that took

about two years in the early 1960s would take seven to ten years by 1980. Our group of companies urges that it is time to rebuild the incentives originally provided by the patent system.

We realize how difficult it is to draft a bill that accommodates all the multiple objectives touched by H.R. 3605. This is a bill that purports both to accomplish patent restoration and to promote the availability of generic drug products. But, amendments are needed to achieve these objectives.

On one hand, the patent term restoration provided by the bill is, in many cases, iillusory because H.R. 3605 contains restrictions on the eligibility of patents for extensions. In fact, at least one provision would actually shrink existing patent protection. That provision, section 202, would reverse the decision recently rendered in Roche Products, Inc. v. Bolar Pharmaceutical Co., No. 84-560 (Fed. Cir. April 23, 1984), by the Court of Appeals for the Federal Circuit, which has appellate jurisdiction over all patent cases. The reversal of Bolar with respect to existing patents is clearly inequitable. On the ANDA side, the bill would create a number of new regulatory problems. Overall, we are concerned that it would reorient FDA's priorities toward approval of ANDAs and release of proprietary safety and effectiveness data and away from approval of important new drug therapies.

This result would be bad policy and could create public health problems.

We submit that encouraging research leading to new drug therapies is at least as important as streamlining the approval process for generic copies of drugs. H.R. 3605 has been described by its proponents as a politically attractive bill because, as a compromise, it has something for everyone: patent term restoration for the research-oriented pharmaceutical industry and increased availability of generic drugs from "me-too" manufacturers. However, as currently drafted, it is not a successful compromise because it severely restricts patents eligible for extension and undermines the basic principles of established patent law. Nonetheless, we firmly believe that the concept underlying this legislation is indeed attractive because both patent term restoration and safe and effective generic products serve the best interests of the consumer. Consumers benefit not only from price competition among the finite number of existing approved drug therapies, but also from the development of new cures and treatments. Obviously, unless a new drug is developed there can never be a generic copy of that drug.

U.S. pharmaceutical companies have been pre-eminent in developing and disseminating health-care products in this country and throughout the world. But this country's continued leadership in this field and its international competitiveness are in jeopardy. The bill under consideration today

could result in a decline in scientific research and innovation.

II. ANALYSIS OF H.R. 3605

A. Unfulfilled Commitment -- Discouraging Innovation by Limiting Drugs Eligible for Restoration

This bill purports to be a fair balancing between the need for swift FDA market approval for products whose patents have expired and the need to restore the portion of patent life lost to regulatory delay. However, patent term restoration as offered in the bill is, in many cases, illusory and the ANDA provisions go far beyond what is necessary to provide prompt approval for generic drug products after the expiration of valid patents. In reality, the bill effectively denies patent term restoration for a variety of new drug products. This result is accomplished through detailed and complicated restrictions on the types of patents eligible for restoration. If the objective of the bill is to restore incentives for pharmaceutical innovation, then patent term restoration must reflect the reality of pharmaceutical research and development, and apply to a broader range of drug patents.

- The Species v. Genus Patent Problem.

Section 201(a) (proposed 35 U.S.C. 156(a)(4)) of the bill prohibits patent term extension for cases in which the applicant holds, or will hold, more than one patent claim-

ing the drug in question. Many new pharmaceutical innovations will thus be ineligible for restoration because they will, in fact, be covered by more than one patent held by the same owner or exclusive licensee. As an example, many drugs are claimed both by a patent with claims of broad scope, the genus, and also by a subsequent patent claiming a specific compound, or species within the genus.

After the initial discovery leading to the genus, pharmaceutical research is ordinarily continued on families of compounds sharing similar chemical structural features and often similar biological characteristics. The objective is to study the entire family and to identify new compounds within the family that appear to provide more of a likelihood of therapeutic promise than other compounds within the genus. The R&D expenses to take a new medicine from discovery to market approval range from $70-80 million. Section 201(a) would prohibit patent term restoration on the species patent if the holder of the genus patent conducts this species research, and would allow it only if the two patents are forever held by separate owners.

For example, the Squibb Corporation obtained a patent on the genus of 9-halosteroids and later was able to develop two popular topical steroids from this genus: Kenalog (triamcinolone acetonide) and Halog (halcinonide). Wyeth Laboratories obtained a patent on a genus of anti-anxiety agents, which has led to the development of four specific drugs--

oxazepam (marketed as Serax), lorazepam (marketed as Ativan), pemazepam, and lormetazepam. Had H.R. 3605 been in effect when these patents were issued, none of these products would have qualified for restoration because each was covered under a species patent and belonged to a family identified in an earlier genus patent. This destroys much of the incentive to develop new compounds under the genus patent.

° The Split Application Problem

Another way in which a compound becomes covered by more than one patent is through division of the patent claims within the Patent Office itself. Under present law, the Patent Office can require that claims in a patent application be divided and prosecuted in separate patents. Over 80% of patent applications for chemical compounds are prosecuted in severed applications. This requirement is met as part of the patent prosecution or by the Patent Office itself upon examination of the application. At this early stage of drug development, the patent applicant is forced under this bill to choose which compound to prosecute first. Under section 201(a) of H.R. 3605 (proposed 35 U.S.C. 156(a)(4)(A)), the first-issued patent of the series would be the only patent entitled to restoration. Subsequently issued patents of the series would be precluded from restoration.

This restrictive provision is ill-advised because it unrealistically and unfairly requires manufacturers to determine in advance of FDA approval and marketing which patent in

a series will cover the valuable products and therefore be worthy of extension. Because only the first-approved application would be eligible for extension, and patent applicants rarely know at the early stages of development -- when patent applications are made -- which aspects of a new product will become most valuable at a later date, patent term restoration becomes a game of chance. Moreover, even if the future commercial success of a new chemical compound was predictable, the patent applicant cannot assure that the patent claiming the potential successful product will be issued before the others, which is what the bill currently requires to ensure eligibility for patent term restoration. H.R. 3605 would thereby fail to provide the certainty requisite for investment and long-term research planning that will stimulate making discoveries available to the public.

° The Overlapping Patent-Product Problem.

Another exception to patent term restoration embodied in section 201(a) of the bill, proposed section 35 U.S.C. 156(a)(8), would apply where a substance is covered by multiple patents, each claiming a different use for that substance, or where a single patent covers two or more FDA-approved drugs. The term of claims in the patent covering the second FDA-approved drug could not be restored.

In the pharmaceutical industry, it is common for additional research on a patented drug product to lead to

the development of new delivery systems, therapeutic indications, or dosage forms of the original product. These later innovations contribute significantly to the safety and effectiveness of drug therapy, and the later-discovered products deserve restoration to the same extent as the initial products of a patent. Yet the bill would provide only one restoration per patent, even when a company has expended considerable resources in developing the subsequent FDA approved products. For instance, in 1972 Merck and Company, Inc. was issued a patent on a beta blocker which resulted in a product called Blocadren, a highly effective cardiovascular drug which is used in the prevention of a second heart attack, the heart attack most likely to cause death. Though widely used in Europe, it was not approved in the United States until 1981 and therefore had only eight years left on the patent once it was brought to the U.S. market.

Merck continued its research on this compound long after it was marketed in Europe as a cardiovascular drug and in 1978 received approval from FDA to market the product for a new use. Merck had discovered that the same compound which was useful in the treatment of cardiovascular disease would also decrease intraocular pressure on the eye when used as eyedrops, making it a useful drug in the treatment of glaucoma. Merck obtained a patent for the glaucoma indication in 1980 and manufactured the drug under the brand name Timoptic. Timoptic, a breakthrough drug which in many cases eliminates

the need for surgery, costs only 22 cents per dose and replaces a surgical procedure which costs approximately $800 per procedure and approximately $200 per day in hospitalization costs.

Under this proposed bill, the Timoptic active ingredient was claimed in the earlier issued patent for Blocadren, it would not be entitled to patent term restoration under subparagraph (4)(A) of section 201 of the bill. On the other hand, Blocadren was not approved in this country until 1981 while Timoptic was approved in 1978. Therefore, subparagraph (7)(A) of section 201 prevents the discoverer from getting restoration on Blocadren because Timoptic was approved first.

Schering-Plough has developed both Valisone (betamethasone valerate) and Diprosone (betamethasone dipropionate) from a single patent, and has turned the Diprosone formula into another form marketed as Diprolene, which has an improved delivery vehicle and allows lower dosages. None of the later improvements to these topical steroids would qualify for extension if H.R. 3605 were law, because they all arise under a single patent.

Just as one patent may cover two drugs, one drug or a family of drugs frequently is covered by more than one patent. Subsequent innovations to an existing drug may result in one product being covered by multiple patents. For example, the drug propranolol (Inderal) was patented in 1967 and is currently indicated for seven indications. Research continued

on the agent and a patent was obtained for the new product, Inderal LA, in 1979. The new form of the drug is considered an improved therapy for four indications, largely because it requires less frequent doses and thereby stabilizes serum levels of the drug and raises patient compliance through less frequent doses. Yet since Inderal LA is covered by both the 1967 and the 1979 patents, the drug would be ineligible for patent term restoration under section 201(a) of H.R. 3605, proposed section 35 U.S.C. 156(a)(4).

Similarly, the compound Cyclapen-W (cyclacillin) received patent protection in 1965 as an antibiotic, and the product was later improved by formulating an anhydrous version that has a longer and more stable shelf life and was patented separately in 1971. Wyeth Laboratories, which now sells only the improved anhydrous version of the drug, would be ineligible for restoration of either patent's term if H.R. 3605 had been law at the time of Cyclapen-W's discovery. These examples show how H.R. 3605 unfairly restricts the products for which patent term restoration may be available, and would deny restoration for the very kinds of new inventions and innovations it purports to encourage.

° The Manufacturing Patent Problem.

Section 201(a) of the bill (proposed 35 U.S.C. 156(a)(5)(A)) limits availability of patent term restoration for patents covering a method of manufacturing (not using rDNA

technology), including the limitation that no other type of patent has been or "may be issued for any known therapeutic purposes" claiming the method of using the product. New advances in pharmacological manufacturing techniques can contribute greatly to reducing the cost of drug therapy, and these innovations should be encouraged by providing for appropriate patent terms.

Furthermore, the bill contains special provisions for biotechnology and rDNA manufacturing techniques. Under proposed 35 U.S.C. 156 (a)(5)(B), the term of a process patent utilizing rDNA technology can be extended only if two tests are met: the patent holder of the method of manufacture is not the exclusive licensee or holder of the patent on the product itself (i.e., different ownership), and no other method of manufacturing the product primarily using rDNA technology is claimed in a patent having an earlier issue date. This second test would eliminate patent term restoration for much of the rDNA work being conducted, because a previously-issued dominating patent claiming rDNA technologies would exclude subsequently-issued "method of manufacture" patents from patent term restoration. This provision is overly broad, particularly where the dominating patent belongs to another party. One example of a dominating patent is the "Cohen-Boyer" patent developed at Stanford University, which covers basic rDNA manufacturing technologies. It would not take many of these broad-coverage, dominating patents to exclude almost

all future rDNA innovations from restoration of term. The existence of these dominating patents will turn the patent term extension promised in proposed 35 U.S.C. 156(a)(5)(B) into a mere illusion.

B. Encouraging Patent Infringements And Premature Patent Litigation

Under present law, a patent has a statutory presumption of validity. Under section 101 of H.R. 3605 (proposed 21 U.S.C. 505(j)(4)(B)(iii)), a competing drug manufacturer, a so-called "second-comer," can submit an ANDA on a patented drug, and give appropriate notice of this submission to the patent holder, who then has 45 days to institute a patent infringement action. Assuming such an action is brought, the second-comer is allowed to market the drug after the expiration of an 18-month period following the notice unless a court declares the patent valid within this period. This provision would institutionalize and provide incentive for a system of attacks on presumptively valid patents. It does serious damage to a patent system that generally -- apart from the regulatory system's inadvertent erosion of effective patent life -- has long served this nation well by fostering and promoting research, invention, and innovation.

Under section 101, the ANDA applicant can also force the patent holder to litigate the validity of the patent within 45 days of the initial submission of an ANDA, whether complete or not. This is in contrast to the current law which

provides that a full NDA must be complete before it is considered filed. ANDAs are often incomplete and require revision and additional work before they are accepted for filing by the FDA. The bill does not require that the ANDA submission be complete, even though there is presently a comparable requirement of "due diligence" in prosecuting an NDA imposed under the patent term restoration side of the bill upon a patent owner seeking an extension of the patent. If a patent suit can be triggered even before a complete ANDA is filed, then some companies and groups of companies will be encouraged to attack unexpired drug patents. Their risk is slight because they will not have to invest in the research required for a complete NDA.

Presumably, section 101's 18-month delay in the ANDA effective date once an infringement suit is filed is intended to permit a court to adjudicate a patent's validity before the ANDA becomes effective. However, this provision is grossly deficient. As the Subcommittee is well aware, the trial of a complex civil suit such as patent litigation is almost never completed within 18 months. Congestion in the courts and the low priority assigned to civil relative to criminal cases can stretch patent litigation out for five years or more. In fact, it has been recently reported that the completion of trials of patent actions (calendar waiting time plus trial time) average 35 months, not counting the time spent in discovery or pre-trial motions. Report of Proceedings of the Ju-

dicial Conference of the U.S., March 16-17, 1983 and September 21-22, 1983, Annual Report of the Director of the Office of U.S. Courts, table C54 (1983).

If enacted in its present form, the bill is certain to generate increased patent litigation. Owners of unexpired patents will need to respond to virtually every second-comer's notice of an ANDA submission with a suit for patent infringement. First, failure of the holder of a valid patent to litigate would permit the FDA to approve the "me-too" company's or companies' ANDAs and permit infringing commercial sales. Profits from the infringing sales could permit the initial and subsequent generic manufacturers to finance patent litigation. Second, failure of the patent owner to respond may support an estoppel or laches defense in subsequent litigation. Patent issues rarely lend themselves easily to quick summary judgment or other prompt resolution. This could result in extended and terribly costly patent litigation to the patent owner during the early stages of a patent -- precisely when unencumbered patent protection is most useful.

If the infringement occurs close to the end of the patent term, a court might eventually issue a final ruling in favor of the patent owner but mandate only payment of monetary damages, rather than also ordering the infringing product off the market. This would further encourage patent infringement and litigation, by allowing a second-comer to market competing

products before expiration of the patent term, merely by paying the equivalent of a licensing fee ordered by the court.

Since patents are presumed valid, an ANDA applicant should not get a free ride on the pioneer's original efforts to obtain an NDA and market a "me-too" drug until a court has fully and properly decided the patent's validity. Further, the bill should be amended to require, at minimum, a complete ANDA filing to trigger the initial steps that could lead to serious patent infringement.

C. Commercial Testing During Patent Term

It is a long-accepted tenet of patent law that the unauthorized use, sale, or manufacture of a patented product during the life of the patent constitutes infringement. This aspect of the rights accruing to the patent owner was underscored recently in the case of Roche Products, Inc. v. Bolar Pharmaceutical Co., No. 84-560 (Fed. Cir. Apr. 23, 1984). The United States Court of Appeals for the Federal Circuit held, consistent with prior rulings, that a generic drug manufacturer may not use another company's patented discoveries for purposes of obtaining FDA approval until expiration of the patent term. This decision is sound law and necessary to prevent damaging, commercially competitive work on a patented substance while the patent owner is still entitled to exclusive rights.

The legislation under consideration today, however, goes further than merely overruling Bolar. It would permit a commercial competitor to engage in acts which would now constitute blatant patent infringement. It is surprising that this restriction on patent rights should be contained in a bill intended to restore patent life and encourage innovation. The competition in today's market for innovative drug products is extremely intense. In order to encourage this research while respecting the rights of the patent owner, adequate patent protection such as was reaffirmed in the Bolar decision is critical.

The bill would eliminate this important patent right not only for patents issued in the future but also for patents already in existence. This provision of the bill raises serious constitutional concerns. By overruling Bolar retroactively, the bill deprives current patent holders of valuable property rights and constitutes a "taking" without due process. Even if Congress wishes to overrule the Bolar decision, it should do so only prospectively and only for those patents eligible for patent extension under the bill.

We believe the provisions of the bill permitting a competitor to conduct commercial testing of an invention covered by a valid patent should be amended. It is one thing to overrule Bolar for drugs that will benefit from the patent restoration provisions of the bill; however it is clearly unfair to remove existing patent rights from drugs

that are ineligible for any benefit under the bill. In any event, the attempt to apply such changes to already-issued patents raises serious constitutional concerns and must be remedied.

D. Government Disclosure to Foreign Competitors Of Valuable Proprietary Information

For over 45 years the FDA has not publicly disclosed, or allowed the release for any purpose not explicitly authorized by an NDA holder, any safety or effectiveness data contained in a pioneer NDA, while these data retain any commercial value. 21 C.F.R. 20.61, 314.11, 314.14. See 37 Fed. Reg. 9128, 9130-31 (May 5, 1972); 39 Fed. Reg. 44602, 44612-14, 44633-38 (Dec. 24, 1974); 40 Fed. Reg. 26142, 26148, 26168-7 (June 20, 1975); 43 Fed. Reg. 12869, 12870 (March 28, 1978). This interpretation of the FDC Act has consistently been upheld in court. E.g., Johnson v. DHEW, 462 F. Supp. 336 (D.D.C. 1978); Webb v. DHHS, Food, Drug, Cosm. L. Rep. ¶ 38,138 (D.D.C. 1981). See also, Pharmaceutical Mfrs. Ass'n v. Weinberger, 401 F. Supp. 444 (D.D.C. 1975); Syntex Corp. v. Califano, Food, Drug, Cosm. L. Rep. ¶ 38,221 (D.D.C. 1979). Cf. Public Citizen Health Research Group v. FDA, 704 F.2d 1280 (D.C. Cir. 1983).

Section 104 of H.R. 3605 would provide for a dramatic and ill-conceived reversal of this long-standing policy, although the bill's sponsors apparently maintain it would merely codify current FDA disclosure policy regarding drugs

subject to ANDAs. It has indeed been FDA policy to allow for limited disclosure of material contained in NDAs. This policy, however, applies to pre-1962 drugs, and since adoption the regulation has applied only to data generated before 1962. The regulation was adopted before any serious consideration had been given to ANDAs for post-1962 drugs. It does not follow that a policy which may be appropriate for data which are at least 22 years old is sound for data developed relatively recently and which are of far greater commercial value. Moreover, in the course of its ongoing rewrite of the NDA regulation, FDA itself intends to revise this regulation to reflect the continuing proprietary nature of these data. The bill would negate this effort.

The bill would permit the public disclosure of all of the extensive and costly research data generated by research-based pharmaceutical companies, at least as soon as FDA approval of a generic version of the new drug could become effective, even though the data may be of significant value to foreign competitors or may retain proprietary value in the United States. Also, it is not clear in section 104 that the term "information" is limited to safety and effectiveness information as distinguished from other confidential data such as manufacturing methods and processes.

The data that would be released can retain commercial value, even though FDA would no longer require another applicant to submit the data to obtain approval for sale in

the United States. These data would be commercially valuable because they could be used to obtain approval to market the drugs in foreign countries.

Senator Orrin Hatch earlier this year drove home the value of U.S.-produced technical data during efforts to tighten the Freedom of Information Act. Senator Hatch said:

> Foreign governments and foreign competitors of U.S. companies are able to obtain very valuable unclassified technical information simply by submitting a FOIA request to the Federal agencies that have paid to have the data developed. In fact, cottage industries have sprung up to systematically obtain and catalog such technical data, which they then market throughout the world.

The data disclosable under section 104 are particularly valuable in those countries which do not recognize U.S. patents. Thus, by providing for the release of these data, the bill hands foreign competitors of U.S. drug firms information which costs many millions of dollars to obtain and which can be used to obtain approval to market drugs in competition with the U. S. owner and generator of the data. This is hardly the way for this legislation to reverse the decline in pharmaceutical innovation and maintain the competitiveness of American industry.

Under section 104, trade secret data that now cost, on average, $70-85 million to generate per new drug would be freely released to anyone requesting them, including the innovating firm's foreign competitors. Competitors will copy the data and submit them to foreign drug regulatory agencies when

they request permission to sell the drug abroad. Unlike FDA, most foreign drug approval agencies give preference in their approval decisions to firms of their own nationality. American firms can expect to lose market shares in these nations and, in some instances, watch a foreign firm get marketing approval instead of themselves.

Section 104, as presently drafted, may jeopardize U.S. pharmaceutical exports and numerous American jobs. The exports at stake are to nations that (a) require data in the application for market approval that, but for section 104, would not be publicly available, and yet (b) do not recognize product patents. (Appendix C).

In effect, under section 104 our government would give foreign firms, for merely the cost of photocopying, private U.S. commercial information needed by the foreign firms to go on the market in their home countries. It would be ironic if such a provision were enacted now, when the U.S. government is vigorously negotiating against international efforts to impose compulsory licensing requirements on U.S. patent holders.

As FDA noted, in its Technical Comments (Appendix D), this provision of H.R. 3605 also has significant resource implications for FDA. Under the FOIA, FDA is obligated to respond to requests for documents in its files, including the voluminous safety and effectiveness data, ordinarily within ten days and in special cases, within twenty days. Since the

enactment of FOIA, FDA has consistently received more requests for documents than virtually any other Federal agency. In 1983, FDA received over 39,000 FOIA requests. One hundred twenty-five "full time equivalents," many of whom are highly trained scientists and doctors, were required to process these requests. Under H.R. 3605, over twenty years of safety and effectiveness data and information for off-patent drugs will be available for disclosure immediately upon enactment. If FDA were to receive requests for even a modest part of those data, the workload and resource burdens would be staggering. It is difficult to see how the public benefits by the FDA being forced to divert scarce resources to processing FOIA requests and ANDAs at the expense of new drug applications.

Despite the toll in jobs and balance of trade, Section 104 is unrelated to the goals of the bill, namely to expedite approval of generic drugs and to restore some of the time lost on patent during regulatory review of human and animal drugs and medical devices. Mandating disclosure of trade secrets would not affect the availability or pricing of generic substitutes, nor does it relate to the type or amount of information necessary for FDA approval of generics. In the United States, generic competitors do not need access to the raw data because the bill authorizes FDA to rely upon the innovator's data in making its decisions on the approvability of the generics rather than require that the generic firm duplicate the data..

Section 104 should be amended to require FDA to make available a detailed summary of safety and effectiveness data, but not the complete raw data. Also section 104 should be clarified so that the term "information" relates only to information on safety and effectiveness.

E. Burdens On The FDA And Its Unnecessary Involvement in Patent Issues

The bill imposes a number of new administrative burdens on the FDA. While many of these bear upon FDA's traditional functions, many others involve FDA for the first time in the administration of the patent system. Contrary to the implication in the Report on H.R. 3605 of the Energy and Commerce Committee, these complex procedures and their effects on FDA have not been considered at any time. They deserve full and careful evaluation. We understand that FDA representatives are making their views known independently on some of these features of the bill and therefore we will leave it to the FDA to address important aspects of these new responsibilities. (Appendix D.)

III. CONCLUSION

In conclusion, our group supports the legislative objectives of this important bill, but we believe that there are changes which must be made to improve and clarify the legislation. We have specific amendments that we believe will improve and clarify this important legislation. Moreover, we

wish to impress upon this Subcommittee the need for careful consideration of the complex and controversial public policy questions raised by the legislation. We stand ready to work with the Committee and its staff so that a meaningful and fair bill can be enacted this session of Congress.

Thank you very much for the opportunity to address this Subcommittee.

APPENDIX A

STUDIES DEMONSTRATING THE COST-EFFECTIVENESS OF PHARMACEUTICALS

Arthur D. Little, Inc., Report 7: Beta-Blocker Reduction of Mortality and Reinfarction Rate in Survivors of Myocardial Infarction: A Cost-Benefit Study (PMA Cost-Effectiveness of Pharmaceuticals Report Series, April 1984).

Arthur D. Little, Inc., Report 8: Use of a Beta Blocker in the Treatment of Glaucoma: A Cost-Benefit Study (PMA Cost-Effectiveness of Pharmaceuticals Report Series, April 1984).

Arthur D. Little, Inc., Report 9: Use of Beta Blockers in the Treatment of Angina: A Cost-Benefit Study (PMA Cost-Effectiveness of Pharmaceuticals Report Series, April 1984).

J. Adams, Report 1: The Societal Impact of Pharmaceuticals: An Overview (PMA Cost-Effectiveness of Pharmaceuticals Report Series, Feb. 1984).

T. Dao, Report 5: Cost-Benefit and Cost-Effectiveness Analysis of Pharmaceutical Intervention (PMA Cost-Effectiveness of Pharmaceuticals Report Series, March 1983).

J. Haaga, Report 3: Cost Effectiveness and Cost-Benefit Analysis of Immunization Programs in Developing Countries: A Review of the Literature (PMA Cost-Effectiveness of Pharmaceuticals Report Series, Sept. 1982).

A. Vinokur, C. Cannell, S. Eraker, F.T. Juster, J. Lepkowski & N. Mathiowetz, Report 6: The Role of Survey Research in the Assessment of Health and Quality-Of-Life Outcomes of Pharmaceutical Interventions (PMA Cost-Effectiveness of Pharmaceuticals Report Series, June 1983).

J. Wagner, Report 4: Economic Evaluations of Medicines: A Review of the Literature (PMA Cost-Effectiveness of Pharmaceuticals Report Series, October 1982).

B. Weisbrod & J. Huston, Report 2: Benefits and Costs of Human Vaccines in Developed Countries: An Evaluative Survey (PMA Cost-Effectiveness of Pharmaceuticals Report Series, July 1983).

COST-EFFECTIVENESS OF PHARMACEUTICALS

A Summary Report

April 1984

Pharmaceutical Manufacturers Association

FOREWORD

This paper summarizes the results of studies sponsored by the Pharmaceutical Manufacturers Association to determine the cost-effectiveness of pharmaceutical products. The studies prove what has long been assumed: that drugs are an economical form of medical therapy and that they can substantially reduce overall health-care costs. For a cost-conscious age, the value of pharmaceuticals cannot be over-emphasized.

This paper is a summary of nine reports:

- The first presents an overview of the social benefits of pharmaceuticals;
- three evaluate the literature on the cost-effectiveness of drugs and vaccines;
- three study the cost-effectiveness of beta blockers in preventing second heart attacks and in treating glaucoma and angina;
- one discusses a model developed for determining the cost-effectiveness of pharmaceuticals, and
- the final report examines ways to measure how drugs improve the quality of life.

Each report was prepared by an independent researcher, except the ones written by Thi D. Dao, Ph.D., Deputy Director of PMA's Office of Policy Analysis, on Cost Benefit and Cost-Effectiveness Analysis of Pharmaceutical Intervention and by John G. Adams, Ph.D., former PMA Vice President for Scientific and Professional Relations on The Societal Impact of Pharmaceuticals: An Overview. Drafts of each primary report were reviewed by experts in economics, medicine and health policy whose names are listed at the end of this document. We are grateful for their advice and assistance in preparing the reports for publication.

Lewis A. Engman

President

EXECUTIVE SUMMARY

In competitive markets, demand gravitates towards those products and services that work best and work cheaply. So it is in the market for medical services where rival therapies compete. Thus, it should come as no surprise to anyone familiar with the costs and benefits of medicines that for decades drugs have been steadily assuming work previously done by other therapies -- increasing their contribution to the nation's health, and doing so as an ever-declining share of health-care spending.

Were one required to define "cost-effectiveness" by example, one would be hard put, even in the hypothetical, to construct a more apt illustration than drugs.

Although scientists and medical academicians have long recognized that medicines are cost-effective, relatively little has been done to document this seemingly self-evident fact.

This paper summarizes nine reports which in the aggregate make this proposition both obvious and unavoidable.

Cost-Effectiveness of Vaccines

In one report in this series, the use of vaccines in developed countries is shown to be cost-effective against measles, mumps, rubella, pneumococcal pneumonia in high-risk groups, pertussis, adenoviral respiratory infections, polio and influenza in the elderly.

One study of measles vaccine, for example, found that benefits were more than 10 times the costs over a nine-year period (that is, the benefit-cost ratio was 10.4:1). The benefit-cost ratio for mumps vaccine ranged from 3.6:1 to 7.4:1, and for rubella vaccine the ratio ranged from 8:1 to 27:1 for girls from 2 to 12 years of age.

Vaccines were also shown to be cost-effective in developing countries. Thus, a study found that benefits were 33 times the costs for measles immunization in Yaounde, Cameroon (a benefit-cost ratio of 33:1). Other studies showed ratios of 2:1 for tuberculosis vaccine in India, 3.3:1 for tuberculosis and DPT prevention in Indonesia and 9:1 for tetanus in Haiti.

Cost-Effectiveness of Drugs

Another report in this series, a literature review, shows that antibiotics, anti-tuberculosis drugs, anti-ulcer medicines, anti-psychotics and anti-hypertensive agents are all cost-effective.

In a study of the preventive use of an antibiotic, for example, the average annual cost of preventing urinary tract infections was found to be $85 per patient, compared to $126 for treating the infection--a saving of 33 percent. In another study, Medicaid expenditures were determined to be approximately 70 percent less for persons using a new anti-ulcer drug than for those not receiving the medicine. And a third study concluded that treating mental patients with an anti-psychotic drug was the least costly of five forms of therapy--lower by 26.1 percent to 62 percent--and was one of the most effective methods.

Cost-Effectiveness of Beta Blockers

Three other reports in this series examine for the first time the cost-effectivenes of beta blockers--a new class of cardiovascular drugs. These studies show that the benefits of these drugs far exceed their costs in preventing second heart attacks and in treating glaucoma and angina. In preventing second heart attacks, the net annual benefits of using a beta blocker were estimated to range from $1.6 billion to $3.0 billion. In treating glaucoma, the net annual benefits of using such a drug instead of surgery were estimated to range from $746 million to more than $1 billion. And in treating angina, the net annual benefits of using a beta blocker were estimated to be as high as $237 million--without even considering the improvement in health associated with a 40 percent reduction in the incidence of the disease.

Social Benefits of Drugs

The economic benefits of drugs do not necessarily include social benefits that cannot be quantified. These benefits are also summarized in the first of the nine reports.

Many contagious diseases that once were the leading causes of death in this country have been controlled through the development in recent years of anti-infective agents. These medicines have cut death rates from such diseases as tuberculosis, influenza, pneumonia, cholera, puerperal sepsis, scarlet fever, meningococcal meningitis, typhoid fever, dysentery, syphilis, smallpox and polio.

During the last 10 years, new medicines have helped reduce the death rate for what had become the leading killer throughout the industrialized world--cardiovascular disease. Medicines also have become increasingly effective against the disease Americans fear most--cancer. By late 1983, the five-year survival rate for cancer had risen to more than 50 percent. Modern medicines have helped to treat a wide range of other diseases--including mental illnesses, epilepsy, diabetes, arthritis, Parkinson's disease and glaucoma.

As the reports summarized in this paper make plain, medicines are cost-effective. They not only save lives, they save money.

INTRODUCTION

Pharmaceuticals are among the least expensive of health-care products and services Americans use when they are seriously ill, particularly when they are hospitalized. At the same time, prescription drugs often are the most effective treatment for many acute and chronic diseases.

These two factors—the relatively low cost of drugs and their obvious effectiveness--support the widespread view within the scientific and medical professions that drugs are cost-effective. Heretofore, only a limited number of studies have been undertaken to establish what has appeared to be self-evident.

For years, health-care studies focused on questions of equity and access — on the availability of health care to different people, rich and poor, black and white, urban and rural. But, recently, as expenditures for health care have risen to 10 percent of the Gross National Product, there has been increasing concern—by government, industry and the general public—about the cost of such care.

The studies summarized in this report respond to that cost concern by demonstrating what has previously been widely assumed--namely that drugs and vaccines are cost-effective medical therapy.

As used in this paper, the terms "cost-effectiveness" and "cost-benefit" analyses refer to systematic economic analytical techniques that compare the negative consequences (costs) and positive outcomes (effectiveness, benefits) resulting from drug therapy. A drug is cost-effective when it achieves the same result as another form of therapy at a lower cost. A drug is cost-beneficial when it confers benefits that exceed costs.

Studies of vaccines (Reports 2 and 3) show that they are cost-effective because they prevent diseases at lower costs than the diseases can be treated. Studies of cimetidine demonstrate that it is extremely cost-effective because it averts the need for more expensive duodenal ulcer surgery. The importance of other drugs as lower-cost substitutes for hospital or other institutional care is shown by the studies of anti-microbial and anti-psychotic drug therapy (Report 4).

The studies reviewed in these reports, however, contain methodological limitations -- some inherent in the analysis but others avoidable if the proper methodology had been used. In Report 4, Judith L. Wagner, Director of Technology Research Associates, stated:

"Consistent definitions and methods of measuring the direct and indirect costs of illness do not exist....Perhaps the greatest shortcoming of the literature is the inadequacy of attempts to deal with the psychological benefits and costs that cannot be captured as indirect costs."

In response to this criticism, a model was developed for cost-effectiveness analysis of pharmaceuticals (Report 5). In addition, the feasibility of applying survey research techniques to measuring the psychological benefits and costs associated with drug therapy was analyzed (Report 6).

In applying this cost-effectiveness model to beta-blocker drugs (Reports 7, 8 and 9), it was found that their benefits far outweighed their costs in preventing second heart attacks and in treating glaucoma and angina. The benefit-cost ratio was estimated to be as high as 14:1, even without the inclusion of psychological benefits.

SOCIAL BENEFITS OF PHARMACEUTICALS

(Report 1)

The development of safe and effective medicines is of relatively recent origin, as explained by John G. Adams, former PMA Vice President for Scientific and Professional Relations, in Report 1.

As late as 1930, drug companies in this country were still essentially simple manufacturing enterprises that undertook little research and development. At that time, there were no antibiotics, no corticoids, no tranquilizers, no anti-hypertensives, no anti-histamines and no vaccines against polio, measles, mumps and whooping cough. More than three-quarters of the prescriptions written by physicians were compounded by pharmacists.

New Therapeutic Age

It was the development of sulfanilamide in 1935 and of penicillin in 1941, combined with needs brought about by World War II, that produced the modern drug industry in the United States--and ushered in a new therapeutic age. A number of drug companies launched crash programs during the war to develop methods to mass-produce penicillin. Thereafter, the companies increasingly engaged in other research efforts that transformed the industry into a high-technology business based on scientific progress.

During 1948-1958, pharmaceutical companies introduced 4,829 new products and 3,686 new compounds. According to a recent study, 150 of the 200 most frequently prescribed drugs in 1982 were developed since 1950.

As a result of this pharmaceutical research, enormous progress has been made in conquering disease. The value of modern medicines has perhaps been most succinctly stated by Victor Fuchs in his examination of health-economic issues, Who Shall Live? (Basic Books, 1974):

"Surgery, radiotherapy, and diagnostic tests are all important, but the ability of health care providers to alter health outcome...depends primarily on drugs....Our age has been given many names--atomic, electronic, space, and the like--but measured by impact on people's lives it might just as well be called the drug age."

Anti-Infective Agents

Many contagious diseases that once were leading causes of death in the United States have been controlled through the development of anti-infective drugs. The use of medicines, particularly antibiotics and other antibacterial agents, also has led to a reduction in surgery for such conditions as osteomyelitis, mastoid infection and brain and lung abcess.

At the turn of the century, just three infectious diseases—tuberculosis, influenza and pneumonia—accounted for more than 25 percent of all deaths in the United States. Since that time, the death rate from tuberculosis has been dramatically reduced in this country partly as a result of the development of effective medicines. Some 10 pharmaceuticals—including several antibiotics—developed since the 1940s have helped to control the disease. In 1980, there were 27,749 tuberculosis cases and only 1,770 deaths caused by the disease in the United States compared to 84,304 cases and 19,707 deaths in 1953—a 91 percent reduction in deaths.

Vaccines

Similarly, anti-infective medicines and vaccines have helped to cut the death rates in this country from influenza, pneumonia and such other serious diseases as cholera, puerperal sepsis, scarlet fever, meningococcal meningitis, typhoid fever, dysentery and syphilis.

Dramatic successes have been achieved against smallpox and polio. During the 1920s, there were more than 530,000 cases of smallpox reported in the United States. Because of widespread vaccination, not one confirmed case of smallpox has been reported in this country in more than 25 years—not one throughout the world since 1977.

As recently as 1952, 57,879 cases of polio were reported in the United States. The Salk vaccine was introduced in 1955, followed by the Sabin vaccine six years later. The result: only eight cases of polio reported in 1983.

Vaccines also have provided immunity against infectious diseases such as measles, diphtheria, whooping cough, tetanus, rubella, mumps, pneumoccal pneumonia, hepatitis B and rabies.

Analgesics

Aspirin—introduced just after the turn of the century—was the first safe and effective non-narcotic analgesic, but its potency was limited. Although analgesics do not cure or appreciably alter the course of a disease, they can relieve pain and bring a sense of well-being in the presence of disease. The first non-opiate drug to match the opium alkaloids in analgesic potency was meperidine, synthesized in 1939. Some of the recently-discovered non-steroidal anti-inflammatory drugs also have excellent analgesic properties.

Cardiovascular Drugs

During the last 25 years, new medicines helped produce a substantial reduction in the death rate for what had become the leading killer in the United States and throughout the industrialized world—cardiovascular disease. In just the last 10 years, deaths from strokes declined by 43 percent, while deaths from heart attacks decreased by 25 percent. New medicines, including the thiazide class of diuretic hypotensives, beta blockers and calcium antagonists, were partly responsible for the improvement.

Anti-Cancer Drugs

Medicines also have become increasingly effective in treating the disease Americans fear the most—cancer. The first anti-cancer drugs, the nitrogen mustards, were introduced in 1942. Since that time, more than 50 other anti-cancer drugs have been developed. In late 1983, the National Cancer Institute reported that more than 50 percent of all cancer patients are surviving for at least five years--up from 33 percent in the mid 1950s—and that most of this group are cured of the disease.

Medicines have helped treat a wide range of other diseases—including mental illnesses, epilepsy, diabetes, glaucoma and Parkinson's disease--and, in all, have helped prolong and greatly improve the quality of life for millions of people throughout the world.

REVIEW OF LITERATURE ON COST-EFFECTIVENESS OF VACCINES

(Reports 2 and 3)

Reviews of the literature on vaccines and vaccination programs both in developed and developing countries result in the same conclusion: their benefits generally exceed their costs, despite differences in evaluative approaches and in the data used.

Vaccines in Developed Countries

In Report 2, Burton A. Weisbrod and John H. Huston of the University of Wisconsin reviewed cost-effectiveness studies of 10 vaccines and vaccination programs in developed countries. The results of their review follow.

Measles: All seven studies of measles vaccine showed that its benefits far exceeded its costs. The unanimity of results was found even though the studies were conducted over many years—from 1963 to 1975—and in many regions of several countries—Austria, Finland and the United States. Of the two studies reporting results that can be expressed in benefit-cost ratios, one found that benefits were more than 10 times costs over a nine-year period (a benefit-cost ratio of 10.4:1), the other that benefits were almost five times costs over a six-year period (a benefit-cost ratio of 4.9:1). And in another study, benefits were shown to exceed costs by $1.3 billion from 1963 to 1972.

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Mumps: Four evaluations of mumps vaccine found benefit-cost ratios ranging from 3.6:1 to 7.4:1 as well as significant net benefits. One study, for example, calculated a net benefit of $5 million for each cohort of 1 million children, while another found a net benefit of about $50 per immunization.

Rubella: Three studies found that benefits greatly exceeded costs when rubella vaccine was routinely given to children. For females from 2 to 12 years old, benefits ranged from eight to 27 times costs (that is, benefit-cost ratios ranged from 8:1 to 27:1).

Pneumococcal Pneumonia: Four studies of pneumococcal vaccine concluded that benefits exceeded costs for persons in high-risk groups, such as the elderly and chronically ill. This conclusion was reached even though no attempt was made to include the value of lives saved by the vaccine. The benefits from immunizing low-risk groups were less clear.

Pertussis: There is only one evaluation of pertussis vaccine, and it found that benefits exceeded costs by more than 150 percent.

The vaccine is given as part of the DPT (diphtheria, pertussis and tetanus) trivalent vaccine, so the costs of patient and physician time for administering the vaccine are minimal. The major costs arise from the infrequent side effects of the vaccine, which can include convulsions and encephalitis.

Adenovirus: A study of military recruits found that the benefits of adenovirus vaccine exceeded costs by 1.56:1.

Tuberculosis: The results of the studies of the BCG (bacille Calmette-Guerin) vaccination for tuberculosis are contradictory. One study, using Austrian data, found that the benefits of the vaccine substantially exceeded costs regardless of the age of those vaccinated. Another study, using British data, found that costs exceeded benefits using a wide range of vaccine costs and many methods of treating tuberculosis. More than anything, the different findings of the two studies probably reflect disparities in methodology.

Polio: Two studies of polio vaccine found it cost-beneficial by a ratio as great as 10:1, with net benefits estimated to be about $1 billion a year in the United States. As with most vaccine studies (and, in fact, all evaluations of medical technology), however, the social benefits were understated because the better health of people for whom the disease was prevented was not taken into account. This is especially significant in the case of polio because of the crippling effects of the disease and the youth of its victims.

Influenza: The evaluations of flu vaccine have focused on the benefits and costs of vaccinating people in various age groups. That is because the consequences of contracting influenza appear to be related to age and to a person's health immediately before infection.

One study—which examined the immunization of persons 25 to 65 years of age—found benefit-cost ratios ranging from 2:1 to 5:1 for two types of workers over a five-year period. A study by the Congressional Office of Technology Assessment found that vaccination of persons at high risk was more cost effective than vaccination of the general populations.

Hepatitis B: Cost-effectiveness analyses for hepatitis B vaccine—which only became available in June 1982—have been undertaken for different vaccination strategies in different population groups. The results are quite speculative, however, because the vaccine is so new. One study found that for a "medium-risk" population--surgical residents in hospitals—the least costly approach was to vaccinate the entire target group.

Vaccines in Developing Countries

In Report 3, John G. Haaga of Cornell University reviewed the literature of some 20 cost-effectiveness studies of immunization programs in developing countries and concluded that the programs substantially improved public health and economic welfare.

One study showed that benefits were 33 times costs for measles immunization in Yaounde, Cameroon (a benefit-cost ratio of 33:1). Other results found benefit-cost ratios of 2:1 for tuberculosis in India, 3.3:1 for tuberculosis and DPT prevention in Indonesia and 9:1 for tetanus in Haiti.

The cost of vaccines, Haaga emphasized, constituted only a small part of total costs. Delivery costs were the largest. The cost per immunization ranged from a few cents to more than $20, with much of the variation attributable to differences in the number of persons immunized and in health-care infrastructures.

Generally, the studies were limited by lack of complete data showing the extent to which immunization programs succeeded in reducing the incidence of disease and mortality. As Haaga reported, however, the available data demonstrate that immunization programs substantially improved the health of people in developing countries.

REVIEW OF LITERATURE ON COST-EFFECTIVENESS OF PHARMACEUTICALS

(Report 4)

In Report 4, Judith L. Wagner, Director of Technology Research Associates, reviewed the literature on the cost-effectiveness of major classes of drugs for which such analyses had been done. A summary of her findings follows.

Anti-Microbial Therapy

Two kinds of studies were reviewed in this drug class: (1) studies evaluating the prophylactic use of antibiotic therapy in higher-risk groups, and (2) those considering the cost-effectiveness of alternative settings for antibiotic therapy.

Antibiotics in Prophylaxis: The prophylactic use of antibiotics shortly before or after surgery is a particularly appropriate subject for cost-effectiveness evaluation. That is because of the potential for savings in hospital costs and physician office visits, and because of the potential for reducing a patient's pain and possibly saving the patient's life. Clinical evidence clearly demonstrated that there is a significant reduction in surgery-related infections with the prophylactic use of antibiotics, but more economic evaluations are needed. The limited economic data also suggested that post-surgery antibiotics saved costs in some situations.

For patients with uncomplicated but recurrent urinary tract infections, the prophylactic use of antibiotics may well save more than the costs of such use. In one study of the prophylactic use of antibiotics, for example, the average annual cost of preventing urinary tract infections was found to be $85 per patient, compared to $126 for treating infections—a saving of 33 percent.

Alternative Settings of Care: Some serious bacterial infections require extended antibiotic therapy administered intravenously. Because of the difficulty of administration, the therapy often is given in a hospital and may be the only reason a patient is hospitalized. Two small uncontrolled studies of home antibiotic programs suggested that third-party reimbursement for such programs would be cost-effective. These small programs, moreover, probably understated the potential savings from home intravenous therapy because savings likely would increase as the number of participating patients rises.

Anti-Tuberculosis Drugs

Pulmonary tuberculosis--once a major killer in the United States—is a relatively rare and curable infectious disease in this country. As late as 1950, the death rate from tuberculosis in the United States was 22.5 per 100,000 people. By 1980, the rate had declined to less than 1 per 100,000.

This dramatic improvement is due at least in part to the development of effective preventive and therapeutic drugs. A succession of chemotherapeutic agents has proven effective against tuberculosis since 1948, when the efficacy of combined anti-microbial chemotherapy was demonstrated in Great Britain.

This success provides strong evidence that tuberculosis chemotherapy in patients with the disease is well worth its costs. Drug therapy is an undisputed bargain when the low cost of most anti-microbial drugs is compared to the cost of other therapeutic approaches, such as long-term hospitalization.

Anti-Ulcer Drugs

The introduction of a new medicine to treat peptic ulcer disease—a relatively common illness—shows dramatically how health-care costs can be reduced by the development of a single drug. In 1976, peptic ulcers accounted for the hospitalization of 620,000 Americans—which is about 175 such cases per 100,000 people. More than 25 percent of the patients who were hospitalized required surgery, the treatment of last resort for ulcer disease. In 1975, the total cost of this disease in the United States was about $2 billion.

In August 1977, a new drug—cimetidine—was approved for use in the United States for the short-term treatment of duodenal ulcers. Clinical evidence has demonstrated that cimetidine helps heal ulcers. The major

question for economic evaluation, however, is whether these clinical effects are translated into net direct, indirect and psychological benefits.

Studies here and abroad have shown that, immediately following the introduction of cimetidine, surgery rates declined. One study also found that cimetidine helped working patients—who previously missed work because of duodenal ulcer problems--return to their jobs more quickly.

A recent analysis of the impact of cimetidine on the costs of ulcer disease in Rhode Island found that surgery rates dropped after the drug was introduced. The authors estimated that this reduction in surgery in 1978 led to state-wide savings of $185,000 to $450,000.

Another study examined the impact of the introduction of cimetidine on health-care expenditures for Michigan Medicaid patients with ulcer disease. The result: Medicaid expenditures were approximately 70 percent less for persons on cimetidine than for those who did not receive the drug.

Most of the economic evaluations of cimetidine did not, however, consider its psychological benefits. Regardless of whether the drug reduces direct health-care costs or improves worker productivity, it may well be worth its cost just because patients suffer less than they would with other therapy.

The evidence on cimetidine, therefore, clearly demonstrates the effect that a single drug can have in reducing health-care costs.

Anti-Psychotic Drugs

The introduction of anti-psychotic drugs in the mid 1950s brought about a revolution in the care of patients with serious mental problems. The use of these drugs radically changed the prevailing view about the way to care for these patients, and the drugs were at least partially responsible for a rapid reduction in the number of patients in long-term mental hospitals in the 1960s. The social implications of the shift from institutions to community-care settings have been debated, but the importance of anti-psychotic drugs in making the move possible is undisputed.

The patients most affected by the development of anti-psychotic drugs are those with schizophrenia, which is characterized by a range of dysfunctional behaviors. In 1968, patients with schizophrenia accounted for an estimated 50 percent of all inpatient treatment for mental illness, and 10 percent of all outpatient visits. The direct and indirect costs of schizophrenia were estimated at about $10 billion nationally in 1973.

Most clinical studies have found that anti-psychotic drugs—such as the phenothiazines for the treatment of schizophrenia—are effective in preventing rehospitalization, although there are few economic evaluations of such drugs.

Not only have anti-psychotic drugs helped schizophrenic patients remain out of the hospital, they also have increased the cost-effectiveness of hospital treatment. A randomized study of 228 first-admission patients in a California state hospital found that drug therapy alone was one of the two most effective treatments—and the least costly—compared to alternatives that included psychotherapy only, a combination of psychotherapy and drug therapy, electric shock treatment and care in a supporting environment. The drug therapy was lower in cost than the other forms of treatment by 26.1 percent to 62 percent.

None of the studies, however, considered the effects of adverse reactions to the phenothiazines. These reactions are dose-related, and have been estimated to occur in approximately 10 to 20 percent of the patients.

A MODEL FOR COST-EFFECTIVENESS ANALYSIS OF PHARMACEUTICALS

(Report 5)

In Report 5, Thi D. Dao of the PMA's Office of Policy Analysis prepared a model for cost-effectiveness analysis of pharmaceuticals. The report describes research activities required to identify treatment protocols, alternative therapies and their respective outcomes, and resource utilization. In addition, it discusses quantification of benefits and costs; expertise requirements; and inherent strengths and weaknesses of cost-effectiveness methodology.

This model was the basis for the cost-effectiveness analyses of beta-blocker drugs in Reports 7, 8 and 9.

ASSESSMENT OF THE CONTRIBUTIONS OF PHARMACEUTICALS TO QUALITY OF LIFE

(Report 6)

In Report 6, Amiram Vinokur and his colleagues at the Institute of Social Research at the University of Michigan reviewed the application of survey research techniques to measuring improvements in the quality of life produced by drug therapy.

THE USE OF BETA BLOCKERS:
NEW DATA ON THE COSTS AND BENEFITS OF PHARMACEUTICALS
(Reports 7, 8, and 9)

A.D. Little, Inc. conducted three cost-benefit studies of the use of beta blockers—a new class of cardiovascular drugs—to prevent second heart attacks and to treat glaucoma and angina. These studies compared the use of beta blockers to non-drug therapy—such as surgery—and to treatment without beta blockers. The results: the use of beta blockers produced benefits that greatly exceeded their costs.

Cost-Benefit of a Beta Blocker in Preventing Second Heart Attacks

In Report 7, in which the use of the beta blocker timolol to prevent second heart attacks was studied, the net annual benefits for the entire potentially eligible population were estimated to range from $1.6 billion to $3.0 billion. (The $1.6 billion benefit is based on a 10 percent discount rate that was used to convert future costs and benefits into their present values, while the $3.0 billion benefit is based on a 2.5 percent rate.) Benefits exceeded costs by a factor ranging from 8 to 14. These results were confirmed by sensitivity analyses, which are statistical techniques used to test the validity of research findings.

Other important findings about the beta blocker have shown that:

—The drug potentially is able to prevent death due to second heart attacks for 27.5 percent of all patients surviving an initial heart attack—approximately 10,000 persons a year.

—It is able to reduce the incidence of non-fatal second heart attacks by 16.0 percent.

--The use of the drug slightly increases the direct cost of treatment, but this is more than offset by a gain in productivity. The net result is a savings ranging from $4000 to $7500 per patient per year.

Cost-Benefit of a Beta Blocker in the Treatment of Glaucoma

In Report 8, the beta blocker timolol was found to be significantly more cost-effective than surgery in treating glaucoma. The net recurring annual benefits of using the drug for the entire potentially eligible population was estimated to range from $0.746 billion to $1.057 billion, based on 10 percent and 2.5 percent discount rates, respectively.

Further, the net recurring annual benefits of the beta blocker exceeded its net annual costs by a factor ranging from 8 to 13. The validity of these results also was confirmed by sensitivity analyses.

Cost-Benefit of Beta Blockers in the Treatment of Angina

In Report 9, in which the use of the beta blockers propranolol and nadolol to treat angina were studied, the drugs produced cost savings and a lessening of pain and suffering for patients. The incidence of angina attacks was reduced by 40 percent, but, since this cannot be quantified, it was not included in the cost-benefit calculation.

Quantifiable benefits of using beta blockers to treat angina, which were substantial in many cases, were due to averted—or delayed—surgery costs and to a reduction in mortality associated with surgery.

The net annual benefits of using beta blockers to treat angina for the entire potentially eligible population were estimated to range from $113 million (beta blockers cost $1.00 per day) to $237 million (beta blockers cost $0.50 per day) at a 10 percent discount rate. At a 2.5 percent discount rate, the beta blockers were found to be more cost-effective than surgery only for persons over 65.

CONCLUSION

Pharmaceuticals have prolonged life and, at the same time, greatly improved the quality of life for millions of people around the world. They have enabled physicians to understand better the causes and manifestations of disease, while giving them the means to be much more effective in preventing and curing illness.

Of all the benefits of pharmaceuticals, however, only those that save costs by reducing mortality and alleviating some types of morbidity are included in formal calculations of their cost-effectiveness. Nevertheless, the evidence shows that drugs are cost-effective.

Drug therapy usually is the least expensive form of medical treatment, generally provides net benefits and reduces net costs and often produces benefits that greatly exceed costs. In a cost-conscious age, pharmaceuticals are of special value.

PRIMARY REPORTS

1. The Societal Impact of Pharmaceuticals: An Overview
John G. Adams, Ph.D., Former Vice-President, Scientific & Professional Relations, PMA

2. Benefits and Costs of Human Vaccines in Developed Countries: An Evaluative Survey
Burton A. Weisbrod, Ph.D. and John H. Huston, Ph.D., University of Wisconsin, Madison

3. Cost-Effectiveness and Cost-Benefit Analysis of Immunization Programs in Developing Countries: A Review of the Literature
John G. Haaga, Ph.D., Cornell University

4. Economic Evaluations of Medicines: A Review of the Literature
Judith L. Wagner, Ph.D., Director, Technology Research Associates, Inc.

5. Cost-Benefit and Cost-Effectiveness Analysis of Pharmaceutical Intervention
Thi D. Dao, Ph.D., Deputy Director, Office of Policy Analysis, PMA

6. The Role of Survey Research in the Assessment of Health and Quality-of-Life Outcomes of Pharmaceutical Interventions
Amiram Vinokur, Ph.D., et al, Institute of Social Research, University of Michigan

7. Beta-Blocker Reduction of Mortality and Reinfarction Rate in Survivors of Myocardial Infractions: A Cost-Benefit Study
A. D. Little, Inc.

8. Use of a Beta Blocker in the Treatment of Glaucoma: A Cost-Benefit Study
A. D. Little, Inc.

9. Use of Beta Blockers in the Treatment of Angina: A Cost-Benefit Study
A. D. Little, Inc.

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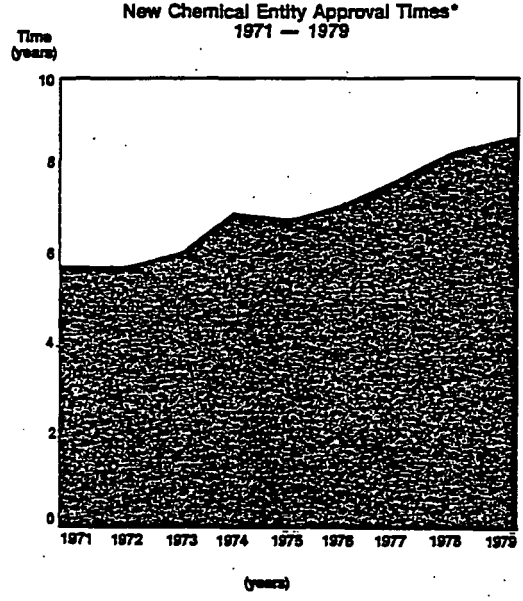
APPENDIX B

[Submitted with Statement of Lewis A. Engman, President, Pharmaceutical Manufacturers Association, Before the Committee on the Judiciary, United States Senate on S.255, the "Patent Term Restoration Act of 1981" (April 30, 1981:)]

The Time Factor in New Drug Development

Even after a new drug has been discovered, it takes 7-10 years to develop it and get it approved for sale.



*Approval Time = time from IND filing to NDA approval by the Food and Drug Administration

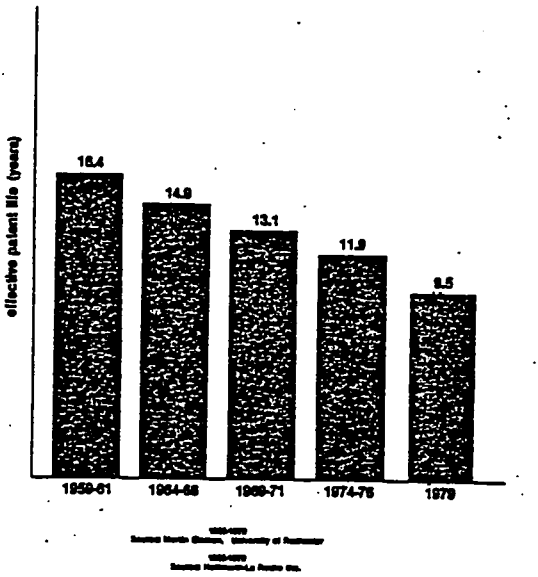
Source: Martin M. Shenon, Ph.D., "Consequences of the Decline in Patent Protection for New Drugs," CSDD, 1980.

[Submitted with Statement of Lewis A. Engman, President, Pharmaceutical Manufacturers Association, Before the Committee on the Judiciary, United States Senate on S.255, the "Patent Term Restoration Act of 1981" (April 30, 1981):]

Declining Patent Protection

These 7-10 years are, in effect, deducted from a drug's patent life. Thus, instead of having 17 years in which to recover its investment like firms in most other industries, the pharmaceutical innovator has only about half that time.

Patent Life Erosion



[Submitted with Statement of Mark Novitch, M.D., Deputy Commissioner, Food and Drug Administration, Office of Assistant Secretary for Health and Human Services Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, House of Representatives, on H.R. 3605 (a 1½-page bill to establish an ANDA procedure for post-1962 drugs) (July 25, 1983:)]

LENGTH OF PATENT PROTECTION FOR POST-62 DRUG PRODUCTS

Between 1962 and 1978 FDA approved over 150 new drug products for the first time. Approximately 20% of these products are considered products which will be candidates for ANDAs under a post-1962 ANDA policy. The remaining post-1962 approved products are not considered ANDA candidates for one of the following reasons. The product is: (1) an antibiotic and is covered under the "Form 6" procedures; (2) in a class of products not covered by the ANDA policy, e.g., insulin, radiopharmaceuticals, LVPs, medical devices, etc.; (3) no longer marketed (either FDA has withdrawn approval or the sponsor has discontinued marketing). Between 1979 and 1982, FDA estimates that another 40-50 products were approved which would be suitable ANDA candidates.

FDA examined the patent status of the 205 1962-1978 candidate products and found that the effective patent life of these products averaged about 13.5 years. However, for products approved in the late 1970s, the effective patent life has averaged only 9 to 10 years. These estimates do not necessarily include all applicable patents, since relevant process or use patents may extend patent protection. In addition, a number of these products had no, or very little, patent protection following approval. A breakdown and list of these products is provided below.

For the 205 drug products approved between 1962-1978, 15 products or 8 percent of the drugs had no effective patent life at the time of approval. Another 36 products, or 18 percent, had comparatively little protection. See table below:

Status Patent	No. Products	Percent of Total
Never patented	3	2
Off-patent before approval	12	6
Less than 7 years patent protection	36	18
TOTAL	51	25

Present data for these drug entities were obtained from the following sources:

1. The Merck Index, Ninth Edition, Published by Merck & Co.
2. 1976 Basic Patents for Major Drugs, Noyes Development Co., 1969.
3. The U.S. Generic Drug Market, Frost & Sullivan, 1976 and 1980.
4. Innovation in the Pharmaceutical Industry, David Schwartzman, The Johns Hopkins University Press, 1976.
5. Dr. Martin Kissen, Center for the Study of Drug Development, the University of Rochester, School of Medicine and Dentistry, Rochester, N.Y.
6. Telephone queries with individual drug sponsors.

POST-1962 ANDA-CANDIDATE PRODUCTS WITH LESS THAN 7 YEARS EFFECTIVE PATENT LIFE*

Products With No Effective Patent Life After Approval Date

- Natural Substances/Never Patented (3)

Approval Date	Chemical/"Generic" Name	Trade Name
1970	Lypression	Diapid
1970	Lithium Carbonate	Lithonate
1978	Lithium Citrate	Lithonate-S

- "Old Chemicals"/Patents Expired Before Approval Date (12)

Approval Date	Chemical/"Generic" Name	Trade Name
1964	Sulisobenzone	Uval
1966	Piprobromain	Vercyte
1967	Clofibrate	Atromid-S
1967	Dextrothyroxine	Choloxin
1970	Mitotane	Lysodren
1974	Dopamine	Intropin
1974	Sodium Nitroprusside	Nipride
1975	Calcitronin-Salmon	Calcimar
1975	Decarbazine	DITC
1976	Lactulose	Cephulac
1976	Lomustine	CeeNu
1977	Carmustine	BiCNU

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* Covers only ANDA-candidate products approved between 1962 and 1978; 205 products were approved during this time period. Includes expiration date of "chemical" or "product" patent only; does not cover "use" or "process" patents.

Products With Less Than 7 Years Effective Patent Life After Approval (36)

Approval Date	Chemical/"Generic" Name	Trade Name
1964	Orphenadrine Citrate	Norgesic
1964	Mestranol & Norethynodrel	Enovid-E
1967	Monocrynal & Idophor	ID Prep
1967	Diphemidol HCl	Vontrol
1968	Lidocaine HCl & Dextrose	Xylocaine HCl w/Dextrose
1969	Testolactone	Teslac
1970	Flavoxate HCl	Urispas
1970	Floxuridine	FUDR
1971	Propoxyphene Napsylate	Darvon-N
1971	Tretenoin	Retin-A
1971	Fluocytosine	Ancobon
1971	Propoxyphene Napsasylate & Acetaminophen	Darvon-N w/APA
1971	Megestrol Acetate	Megace
1972	Bupivacaine HCl	Marcaine HCl
1972	Bupivacaine HCl w/ Epinephrine	Marcaine HCl w/Epinephrine
1972	Desonide	Tridesilon
1972	Dexamethasone Sodium Phosphate & Xylocaine	Decadron w/Xylocaine
1973	Betamethasone-17-Benzoate	Beniasone
1973	Dexamethasone Acetate	Decadron-LA
1974	Halcinonide	Halog
1975	Oxybutynin Chloride	Ditropan
1975	Betamethasone Dipropionate	Diprosone
1975	Clotrimazole	Lotrimin
1975	Clonazepam	Clonopin
1976	Prazepam	Verstran
1976	Naproxen	Naprosyn
1976	Danazol	Danocrine
1976	Beclomethasone Dipropionate	Vanceril
1977	Clemastine Fumarate	Tavist
1977	Disopyramide Phosphate	Norpace
1977	Azatadine Maleate	Optimine
1977	Lorazepam	Ativan
1977	Descinolone	Topicort
1977	Chlordiazepoxide & Amitriptyline	Limbitrol
1978	Sodium Valproate	Depakene
1978	Hydrocortisone Valerate	Westcort

APPENDIX C

EXPORTS OF PHARMACEUTICAL AND MEDICINAL PRODUCTS to countries that Both (a) Require, in Applications for Market Approval, at Least Some of the Safety and Effectiveness Data and Information that Section 104 of H.R. 3605 / S. 2748 Mandates FDA Release and (b) Do Not Effectively Recognize Product Patents

1983

(in U.S. dollars)

Country	1983 Dollars
Argentina	$29,598,743
Austria	28,534,110
Canada	185,762,008
Chile	6,425,637
Columbia	25,627,437
Finland	2,831,316
Greece	13,346,025
Mexico	37,227,033
Norway	1,656,800
Venezuela	31,322,270
Ecuador	7,948,230
India	8,895,291
Iran	4,194,037
Peru	12,554,083
Poland	5,914,782
Spain	56,833,053
Soviet Union	950,198
Yugoslavia	3,989,632
Egypt	11,974,266
Kuwait	2,504,820
	$478,089,771

Source: EM455, F.T. Exports, Foreign Trade Room
Department of Commerce Main Building
U.S. Bureau of the Census

APPENDIX D

[FDA's "Technical Comments" on the June 2, 1984 Discussion Draft of the Patent Term Restoration/ANDA legislation (retyped verbatim):]

TECHNICAL COMMENTS ON JUNE 2 DISCUSSION DRAFT
ANDA/PATENT TERM RESTORATION LEGISLATION

Comments are keyed to page and line number of the June 2 draft.

GENERAL COMMENT

1. The June 2 draft fails to include a transition provision. We have pointed out in previous comments that a transition provision is needed to protect the agency from a substantial increase in workload during the first few years immediately following enactment. As currently drafted, the bill would immediately open to ANDA eligibility all drug products approved from 1962 through 1981 other than those that are subject to patent protection. FDA's analysis of resource requirements associated with a possible post-1962 ANDA procedure established that the immediate eligibility for ANDA approval for drug products approved between 1962 and 1972 would produce unacceptable backlogs of ANDAs (reaching a peak of about 1,300 applications more than 180 days old). However, the agency found that by taking an initial 5-year group, allowing three years for processing, then adding the next 5-year group for a second three year period, it could handle the workload with the addition to staff of only four persons. If the agency were to timely process an initial 10 year period of applications, its analysis showed that it would need 21 additional ANDA reviewers, and these extra reviewers would need to be relocated after the initial submissions had been processed, because FDA estimated that the increased level of staffing would not be needed beyond the first three years.

To prevent unacceptable backlogs of pending applications and to avoid substantial resource increases that would be needed for only a relatively short period of years, a transition provision should be incorporated in the bill. As we have pointed out, a transition provision that opened only the 1962-67 period to ANDA approvals for the first three years after enactment would alleviate the immediate resource impact of the legislation but would still make immediately available for ANDA approval most of the drugs that would be available under the bill as currently drafted, including six of the drugs that are among the top selling prescription drug products.

ANDA PROVISIONS

2. The definition of the term "therapeutic alternative" has been deleted from the June 2 draft, but the bill still includes the concept (page 3, lines 24-27; page 4, lines 1-3) and the associated petition procedure for combination drugs (page 6, line 24; page 7, line 9). The petition procedure would permit prospective applicants to seek permission to file for ANDA approval of combination drugs that have not been previously approved. These new combinations would be required to include at least one ingredient that is the same as an ingredient in a listed (previously approved) drug. Because ANDA approval would appear to be authorized for a combination of active ingredients that had not been previously approved, the petition procedure and its associated "therapeutic alternative" concept are plainly inconsistent with the medical and scientific rationale that supports FDA's current ANDA procedure.

In addition, the petition procedure appears to be inconsistent with FDA's combination policy, 21 CFR 300.50, which generally requires a showing through appropriate studies comparing the combination with its individual active ingredients that each ingredient contributes to the safety or effectiveness of the combination drug. A number of provisions in the June 2 draft would appear to restrict FDDA to consideration only of the safety and effectivenes of the different active ingredient in the new combination rather than to the new combination as a whole:

- ANDAs for new combinations would be required to include information showing that the different active ingredient had been previously approved (apparently either as a single ingredient or as part of another combination), or that the different ingredient was no longer a new drug, and any other information with respect to the different active ingredient with respect to which a petition was filed as the Secretary may require (page 3, lines 1-8).

- The petitions procedure (page 6, line 24 -- page 7, line 9) requires that a petition for ANDA eligibility for a new combination be approved unless the Secretary finds that investigations are needed to show the safety or effectiveness of the active ingredients in the new drug which differ from the listed drug.

- Approval of an ANDA authorized through the petition procedure may be denied if the ANDA fails to contain information required by the Secretary respecting the active ingredient in the new drug which is not the same as in a previously approved drug (page 9, lines 6-11).

- Approval of an ANDA authorized through a petition may be denied if the application fails to show that the new drug can be expected to have the same therapeutic effect as the listed drug (page 9, lines 12-24).

Under FDA's current policy, approval of combination drugs that have not been previously approved would require data showing that the new drug (not just one of its ingredients) will have its intended effect. Consistent with the agency's current policy, the abbreviated procedure should be limited to drugs with the same active ingredients. Combinations of drugs with active ingredients different from previously approved drugs should be the subject of investigations to establish whether they are safe and effective.

For these reasons, the petition procedure that would authorize ANDA approval for combination drugs that have not been previously approved should be removed from the bill. The statutory ANDA procedure should be limited to duplicate versions of previously approved drugs under previously approved conditions of use.

3. Page 6, line 24. If a petition procedure consistent with FDA's current policy for ANDA approval and the approval requirements for new combination drugs were to be incorporated in the bill, it should eliminate consideration of ANDAs for drugs with different "active ingredients." The procedure should be limited to minor differences in route of administration, dosage from, or strength. Under FDA's current ANDA policy, different "active ingredients" as therapeutic alternatives are not permitted. There may be circumstances in which route of amdinistration, dosage form or strength may differ slightly from those for a previously approved drug product. However, it should be stressed that even minor changes would not routinely be subject to implementation through ANDAs without clinical data.

4. Page 10, lines 6-14. The June 2 draft provides for denial of ANDA approval if the information submitted in the application or other information available to the Secretary shows that the inactive ingredients of the drug are unsafe or the composition of the drug is unsafe due to the type or quantity of inactive ingredients or the manner in which the inactive ingredients are included in the new drug. We had suggested such a revision, but our suggested revision also included, as a ground of denial, the failure of the information submitted to provide sufficient information to establish the safety of the inactive components or the composition of the new drug for its intended uses. Because it is the applicant's obligation to provide the information needed to support ANDA approval, the provision should be revised to provide for denial of ANDA approval if the information submitted is insufficient to show the safety of the inactive ingredients or composition of the product for its intended use. The following revision is suggested:

> (H) information submitted in the application is insufficient to show that (i) the inactive ingredients of the drug are safe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is safe under such conditions because of the type of quanitity of inactive ingredients included or the manner in which the inactive ingredients are included, or (iii) such information or any other information available to the Secretary shows that the inactive ingredients are unsafe or the composition of the drug is unsafe under such conditions.

5. Page 11, lines 1-5. The June 2 draft continues to provide that the 180 day period for ANDA approval or disapproval runs from the initial receipt of the application. Consistent with the statutory provision for full NDAs, the period should run from the filing of the application, rather than the time of submission. There should be no implication that FDA may not refuse for filing an ANDA that is facially deficient nor should the agency be required to develop different procedures to deal with such problems than those already established for full NDAs. The provision should be revised to read as follows:

(4)(A) Within 180 days of the filing of an application under paragraph (2), or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall approve or disapprove the application.

6. Page 11, line 6 et. seq. The June 2 draft continues to condition the effective date of ANDA approval on the patent information field for pioneer drugs and on the patent status of pioneer drugs. FDA would continue to be required to consider whether an ANDA is the "first application which contains" a certification, to hold application approvals pending applications for preliminary injunction to district courts, to hold the approval of applications pending a request for a reexamination of patentability to the Patent Office, and to hold the approval of subsequent applications until the first application involved in a patent dispute has been marketed for 180 days.

As pointed out previously, the provisions which key the effective date of ANDA approval to the patent status of the pioneer product would impose burdensome requirements upon the agency. Although the requirements are not intended to require judgmental determinations by the agency with respect to patent status, the complexisty of the recordkeeping requirements and effective date of ANDA approval provisions will be burdensome and will be inconsistent with the kind of recordkeeping for which the agency is currently responsible. From a pracatical viewpoint, moreover, a successful litigant in a patent suit would learn of a court decision before FDA could be officially notified and could attempt to pressure the agency to issue an approval prior to the official notification.

As also pointed out previously, the patent status of the pioneer product would be adequately protected through a notice provision like that already incorporated in the revised bill. See page 5, lines 10-22 (ANDA applicant required to notify patent owner of application which applicant believes does not infringe a valid patent). Notification of the pioneer firm by the applicant, which would precede ANDA approval in every case by six months or more, would enable the pioneer manufacturer to protect its patent rights through judicial remedies and would not require FDA to divert its limited resources to issues that are peripheral to its primary public health protection responsibilities.

45-024 O - 85 - 7

The complex effective date provisions, which would impose a burdensome requirements on FDA, ovbiously are intended to prevent duplicate product marketing before issues concerning the pioneer's patent status are resolved. Those provisions should be replaced by a provision which prohibits the duplicate applicant from marketing the duplicate product -- even if it has received ANDA approval -- until the patent issues are resolved. Since the patent issues will already be involved in litigation before the courts, a statutory prohibition on marketing could be easily enforced as part of the litigation. Note that the patent term extension provisions already authorize a court to establish by order the effective date of approval for a duplicate product involved in a patent infringement suit (page 44, line 25 et. seq.). Under such an approach, FDA would be relieved of complex administrative responsibilities and it would be permitted -- as it is now -- to act on ANDAs without regard to patent controversies.

7. Page 20, lines 2-6. The June 2 draft continues to provide for the amendment of section 505(e) to authorize the withdrawal of pioneer NDA approval if the patent information for the pioneer product was not filed "within 30 days after the receipt of written notice from the Secretary specifying the failure to file such information." The agency continues to be concerned that the provision may impose additional burdens on the agency if it contemplates that FDA would be expected to take affirmative action to require pioneer manufacturers to supply information to the agency conerning the patent status of their products.

8. Page 23, line 9 et. seq. The June 2 draft continues to establish effective dates for the approval of paper NDAs based on the applicant's certification of the patent status of the pioneer drug product. Although paper NDAs may be less attractive to generic manufacturers if a post-1962 ANDA procedure were available, the new provisions would impose additional burdens on the agency that could be resolved by a less burdensome procedure, discussed above, which would require notification by the paper NDA applicant to the pioneer NDA holder and a statutory prohibition on market introduction pending the resolution of the pioneer product's patent status.

Patent Extension Provisions

9. Page 34, line 17. The June 2 draft continues to require the applicant to submit the Commissioner of

Patents a brief description of the applicant's activities during the regulatory review period and the significant dates applicable to such activities. The Commissioner of Patents would be required to send a copy of the application containing the information to the Secretary who would be required within 30 days to determine the applicable regulatory review period. See page 35, lines 9-19. These burdens could be eliminated if the applicant were required to determine the regulatory review period in its application to the Commissioner of Patents. The applications could be made available to the FDA for inspection or audit at FDA's discretion, on the same enforcement basis that other reports, such as income tax filings, are regulated. Since the patent term extension is tacked on to the end of the patent term FDA continues to believe that there is no public health reason to require the agency to determine the regulatory review period under a restrictive 30-day time schedule. The validity of the regulatory review period may be adequately addressed through applicant determination and a discretionary enforcement approach.

10. Page 35, line 20 et. seq. The June 2 draft continues to provide for a due diligence determination to be made by the Secretary if petitioned to do so within 180 days after the publication of the patent extension determination. The June 2 draft, despite our earlier comment, also continues to provide that the authority to make the due diligence determination may not be delegated to an office below the Commissioner of Food and Drugs. FDA had objected that the agency did not have an adequate perspective to make a due diligence determination. This objection was raised with respect to the first draft, which would have permitted the due diligence determination to be made by the FDA organizational component directly responsible for the application. As pointed out previously, the due diligence determination will be even more difficult if the determination may be made only by the Office of the Commissioner. In effect, the revised bill would require a de novo review by personnel who have not had any prior familiarity with the application or with the problems associated with the development of the product or its investigation and approval. Since patent term extension is subject to a 14 year cap, counts only 1/2 of the investigational period, and is limited to a 5 year extension in any event, it continues to be FDA's view that a requirement for a de novo due diligence determination would clearly impose a burdensome resource requirements on the agency with

little, if any, public benefit in the earlier availability of generic drug products. In FDA's experience, based on the latest year for which calculations were made, the average new chemical entity gaining NDA approval would have been entitled, under the proposed formula, to the maximum 5 years of patent term restoration (based only on review time). Assuming that the average application was pursued with diligence, it would seem unlikely that the 5 year maximum extension would ever be reduced for lack of due diligence. Nonetheless, FDA will have been required to promulgate regulations, review petitions, and prepare due diligence determinations. As a practical matter, therefore, it appears that a complex system is being established that will require FDA resources to implement and maintain for no public benefit.

11. Page 36, line 8 et. seq. The due diligence determination is required to be published in the FEDERAL REGISTER with a statement of the factual and legal basis for the determination. The June 2 draft still provides that any interested person may require the Secretary to hold an informal hearing on the determination. The owner of the patent involved is entitled to notice and may participate in the hearing. The Secretary is provided only 30 days after the completion of the hearing to affirm or revise the determination of due diligence. There is no provision that would limit judicial review. See page 36, line 20 et. seq.

The FDA continues to regard the due diligence provision as imposing unnecessary and burdensome requirements on the agency. While the petition requirement may limit the number of determinations, the procedural restrictions imposed on the agency would provide no public health benefit and may divert scarce resources from more important matters, especially the review of other new drugs. In view of the limitations associated with patent term restoration, as noted above, the due diligence provision should be deleted on the ground that it will provide no public health benefit.

[Statement of Mark Novitch, M.D. Deputy Commissioner, Food and Drug Administration, Office of Assistant Secretary for Health, Department of Health and Human Services Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, House of Representatives, on H.R. 3605 (a 1½-page bill to establish an ANDA procedure for post-1962 drugs) (July 25, 1983):]

Dr. NOVITCH. Thank you, Mr. Chairman. I appreciate the opportunity to discuss the extension of the new abbreviated new drug application [ANDA] procedure to drugs first approved after 1962, post-1962 drugs.

You have proposed legislation that would authorize ANDA's for post-1962 drugs. As you know, ANDA's were first used by the Food and Drug Administration [FDA] under the Drug Efficacy Study Implementation [DESI] program for the approval of generic versions of drugs first approved only for safety between 1938 and 1962, the year in which Congress amended the Federal Food, Drug, and Cosmetic Act to require that drugs be shown to be effective as well as safe.

A similar procedure has not been established for post-1962 drugs. In recent years, however, patents have begun to expire for many post-1962 drugs. As a result, generic drug manufacturers have become increasingly interested in changing FDA's drug approval system to eliminate the current requirement for the submission of full reports of safety and effectiveness studies for duplicate versions of drugs already approved in accordance with a full new drug approval [NDA] submitted by the pioneer manufacturer.

FDA, too, is interested in streamlining its approval system for post-1962 drugs so as to reduce requirements for duplicative testing, which wastes resources and causes unnecessary human testing. For this reason, FDA is actively engaged in developing a proposal for an ANDA system for post-1962 drugs and to establish such a system through rulemaking.

A post-1962 ANDA procedure would be consistent with a number of FDA programs that have aided the marketing of generic drugs. In addition to the pre-1962 ANDA procedure, FDA has permitted generic applicants for post-1962 drug products to rely on reports of studies published in the open scientific literature. This has become known as the paper NDA policy. It eliminates the need to duplicate the expensive clinical and animal testing for safety and effectiveness, but it is limited by the availability of published literature.

In addition, the agency in the mid-1970's developed a vigorous program to review and assure the bioequivalence of generically available drugs. In 1980, we began to publish a list of all approved drugs with therapeutic equivalence evaluations to aid States and purchasers of generic drugs to substitute such drugs with confidence.

• The development of a post-1962 ANDA procedure raises a number of important and difficult issues. Because we are currently in the process internally of reaching a position on proposed rulemaking that would address these issues, I am not in a position to comment specifically either on FDA's internal working drafts or on

the specific amendment contained in your bill. I can, however, identify and discuss some of the issues that must be dealt with before a post-1962 ANDA system can be instituted.

First, should there be a minimum preeligibility period to assure maximum protection of the public health? When a new drug is first approved for marketing, that does not mean that there is nothing further to be learned about its safety or effectiveness. Approval is based on carefully evaluated evidence in numbers of patients sufficient for us to conclude that the risk of unanticipated side effects is small and justified in comparison to the drug's benefits.

What makes the initial marketing period so important is that it gives us an opportunity for the first time to look for reactions of low incidence, especially serious ones, that could not reasonably be expected to appear in clinical trials. In most cases, due to patent protection, the innovator's drug is the only one on the market for the first several years after FDA approval.

For this reason, any adverse drug effects will be used only by that manufacturer's drug and will be reported only to that manufacturer. Because the innovator manufacturer is familiar with the preapproval testing, it is in a good position to evaluate the adverse reactions.

There will, however, be drugs that have no patent protection after FDA approval, and which may therefore be immediately marketed by both the innovator firm and by generic manufacturers. We therefore believe that it is important to consider whether there should be a preeligibility period, on the order of a few years, during which ANDA's would not be permitted. One may argue that generic drug firms are required to report adverse drug reactions to FDA, and that FDA can therefore evaluate their significance.

But most adverse drug reaction reports are to some extent evaluated by the firm receiving them, and the quality and timeliness of that review is important to the process.

FDA regulations require that only unexpected adverse reactions or clinical failures be reported by the firm to FDA within 15 working days. The others are submitted quarterly during the first year. If adverse reaction reports were received by firms unfamiliar with the clinical trials, and, because of the nature of their business, lacking ties with the research community, we are concerned about the adequacy of the reports we would receive. The holder of the pioneer NDA is frequently of considerable help to FDA in identifying adverse reaction trends and other drug effects bearing on the safe and effective use of a newly developed drug therapy.

Second, should there be a lengthier preeligibility period before ANDA's are permitted to avoid disincentives to drug innovation? This is a controversial issue on which many people have expressed strong views, and we believe it is a legitimate subject for debate. Those who oppose establishing a preeligibility period to preserve incentives for drug innovation argue that Congress has established a patent system for the specific purpose of encouraging invention and that FDA should not impose requirements designed to achieve the same objective.

Others argue that, as a public health agency, FDA cannot ignore the effects of changes in the drug approval system on the incentive to develop new drug therapies. That will improve the health of the American people. They also note that some drugs cannot be patented, and that others have little patent life remaining after FDA approval.

If one assumes that there should be a preeligibility period to preserve incentives for innovation, at least for some drugs, one must then address the question of how long such a period should be. Should it track the patent period, on the assumption that it is intended primarily for drugs for which patents are unavailable; or should it be some shorter period that is still regarded as adequate to encourage innovation but that would allow competitive products to enter the market sooner?

The third issue is, what kind of transitional provisions should be included in any post-1962 ANDA system to assure that FDA's administrative capacity is not overwhelmed by an early flood of ANDA's and that the agency can concentrate its resources on those drugs most likely to be marketable without patent restrictions assuming that ANDA is approved? We believe that a phased implementation period is essential to avoid being inundated by more applications than we can reasonably handle.

Although these are not the only issues that must be considered in determining what kind of post-1962 ANDA system best serves the public interest, I think they illustrate that we are not dealing with a simple subject that lends itself to an easy solution. Although we believe that we have the legal authority to implement a post-1962 ANDA system and that we should continue to pursue our efforts to establish such a system through rulemaking, we stand ready to work with the committee on the problems associated with developing appropriate procedures for the approval of generic versions of drugs first approved after 1962.

At this point, Mr. Chairman, I would like to express our views on H.R.1554, a bill to eliminate the statutory prohibition in section 301(l) of the Federal Food, Drug, and Cosmetic Act which prevents a drug manufacturer from making representations regarding FDA approval in labeling or advertising of any drug. • • •

Mr. Chairman, that concludes my formal statement. We will be happy to attempt to address any questions you or other members of the committee may have.

APPENDIX 2

SATURDAY, MAY 23, 1981

The New York Times

Founded in 1851

ADOLPH S. OCHS, *Publisher 1896-1935*
ARTHUR HAYS SULZBERGER, *Publisher 1935-1961*
ORVIL E. DRYFOOS, *Publisher 1961-1963*

The Half-Life Patents

For reasons long since forgotten, Congress a century ago chose to set 17 years as the appropriate period for patent protection. To encourage bright minds and investors, any invention was promised exclusivity in the market for that length of time. But in recent years, without anyone intending it, Federal health and safety regulations have eroded the effective life of many patents. For some products, the exclusive marketing period has shrunk to less than 10 years. The system discriminates unfairly against some of the most important research-oriented industries.

Consider the case of new drugs. When a pharmaceutical company uncovers a promising compound, it generally files for a patent immediately and usually gets it within two years. But before the compound can be marketed, it must pass stringent tests of safety and effectiveness. The regulatory review, required to protect the public, can itself take seven or more of those patented years. So the average effective patent life for drugs dropped from 17 years in 1959 to 9.5 years in 1979. The meaningful patent life for pesticides is now down to 12 years.

This discrimination is clearly accidental. Perhaps the best of several remedies is embodied in legislation just approved by the Senate Judiciary Committee and awaiting hearings in the House. It would simply extend the patent term for each product to compensate for time lost in clearing regulatory hurdles, up to a maximum of seven years.

Some argue the change would stimulate more research, lower costs, assist small business, help universities and promote exports. Others fear higher product prices in the protected industries without any significant benefit.

But that debate seems beside the point. The central issue is fairness and uniformity. If 17 years is to be the appropriate life for a patent, then a patent should be meaningful for 17 years. And if there is reason to distinguish between one industry and another, that should be done directly, not by inadvertence. It would seem to make no sense to protect a toy for 17 years but an important drug or agricultural chemical for only half that time. What Government grants at the patent office should not be taken away by its regulatory arms.

Footnote (1)

THE NEW YORK TIMES, SATURDAY, AUGUST 7, 1982

The New York Times

Founded in 1851

ADOLPH S. OCHS, *Publisher 1896-1935*
ARTHUR HAYS SULZBERGER, *Publisher 1935-1961*
ORVIL E. DRYFOOS, *Publisher 1961-1963*

ARTHUR OCHS SULZBERGER, *Publisher*
A. M. ROSENTHAL, *Executive Editor*
SEYMOUR TOPPING, *Managing Editor*
ARTHUR GELB, *Deputy Managing Editor*
JAMES L. GREENFIELD, *Assistant Managing Editor*
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J. A. RIGGS JR., *Sr. V.P., Operations*
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ELISE J. ROSS, *V.P., Systems*

An Unwarranted Patent Stretch

The pharmaceutical industry is about to receive an extraordinary favor from Congress: the right to extend the patent protection of new drugs up to seven years beyond the conventional period of 17. Congress has let itself be persuaded, after a hasty review, that the extension is fair and will foster innovation. But the drug industry's case is dubious.

Its chief premise is that extension will restore the time unfairly lost from patent life by having to prove to the Government that new drugs are safe and effective. But the testing of drugs in animal and clinical trials is something that any responsible company would wish to do anyway.

Besides, the complaints gloss over the common practice of "evergreening" — filing a patent application early, so as to beat any rival, but then filing new applications that modify or extend the original to postpone the time at which patent life actually starts.

For example, the original patent for the tranquilizer Valium was first filed in 1959 and gained the Food and Drug Administration's market approval in 1963. But because of a series of renewed applications, as well as a rival claim, the patent was not issued until 1968. When it expires in 1985, the drug will have enjoyed 22 years of protection.

The eight best-selling drugs in the United States in 1980 enjoyed an exceedingly healthy average patent life of 15.1 years, according to statistics kept at the Office of Technology Assessment. Even when a brand-name drug comes off patent, companies can still protect its market share by advertising; one study of off-patent drugs showed that half retained a 97 percent market share against companies selling the identical chemical under different names.

The industry contends that effective patent lifetime has been dropping, from 14 years for pre-1965 patents to 10 years or less for those now being issued. But the law did not intend to guarantee every inventor a clear 17 years of market monopoly. Many inventions, not just drugs, enjoy less patent protection because of obstacles on the path to market. The drug companies complain that Government delays hold them back. But the bills that have passed both Senate and House committees grant an extension that goes far beyond any delay attributable to Government review.

The companies also contend that reduced patent life has discouraged investment in research and development. But figures from the technology assessment office show that the industry's investment in R & D has increased every year from 1965 to 1978, and has remained a strikingly constant percentage of sales. There is no proof that the windfall profits from a patent extension would in fact be plowed back into research. Even if research were in decline, Congress has many other means, like tax incentives, to reverse it.

The pharmaceutical industry is efficient, profitable and healthy. It has no demonstrable need for any special break. The patent system as a whole may need reform, but that is a different issue. Monopoly rights should not be doled out to anyone with a hard-luck story, as Congress seems to believe. The proposed extension is unjustified, unsuited to the stated purpose of increasing research and offensive to the basic principle of a free economy.

WEDNESDAY, MAY 20, 1981

The Washington Post

AN INDEPENDENT NEWSPAPER

Patently Fair

THE DRUG industry is said to be at the brink of a new age of medical breakthroughs. It now hopes to strengthen its chances for solid returns on its research investments through a bill reported yesterday by the Senate Judiciary Committee. The bill would assure the drug companies and other industries subject to regulatory review that the protection afforded by patent laws is not seriously eroded by the often lengthy period of testing and review required before marketing is allowed. This is a reasonable assurance to require, and the Senate should approve the measure.

For reasons we assume have nothing to do with the locust cycle, patent law deems 17 years the appropriate period for protecting inventors from copycats. Since 1972, when requirements for more rigorous testing of drugs were added to the law, the time required for such preliminaries has stretched from seven to 10 years. As a result, by the time a drug is ready for market almost half the patent life has elapsed.

Since drugs are very expensive to develop, the industry argues that the effective curtailment of patent life discourages new research. Against the arguments of consumer advocates that longer patent lives will increase drug prices by delaying competition, the companies respond that encouraging more research will increase competition and thus lower prices; that drugs, however priced, are far and away the cheapest form of medical treatment and that longer patent protection may discourage high initial price markups now needed for quickly recouping costs.

There are merits on both sides of the price argument. The drug companies, moreover, with their enormous and durable profitability, do not make anyone's list of neediest cases. But there are stronger arguments in favor of patent life assurance. One is simple fairness. If 17 years is the right period for protecting the exclusive rights of inventors, there is no reason why those subject to federal regulation should be denied it solely by reason of that regulation.

There is also the strong desirability of reducing unwarranted pressure on the regulatory process. You don't have to be in favor of mindless bureaucratic delay to recognize the tremendous importance of thorough testing of drugs before they are widely peddled as the latest miracle cure. Some risk may be unavoidable, but no one can want to increase the chances of producing deformed infants.

Stronger regulation not only has reduced that possibility, but it may also have had other beneficial side effects. The higher cost of introducing new drugs, it is said, diverted companies from trial and error research and from the marketing of slightly better products into the basic biological research that is now promising to produce real cures for ailments ranging from asthma to heart disease and cancer.

There are probably ways that the FDA could further speed up clearance of major drug discoveries without jeopardizing the testing process. But assuring drug companies of a substantial period of patent protection is a reasonable and fair way to avoid having the desire for such protection translate into an unhealthy pressure on the review process.

THURSDAY, MAY 28, 1981

THE WALL STREET JOURNAL.
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Long Life to Patents

The words "patent law" can hardly be said to possess a life-or-death ring. Not compared to words like penicillin or Salk vaccine. Yet the recent impact of the patent law on the drug industry could well be inhibiting those very kinds of discoveries.

Patents are a bribe: If you invest your time and money on risky endeavors, society will reward your success by granting you a temporary monopoly. U.S. patent laws confer a monopoly for 17 years during which the inventor can, presumably, earn a rate of return that makes the investment worthwhile. Society gets a reward too, of course; it gets an invention it might not otherwise have had.

This bribe is crucial to the drug industry. It's very costly, very time-consuming and very risky to develop a new drug. Currently, the process takes about 10 years, costs $70 million and has a failure rate of 90%. The promise of patent protection kept things humming until, in 1962, the thalidomide tragedy convinced everybody that new drugs needed more rigorous testing. This, in turn, meant more time elapsed before drugs could be brought to market.

Thus, the length of time between patenting a drug and getting FDA approval gradually ballooned from about one year, pre-1962, to over seven years now. In other words, drugs making their debut today have less than a 10 year monopoly life—not 17.

The telescoping of effective patent life has reduced rates of return to drug research and development. Industry studies show that over the past two decades, rates have been sliced in half. Since new products need anywhere from 12 to 19 years to generate R&D returns above 8%, the current life span of less than 10 years looks especially grim. After all, prudent financial management could earn a bigger bang-for-the-buck by buying government long bonds. As it is, drug companies have been diversifying into businesses like cosmetics and salad dressings where returns are nearer to market.

Falling rates of return have, quite naturally, translated into falling R&D. The ratio of R&D to sales has declined from 13 in 1962 to 8 in 1979. Moreover, this decline is mirrored in the decline in the number of new drugs: In 1960, the $3.5 billion drug industry brought forth 50 new drugs; in 1980, a $22 billion industry produced only 12 new medicines.

Other than the obvious implications of this drying-up of R&D, we might note one particular ill-effect—the impact of health care costs. Drugs are amazingly cost-effective. Consider two examples. Tagamet, an anti-ulcer drug, saves millions of dollars in surgical costs a year and the advent of a new class of heart drugs, calcium blockers, (due out any minute) might totally eliminate coronary bypass surgery.

There is a simple way to help restore R&D incentive to the drug industry: guarantee the full 17-year protection by starting the patent clock ticking *after* FDA approval, not before. Companies need an assured time horizon to make investment decisions and they should, in the present cost climate, be able to count on a full 17 years. Such a guarantee would reduce uncertainty over expected returns and cash flows, and, we hope, create the incentive to cure our hay fever.

Both the House and the Senate have bills to restore 17-year patent protection to the drug industry. We know that congressional action on patent law reform will not excite the network news into prime-time coverage. But that doesn't make it unimportant and there is every reason to believe, as even the sternest free market economists do, that society's return on this kind of bribe is well worth the payment.

The New York Times

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How Much Haven for Drug Pioneers?

A long and stormy battle between rival groups of pharmaceutical manufacturers is near resolution in an important bill designed by Representative Henry Waxman of California. Despite objections by a break-away faction of large drug houses, the Waxman bill is a just compromise that will foster invention of new drugs and lower the price of older drugs coming off patent.

The struggle pits companies that develop their own drugs against makers of "generics," drugs that are chemically identical to the original and marketable after its patent has expired. Generics end the monopoly position of the patent-holder and force down high drug prices. That's greatly in the public interest. But so is insuring profit incentives for manufacturers to invest in the research and development of new drugs.

Generic drugs have eaten into the sales of off-patent brand-name drugs, and the Pharmaceutical Manufacturers Association has advocated longer patent terms for drugs to compensate for the time consumed by Government review. Patent term "restoration" of up to seven years is needed, the association contends. Otherwise, there's not enough incentive for costly research; fewer drugs would be invented and medical costs would rise.

Congress almost passed such a seven-year bill in 1982 but balked at the last minute. It has also resisted bills to let generic drugs onto the market as soon as the originals go off patent.

From this impasse, Mr. Waxman has created a compromise serving both interests. The new-drug companies will be compensated for up to five years in patent life lost in the approval process. The generic drug makers will get faster and simpler Government review for the class of drugs now coming off patent. Both the P.M.A. and the Generic Pharmaceutical Industry Association have agreed to the deal, which is also supported by Mr. Waxman's Senate counterpart, Orrin Hatch.

A dissenting group of 10 of 32 P.M.A. companies opposes the deal; they apparently stand to profit if the bill is delayed or dies. Each has important drugs coming off patent soon. Hoffmann-La Roche's tranquilizer Valium, for example, with 1983 sales of $250 million, comes off patent in 1985. The patent of American Home Products' heart drug Inderal, with sales of $300 million, expires this year. As long as the generic equivalents are denied speedy review, these drugs will enjoy an exclusive market.

The Waxman bill is eminently fair to the drug companies' interests. The association contends the effective patent life of drugs has fallen to less than 7 years. Mr. Waxman's staff estimates from P.M.A. data that top selling drugs average more than 14 years of patent life, although the overall average is lower because it includes small-volume drugs that the companies don't rush to market.

A 14-year patent life for drugs compares favorably with that enjoyed by other kinds of inventions, which also face obstacles on the way to market. Mr. Waxman's bill restores lost patent time up to a total of 14 years. As most of the pioneer drug companies agree, that's ample incentive to invent new drugs.

Patents Encroaching on Research Freedom

A tradition of disregarding patent infringement when it involves experimental use of an invention may be eroding for biologists

Some two dozen researchers at universities, companies, and government laboratories recently received letters from Johnson & Johnson warning them that the use in research of particular cells that produce monoclonal antibodies may infringe the company's patent rights. The letter raises the tricky question of the extent to which patent law can be used to restrict research uses of patented products and processes.

A similar issue was raised recently in a court decision concerning clinical testing of a patented drug. The U.S. Court of Appeals for the Federal Circuit, which now hears all patent appeals, ruled that Bolar Pharmaceutical, a generic drug manufacturer, broke the law by testing its version of a drug made by Roche Products before Roche's patent had expired. Some patent attorneys are concerned that, if the ruling is interpreted broadly, it could be used to restrict a variety of research activities.

Although Johnson & Johnson's warnings and the contest between Roche and Bolar are not directly related, they both address an area of patent law that is in a considerable state of flux. The statutes spell out in plain language how a patent grants a 17-year monopoly to an inventor, prohibiting others from making, using, or selling the invention. However, a tradition that began in the early 19th century has usually exempted experimental use of an invention from being construed as infringement. The issue at stake now is how to define when experimental use of patented technology becomes commercially threatening to an inventor and therefore no longer is entitled to that exemption. Some resolution of this ambiguity will be vital to the biotechnology industry, which is so heavily dependent on basic and near-basic research activities.

The contest between Roche and Bolar has been closely watched in the pharmaceutical industry. Early in 1983 Bolar began an effort to get federal approval to market flurazepam hydrochloride, the active ingredient in Roche's highly successful sleeping pill, whose trademark is Dalmane. Although the safety of this drug already was established, the Food and Drug Administration requires a generic drug manufacturer to prove it can meet the same standards. However, if the generic manufacturer is forced to wait until a drug's patent expires before such tests begin, the original manufacturer effectively gains a considerable extension on the patent's lifetime. [Legislation now being drafted by Representative Henry Waxman (D–Calif.) would resolve some of these problems (*Science*, 27 April, p. 369).]

Roche's patent for Dalmane expired on 17 January 1984, but Bolar began clinical trials long before that date. Roche brought a patent infringement suit against Bolar in July 1983. In October, the U.S. District Court in the Eastern District of New York ruled in Bolar's favor, but on 23 April 1984 that ruling was reversed on appeal. Bolar currently is planning to petition the Supreme Court to review the case, says attorney Robert Marrow, who represents the company.

> The issue is how to define when experimental use is no longer entitled to an exemption from the patent laws.

"From the scientific point of view, the real threat [in the appeal court's decision] is it effectively prohibits any experiments with a patented product if it tends toward commercial development," Morrow says. "This is a far-reaching opinion that [could] negate the experimental use exception, unless it's for pure amusement."

Morrow's interpretation is something of a worst-case reading of the opinion handed down by Judge Philip Nichols, Jr. But other attorneys are also speculating about how far his opinion goes in this direction. "The experimental use exception is not gutted," says Jorge Goldstein, a patent attorney for a Washington, D.C., firm that represents a broad spectrum of corporate clients (but with no direct stake in the Roche-Bolar contest). "But for a company to argue that it's 'just doing research,' won't fly if it has a substantial commercial purpose."

The ruling "may not be a serious inroad" on the experimental exception to patents, says James Weseman, a patent attorney with a San Francisco law firm with biotechnology company clients. But certain passages in Judge Nichols' opinion where he uses "expansive language to define experimental use" are worrying, Weseman says.

For example, Nichols wrote: "Bolar's intended use is solely for business reasons and not for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry [and] is thus an infringement. . . . We cannot construe the experimental use rule so broadly as to allow a violation of the patent laws in the guise of 'scientific inquiry,' when that inquiry has definite, cognizable, and not insubstantial commercial purposes."

"The biotechnology industry is sensitive to anything that affects what they do best—research," Weseman continues. "If case law develops so that even in the earliest stages companies must avoid patent infringement, it will really restrict their abilities and stultify their research. There's plenty to worry about."

The recent actions by Johnson & Johnson could be another step toward restricting use of patents that is a cause for more worry. Johnson & Johnson patent attorney Geoffrey Dellenbaugh has been sending out letters to researchers warning against the use of particular monoclonal antibody–producing hybridomas, which the company has deposited with the American Type Culture Collection (ATCC) in the course of obtaining patents. "The fact that you have obtained samples of these hybridomas from the ATCC in no way grants you any right or license under our patents in the United States or other countries," one of the letters, sent to a researcher at the National Institutes of Health (NIH), says. "Your use of these hybridoma samples may constitute infringement of one or more of these patents, regardless of whether the thus-produced antibody is subsequently used or sold."

About two dozen researchers from universities, companies, and government research institutions including NIH are involved so far. The letters were sent out because of the concern that "people might use the cells in a way that infringes the patent and deprives us of sales of antibodies," explains Dellenbaugh. The cells can be obtained from ATCC at a nominal cost, whereas Johnson & Johnson's subsidiary, Ortho Diagnostics, is marketing the antibodies (for research and diagnostic purposes) to make a profit. The company quite naturally would

to protect its commercial interests develop a market for its patented oclonal antibodies. Researchers ld like to use those antibodies (some iem are to T cells, which are part of mmune system). And scientists with the right know-how undoubtedly can make the antibodies—from the company's cell lines, obtained perfectly legally from ATCC—more cheaply than they can be bought.

"The reason we wrote those letters was to inform people of the possible legal consequences. We intend, in appropriate circumstances, to protect our rights," Dellenbaugh says. The question, as with the Roche versus Bolar ruling, is "How far does that extend?" he adds. "If

DOD Springs Surprise on Secrecy Rules

Pentagon officials have moved to resolve a major issue in eir dispute with university scientists about government forts to control militarily sensitive research. The Depart- ent of Defense (DOD) has decided to abandon its search r a formula to govern so-called gray areas of research— search which is not classified but is deemed militarily eful. Under the proposed policy, federally supported ndamental research would be treated on an either-or sis as classified or unclassified.

The immediate reaction from academic observers is that : decision has the merit of creating a clearly defined licy. Whether the new policy will satisfactorily resolve : controversial issue of prepublication review of nonclas- ed but sensitive research, however, is far from clear. e debate on scientific communication has caused divi- ns among policy-makers at the Pentagon and there is ne skepticism about how fully the new policy has been :epted along the chain of command. A major issue is the . rking definition of fundamental research under the new · icy and, therefore, what research will be covered. Some :ervers suggest that under the proposed policy, the ntagon would put more and more types of research into classified category.

'or more than a year, DOD's effort to find forms of tection short of classification for gray-area research has n a major sticking point for Pentagon policy-makers and versity officials debating the tightening of controls on :ntific communication (*Science*, 3 June 1983, p. 1021). :ently there had been signs of a split in opinion within tagon ranks, with DOD under secretary for research engineering Richard D. De Lauer identified as ques- ing the creation of a new category of controls on :arch (*Science*, 4 May, p. 471). But the decision caused)rise among outsiders.

ı testimony at a House hearing on 24 May, deputy 'etary for research and engineering Edith W. Martin that DOD officials had decided "not to pursue the '-area concept" because the option had proved to be)re complicated than it had seemed," and "the trade- unclear."

artin's comments at the hearing were the first public tion of the decision. In a brief summary of the new :y, which did not appear in her prepared testimony, described it as a "draft policy" that is still under ıssion in DOD and in other federal agencies. To a tion, however, she replied that she expected the :y to be accepted in substantially its present form and)ply to fundamental research sponsored by all federal cies.

response to a question of when and why the decision made from Representative Doug Walgren (D–Penn.) chaired the hearing, Martin said that the possibility of taking the "classification-nonclassification approach" had been considered from the beginning of DOD deliberations on the matter and, after discussions extending over more than a year, the conclusion evolved to adopt the classification alternative. This occurred 3 or 4 months ago, but was being enunciated publicly for the first time at the hearing.

The policy statement made available at the end of the hearing is as follows: It is the policy of this administration that the mechanism for control of fundamental research in science and engineering at universities and federal laboratories is classification. Each federal government agency is responsible for: a) determining whether classification is appropriate prior to the award of a research grant or contract and, if so, controlling the research results through standard classification procedures; b) periodically reviewing all research grants or contracts for potential classification. No restrictions may be placed upon the conduct or reporting of research that has not received national security classification.

The face-off between the universities and the Pentagon over gray-area research dates from the publication in 1982 of the Corson report, a National Academy of Sciences–sponsored study, "Scientific Communication and National Security," headed by Cornell University president emeritus Dale Corson. The study defined the research universities' concern about the problem. Corson appeared at the hearing and raised the issue of what he called "creeping grayness," noting that "There appears to be growing interest on the part of sponsoring agencies to extend the concept of grayness to ever more areas." But Corson and other university and industry witnesses by no means confined their criticism to the gray-area problem. By and large, they were most concerned with the application to research of legislation designed to control the export of militarily useful equipment and materials. In particular, they criticized the use of such legislation to restrict foreign nationals studying or working here.

Government witnesses were scheduled last at the hearings, but Martin did not deal directly with the criticisms by earlier witnesses. In effect, she trumped them with her announcement of the policy decision. There was no real exchange on the testimony since it came after a long session punctuated by intermissions for roll-call votes on the House floor and the Pentagon party had to depart for another engagement.

With details of the new policy unavailable, let alone information on interpretation and implementation, a wait-and-see attitude seems to dominate in the universities. But a snap reaction among knowledgeable observers is that the effect of the decision may be to return the debate on gray-area research to where it was before the Corson report.

—JOHN WALSH

ine made an improvement that your patented invention and uses or commercial purposes—whether e in a university or not—that is gement of your patent."

e've had correspondence with out have not resolved the issue," NIH patent attorney Thomas Fer- We don't consider it infringement searchers to use cell lines] as long s experimental." In letters to Del- gh, NIH patent attorneys have "[W]e will cooperate in your at- to enforce your patent rights while same time recognizing that the sts of the research programs of the must be paramount, if it should prove to be more practicable to purchase hybridomas from ATCC for research purposes. We suggest that you promote your own sale of hybridomas by publicizing their availability to the NIH research community."

Dellenbaugh replied that each case should be considered individually, and that a determination should not rest "simply on whether the use is 'experimental.' . . . Since [there is] clear economic harm to Ortho, the rationale sometimes used for excepting experimental use from infringement should not apply."

NIH recently convened a meeting of its internal patent board, a group that includes patent attorneys and representatives from the various institutes, to consider the policy implications of the letters and has considered making recommendations on these issues to the Department of Health and Human Services. Currently, NIH is telling researchers "to go along the way they are."

Though Johnson & Johnson is not planning legal action to enforce its patent rights, according to Dellenbaugh, "If we decided an example needs to be made of an egregious infringement, we might do it." Hence, Ferris says, no matter what policy is laid down, such issues "ultimately can only be resolved in the courts."—JEFFREY L. FOX

Judge Curbs Use of Toxic Shock Data

In a legal victory for the Procter & Gamble Company, a deral judge in St. Louis last month ruled that the deposi- on of a researcher at the University of Wisconsin cannot used in a suit against the company because his research as "preliminary." The researcher's findings are said to ik Procter & Gamble's Rely tampon with the production toxin associated with toxic shock syndrome.

The ruling is the latest development in a continuing legal ittle over the data of microbiologist Merlin S. Bergdoll id its use in court. The controversy has raised questions out access to sensitive research findings during litigation *Science*, 13 April, p. 132).

The court decision is contrary to an earlier decision by nother federal judge, who allowed the data to be discussed a trial. A Procter & Gamble spokeswoman characterized ie St. Louis ruling as a "strong precedent," while the laintiff's lead attorney, Tom Riley, remarked that the vo decisions "send conflicting signals." The lawsuit as filed by Michael W. Rogers, whose wife allegedly ied of toxic shock syndrome after using Rely tampons in 980.

Bergdoll, with support from Procter & Gamble and other ompanies, has studied the production of toxic shock toxin tampons since 1980. He has not released or published his ata because he believes his findings are preliminary and nconclusive. But lawyers for toxic shock victims point out iat Bergdoll has discussed his findings with the company nd that the company has replicated his findings.

Although Bergdoll and Procter & Gamble have successully fended off many attempts by lawyers to use the data in ourt, a U.S. District judge in Fort Worth ruled in 1983 that he data are admissible as evidence. During that trial, lergdoll's data were revealed for the first time in detail by n expert witness for the plaintiffs, who reported that in aboratory tests Bergdoll found Rely tampons produced nore toxic shock toxin than any other brand of tampon.

Bergdoll still contends that his research is incomplete nd reiterated this point in a deposition in the Rogers case. J.S. District judge James Meredith agreed with Bergdoll nd emphasized the need to protect preliminary research indings in general.

He wrote, "Dr. Bergdoll's research is preliminary in nature; . . . it would be misleading to the jury given the inconclusiveness of its nature. [T]o use [Bergdoll's] deposition in this trial would hinder his research efforts as well as other research efforts at universities throughout the country." Furthermore, "[A] release of incomplete data will harm Dr. Bergdoll's professional reputation and impair his ability to complete and publish the final results of his research efforts. Premature public disclosure of research is not harmful in this case alone, but will have an adverse affect [sic] on research into controversial areas conducted throughout the nation." Meredith ruled that Bergdoll's deposition and documents introduced at the deposition be placed under seal. The case was settled before trial.

Procter & Gamble spokeswoman, Sydney McHugh, said that the ruling was significant because, for the first time, a judge heard Bergdoll himself describe what conclusions could be drawn from his research.

Meredith said that Bergdoll "is not associated with defendants. . . . He denies that his research will assist the jury in this lawsuit. Under the circumstances, his testimony and data will be excluded." Riley, the plaintiff's attorney, contends, however, that because Bergdoll receives substantial support from Procter & Gamble, he "is not an impartial witness."

Michael Liethen, legal counsel for the University of Wisconsin, who along with Procter & Gamble represented Bergdoll, rejects any suggestion that Bergdoll has been improperly influenced by Procter & Gamble. Liethen says that company money is paid to the university and the university then allots the money to Bergdoll. The company "ought to be congratulated for funding toxic shock research. The federal government doesn't support it. If not for P&G funding, the research wouldn't be done."

Liethen says he is not sure what meaning the St. Louis ruling will have in other cases. "As a practical matter, each case has to be weighed on its own merits. In this case, there was extensive balancing of public and private interests." Given the hundreds of toxic shock lawsuits still pending, the issue of Bergdoll's data and its use in court is far from settled.—MARJORIE SUN

The Push to Protect Patents on Drugs

The drug industry nearly won last year, but then the political winds changed

For nearly 3 years, the pharmaceutical industry has been campaigning for a change in patent law that would extend patent protection for drugs and pesticides. The industry contends that the change is needed to redress an injustice: whereas patents convey 17 years of exclusive use on most products, the patent life of drugs is shortened by the time consumed by regulatory review. The industry argues that this reform will encourage innovation and help stave off increasing foreign competition, by making available billions of dollars in new revenues that the industry can spend on research. But the bill's principal effect—the enrichment of one of the country's most profitable industries—is also its main political liability.

Just a year ago, legislation that would have achieved industry's objectives was on the brink of victory. A bill had passed unanimously in the Senate and a similar measure was moving easily through the House. But the political situation has changed dramatically in the past few months and now the legislation's future is at best cloudy.

The chief roadblock is in the House. Two key legislators, Representatives Albert Gore, Jr. (D–Tenn.), and Henry Waxman (D–Calif.) strongly oppose the legislation and have been instrumental in blocking its passage. However, Waxman has introduced a bill designed to aid manufacturers of so-called generic drugs. He badly wants the legislation passed and there is speculation that he may work out a compromise with supporters of patent extension to push his own bill through.

The industry's case is being pushed by the Pharmaceutical Manufacturers Association (PMA). A PMA briefing paper states that "lost patent life reduces incentives to invest in drug research, retards the rate of medical innovation, erodes the U.S. competitive position in an important high technology, and raises the cost of medical care at a time when medical expenditures are a critical national problem."

The PMA paper says that the legislation now before Congress is a "simple and direct antidote." The measure would give companies an incentive to put more money into research and develop new and better drugs. The industry notes that it is taking longer and longer to develop a drug and obtain approval by the Food and Drug Administration (FDA). For example, according to PMA figures, drugs approved in 1981 lost an average of 10.2 years of the statutory 17-year patent lives before their first sale. The number of drugs that come on the market and are new compounds has remained stable. The PMA paper says, "It should be a matter of concern that an industry which has quadrupled in size in two decades has not been able to afford to increase innovation at a comparable rate."



Representative Henry Waxman

A possible wedding of his generic drug bill with industry's patent term legislation.

Opponents speculate that the profit windfall created by patent law reform will primarily benefit corporate stockholders, not researchers or the public. Government figures show that the drug industry has consistently spent the same percentage of sales on research and development for several years despite an alleged decline in innovation. Critics also question the reliability of the industry's conclusions. Waxman and Gore, for example, note that the raw data on which the industry's argument is based have not been reviewed by independent analysts. The two legislators have repeatedly asked PMA for data that may resolve a dispute about the real patent lives of drugs. They charge that PMA has looked at only a selected number of drugs and want a complete list. Although the data were requested 2 years ago, PMA did not submit the information until just last week. Waxman and Gore plan to ask the Office of Technology Assessment to analyze the data.

Opponents call attention to other information to undercut the PMA's arguments. They point out that industry as a whole received a 25 percent tax credit on R & D in 1981. In contrast to industry's contention, top selling drugs in 1980 had a marketing life nearly equal to a 17-year patent term. Opponents also find it difficult to believe PMA's statement that an extension of patent terms would "do no economic harm to generic firms." Generic firms have been fighting an uphill battle in the marketplace because the large, established drug companies even dominate generic drug sales. The established companies market branded drugs under the trade name or generic name accompanied by the imprimatur of the firm's name, making it difficult for generic firms to compete.

Much of the information that opponents cite is based on findings in a 1981 report by the congressional Office of Technology Assessment (OTA). While OTA officials testified before Congress that the report "neither supports nor refutes the position that innovation will increase significantly because of [patent term] extensions," the report played an important role in the downfall of the House bill last year. Perhaps most significantly, it argued that innovation could be measured several ways and concluded that it is not clear whether innovation in the drug industry had indeed declined. The report also pointed out various ways in which a company can protect its product. For example, according to Donna Valtri, assistant project director of the report, drug companies, in some instances, can secure additional patents on a product. She testified at a House hearing that in some instances, process patents "can be an effective means for ensuring exclusive market positions." The report also said it was unclear whether patent extension would give companies an incentive to increase research in the United States. Valtri points out that domestic companies are increasingly licensing drugs invented by foreign

firms and also testing the drugs abroad where the cost of labor and research is cheaper.

In August 1982 the PMA was almost sure that patent extension legislation would pass Congress. The House Judiciary Committee had already approved a bill. The measure went before the Rules Committee where, according to a count by PMA, a majority of committee members favored the proposal. Furthermore, the bill had the backing of the Reagan Administration and a battalion of other groups, including the American Bar Association, the Chemical Manufacturers Association, the U.S. Chamber of Commerce, the American Heart Association, numerous professional medical societies, and several universities such as Massachusetts Institute of Technology.

But Richard Bolling, former Democrat from Missouri, who was then chairman of the Rules Committee, opposed the bill and refused to bring it up for a vote. The PMA, confident that it had overwhelming support, circumvented the Rules Committee by having the bill brought to the floor under the suspension rule. The rule is designed to assure the passage of noncontroversial bills and requires the approval of a two-thirds majority. But shortly before the floor vote, the political environment changed.

The *New York Times* reversed its position on the bill and, in an editorial that relied heavily on the OTA report, denounced the measure as "unjustified, unsuited to the stated purpose of increasing research, and offensive to the basic principle of a free economy." Gore and Waxman circulated the editorial to all House members. Shortly thereafter, Congress Watch, a Ralph Nader group, released a report, "Sugar Coating a Monopoly, A Study of the Drug Patent Restoration Act." The manufacturers of generic drugs lobbied legislators that a vote for the bill was a vote against the consumer. The legislation lost by four votes.

Frank Fowlkes, PMA vice president of communications, said in a recent interview, "The *Times* editorial hurt a whole lot." The combination of the editorial and the Nader report "scared enough fence-sitters who were up for reelection that the bill was anti-consumer."

Now the drug industry, so close to victory last year, finds itself on the defensive and trying to win back supporters. The issue has become particularly sensitive in an election year because opponents of current legislation now include the American Association of Retired Persons and the AFL-CIO.

For the time being, there is a lull in the action. Congressional aides from the Senate and the House say there is not likely to be much movement on the issue until the new year and even then, it is hard to say what will happen. The OTA analysis of the industry data, which were recently submitted to Waxman and Gore, could also delay legislative action. But PMA is still hopeful and has continued to push the issue hard. Association staff members have blitzed 140 newspapers around the country with packets of information about the bills and have criss-crossed the nation to meet with editors of 75 of the newspapers.

Identical bills, similar to last year's legislation, have been reintroduced in both chambers. They would extend patent protection to drugs and pesticides for a period equivalent to the time the products are filed or registered with the federal government and undergo agency review before approval. The legislation limits the extension to 7 years beyond the patent expiration date.

> Patent term legislation has become a particularly sensitive issue in an election year because opponents now include organizations such as the AFL-CIO.

Fowlkes predicts that the bill will again pass easily in the Senate. According to a staff aide to the Senate judiciary subcommittee on patents, copyrights, and trademarks, the bill may be marked up by the subcommittee some time in November. Again, the biggest hurdle will be in the House where the situation has become very complex.

Although the House bill was introduced in June, a judiciary subcommittee has not yet held hearings on it. Subcommittee chairman Robert Kastenmeier (D–Wis.), who sponsored patent extension legislation last year, is opposed to this year's version of the bill which would allow a greater number of drugs to qualify for the extension. Gore is still fighting the legislation.

At present, attention is focused mainly on Waxman. He has been a formidable foe of patent extension. Fowlkes said, "We didn't anticipate that Waxman would make the legislation a do-or-die issue like he did." But it may be Waxman, a master of compromise and political tactic, who will provide a legislative vehicle that will achieve his goal and that of the drug industry.

For several years, Waxman has championed the need for generic drugs and, in July, introduced legislation that is designed to encourage their production and reduce the cost of drugs for the consumer. In essence the bill would make it much easier for generic companies to copy drugs whose patents have expired. The bill, however, has not gone far in the House. To ease the bill's passage, Waxman is now talking with PMA to see if there is a way to combine his wish list with theirs.

Waxman's bill addresses a gap in FDA policy that has constrained the production of a wider variety of generic drugs. The agency imposes few restrictions on generic drugs that were approved before 1962. (In 1962, FDA reformed its drug regulations and required drugs to be not only safe but effective.) In effect, generic companies do not need to conduct lengthy clinical trials to again prove the safety and effectiveness of an old drug.

But FDA treats off-patent drugs approved after 1962 much differently. The agency says that to duplicate post-1962 drugs, a generic company must either conduct clinical trials or submit data from scientific journals that show the duplicate drug is safe and effective. Generic companies have problems meeting either requirement because the firms, which frequently are small, cannot afford the research and because studies on patented drugs are usually considered proprietary information and are not reported in the scientific literature.

Waxman's bill would eliminate the distinction between the pre- and post-1962 drugs. Fowlkes says that PMA has no problem with the concept provided that the drugs have adequate patent protection before they are duplicated by the generic companies. PMA in fact submitted a draft bill to Waxman in September which sandwiched together proposals for generic drug production and patent restoration. But Waxman rejected the entire proposal because it was so lopsided in favor of PMA members. That Waxman even entertained a draft proposal from PMA has led some observers of the fray to venture that some sort of compromise might eventually be struck.

Waxman's bill may be complicated by an FDA proposal that is now before Margaret Heckler, Secretary of Health and Human Services. Like PMA's bill, the FDA proposal contains provisions on generic drug production and patent extension.

The plan would provide more encouragement than PMA's draft bill for the

production of generic drugs, but not as much as Waxman's legislation. The main potential problem with the proposal is that it attempts to extend the patent life of drugs by an administrative ruling rather than through legislative change in patent law. The plan would guarantee that drugs could not be duplicated generically for up to 15 years after FDA approval. At a hearing in August, Waxman challenged FDA's authority to carry out the proposal and the measure would almost certainly be challenged in court if approved by Heckler.

Although it appears that all the parties involved are at loggerheads, there may be room for compromise. Some opponents of patent extension, such as Public Citizen Litigation Group, have suggested a modest form of patent extension that even PMA says would be better than nothing. PMA's best hope is that the period of patent extension would be measured from the date when a company applies to FDA to begin clinical trials to the date when the drug is approved. Public Citizen has proposed that the clock start running when a company applies to FDA for permission to begin marketing the drug. The consumer group argues that this is actually the period when a drug undergoes federal review. This period would add perhaps 2 years, far fewer than the time allotted by the draft legislation. A House aide involved in the issue said that the shorter way of measuring the patent extension "is a major improvement" over the current legislation. Nevertheless, according to this aide and others, Gore and Waxman still believe that the drug industry has yet to prove its case.—MARJORIE SUN

World Model for the Joint Chiefs

The Joint Chiefs of Staff (JCS) are getting a new toy that should make other government agencies green with envy: a computerized global model of political, resource, and social data that represents a step toward catching up with private sector capacities.

The system, called FORECASTS, is in its second year of development, at a cost of $1.2 million. It will be tested for 6 months by the Army Corps of Engineers before the Joint Chiefs get it next year. The primary reason for the acquisition is to help the JCS make their 4-year Joint Long Range Strategic Appraisal, a new exercise, started in 1980, to evaluate global and national trends up to 30 years hence. The services, which do their own appraisals, will also be using the model.

For several years the JCS has had the use of the World Integrated Model (WIM), FORECASTS' predecessor. But the new one goes far beyond WIM, according to Patricia G. Strauch, president of Prospective Decision Models, Inc., the contractor. WIM, which is in use in several other government agencies, has a much smaller data base, it divides the world by multination regions, and contains little information on such critical areas as the environment.

Unlike WIM, which is designed for long-range projections, FORECASTS has three modes of operation: a data base covering the years 1960 to 1980, short-range statistical procedures for extrapolations up to 5 years, and a long-range program which contains complex feedback and interactive capacities for projections up to 30 years in the future.

While most global models divide the world into regions or sectors (such as agriculture), FORECASTS can present data on a national as well as a regional basis. The vastly expanded data base contains information on vital characteristics ranging from land use to international political agreements. There is a new "political stability" module capable of being decoupled if security demands it. The model contains extensive detail on population, including sex, fertility, employment, urban-rural distribution, and migration, as well as social, religious, and linguistic subdivisions.

In recognition of the discontinuities that mark the present and probable future, says Strauch, a fundamental premise of the model is that "the past won't repeat itself." In facilitating economic analysis, for example, designers of the model place reliance on detailed data about human-resource interactions rather than building in traditional and now-dubious assumptions about the causes and effects of inflation or unemployment.

Knowing the capacities of the new system does not answer questions about how it will be used. What sort of questions, for example, is it uniquely equipped to address? Colonel James Edgar of the JCS submits that it would be interesting to know if 20 years ago FORECASTS could have cued analysts in to the emergence of the Middle East as the world's energy fulcrum. It might also be asked whether the model will be used by the military to reinforce prior assumptions, or whether it will result in the introduction of a greater variety of nonmilitary, nonpolitical factors and a keener awareness of global interdependencies into defense analyses. Says Mihajlo Mesarovic of Case Western Reserve University, who developed WIM: "Using strategic planning models is absolutely essential in analysis of long-term policies, but in the hands of people without insight into future options it would be grossly misleading and dangerous to use—like a gun."

It would be interesting to speculate how this capability might alter the relation of the defense establishment to the Central Intelligence Agency and the State Department when it comes to assessing long-range political trends. State, in particular, is deeply attached to traditional ways and, says an official, tends to think of long-range planning as "anything over 6 months." Gerald O. Barney, who headed President Carter's Global 2000 effort, says the department has "very little expertise in the use of models" and little interest in them. Yet, he asserts, they are "ultimately going to have a big impact on the way foreign policy is formulated."

Comprehensive attempts at global modeling, starting with *Limits to Growth* in 1972, are often associated with "gloom and doom" visions of the world's future (*Science*, 22 July, p. 341). The White House, for example, has criticized calls for a centralized "foresight" capability as being motivated by an anti-free market, progovernment intervention ideology. Perhaps, then, the most significant contribution of FORECASTS will be to decouple global modeling from ideology and present it as a valuable tool in a world where some mistakes have become too costly to make.—CONSTANCE HOLDEN

Robert C. Dorr
Bradford J. Duft

PATENT PRELIMINARY INJUNCTIVE RELIEF

Introduction

In a patent infringement suit, the patentee who considers preliminary injunctive relief has traditionally *not* pursued such relief. Rather, the patentee customarily seeks the final remedies at trial of a permanent injunction and the recovery of money damages. This has been true even though the actual injury to the patentee cannot be adequately compensated for in money damages.

The authors are of the opinion that seeking preliminary relief may well be an "overlooked" remedy that is ill-known, clouded with uncertainties and, therefore, seldom employed, or, on the other hand, improperly pursued. In *Teledyne Industries, Inc.*, v. *Windmere Products, Inc.*,[1] the authors' firm successfully pursued an award of preliminary relief to enjoin the infringement of three young patents.[2] The entire prosecution lasted only seven months and resulted in a settlement of the case after the award. Had traditional litigation to the merits ensued, there is no doubt that many years of expensive litigation would have transpired.

The favorable comments received after the *Teledyne* case prompted the authors to further investigate the award of preliminary injunctions in patent infringement cases. It was readily apparent that little had been written on this topic.[3] The purpose of this paper, there-

[1] 433 F. Supp. 710, 195 U.S.P.Q. 354 (S.D. Fla. 1977). Teledyne manufactures and markets a wall mounted adjustable showerhead known as the "WaterPik SHOWER MASSAGE". Teledyne was awarded a preliminary injunction which prohibited Windmere from importing and marketing a device similar in appearance which contained virtually identical parts.

[2] At the date of the decision the patents stood as follows:
1. Patent 3,762,648: age 4 years (issued 10/2/73).
2. Patent 3,801,019: age 3 years (issued 4/2/74).
3. Patent 3,958,756: age 1 year (issued 3/25/76).

[3] 3 Robinson, *The Law of Patents for Useful Inventions* (1890); P.D. Rosenberg, *Patent Law Fundamentals* (1975); R.A. White, *Patent Litigation: Procedure and Tactics* (1977); Latman, *Preliminary Injunctions in Patent, Trademark and Copyright Cases*, 60 Trademark Rptr. 506 (1970); Pravel and Hewitt, *Preliminary Injunctions in Patent, Trademark, Copyright and Unfair Competition Cases*, Patent Law Annual (1973); Schwartz, *Injunctive Relief in Patent Infringment Suits*, 112 U. Penn. L. Rev. 1025 (1964).

fore, is to present to the reader the results of a 25-year survey of all reported patent cases wherein preliminary injunctions were sought,[4] to set forth various guidelines which will be of assistance in the successful pursuit of or defense against preliminary relief, and to offer several tactics used successfully in the prosecution of the *Teledyne* case.

As will be discussed more thoroughly, the compilation of statistics from the survey, on a circuit-by-circuit basis, reveals several interesting insights. First, contrary to the popular belief that preliminary injunctions are infrequently granted, of those applied for, *over* 41% *were granted* by federal district courts. The choice of *forum* in which to seek preliminary relief can be crucial—only 8% of the motions for preliminary injunction were granted (and upheld upon appeal) in the Second Circuit, whereas 86% were granted (and upheld upon appeal) by the Fifth Circuit. The *age* of a patent is also significant. Preliminary injunctions are much more frequently granted for patents 10 years of age or older than for patents less than 5 years old (56% v. 8%). Notably, the two most common reasons for denying preliminary relief were that the movant did not prove the patent to be probably *valid* and did not demonstrate sufficient *irreparable harm.*

In the following text, the nature of a preliminary injunction will be set forth and the results of a 25-year case study will be analyzed based primarily on facts and arguments presented in support of or in refutation of the propriety of issuing a preliminary injunction. After presenting these results, various practical considerations for seeking preliminary relief will be addressed.

I. Nature of a Preliminary Injunction

The award of a preliminary injunction in patent infringement situations is authorized by 35 U.S.C. §283

[4] Cases reported in United States Patent Quarterly from January 1953 to September 1978. The survey does not include non-published decisions.

and is procedurally made possible by Rule 65(a) of the Federal Rules of Civil Procedure. As with any equitable award, the allowance or denial of a preliminary injunction is based upon a substantial number of seemingly significant and insignificant factors. Those factors, no doubt, affect each judge differently and, perhaps, the same judge differently at different times. It can be *emphatically* stated that the award or denial of a preliminary injunction rests entirely with the judge to whom it is presented.

The award of a preliminary injunction is intended to prevent *prospective* injury and, therefore, is applied only when the right affected is *probable* and the invasion of that right is *apparent*.[5] The best way to prevent future injury, of course, is to preserve the *status quo* of both parties pending the outcome of a trial on the merits.[6]

Most courts view their role in granting or denying preliminary relief as "an exercise of a very far reaching power, never to be indulged in except in a case clearly demanding it."[7] Despite this "case-by-case" approach, the courts are obliged to follow equitable principles and have traditionally placed greater judicial weight on certain classes of facts than others. It is well accepted that the following classes of facts must be proven by the movant at a standard of proof generally considered to be higher than the standard required at trial:[8]

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[5] 3 Robinson, *The Law of Patents for Useful Inventions* 558 (1890).

[6] Superior Electric Co. v. General Radio Corp., 194 F. Supp. 339, 344, 129 U.S.P.Q. 248, 253 (D. N.J. 1961). *See also* American Nicholson Pavement Co. v. Elizabeth, F. Cas. 312; Hamilton Watch Co. v. Benrus Watch Co., 206 F.2d 738, 742 (2d Cir. 1953); Artmoore Co. v. Dayless Manufacturing Co., 100 F. Supp 110 (N.D. Ill. 1951); Diamond Power Specialty Corp. v. Bayer Co., 95 F.2d 541, 37 U.S.P.Q. 233 (8th Cir. 1938); Meccano, Ltd. v. John Wanamaker, 253 U.S. 136 (1920).

[7] Warner Bros. Pictures, Inc. v. Gittone, 110 F.2d 292, 293 (3rd Cir. 1940).

[8] Norwich Pharmacal Co. v. International Brokers, Inc., 296 F. Supp. 937, 159 U.S.P.Q. 417 (N.D. Ga. 1968); Knoll International, Inc. v. Continental Imports, Inc., 192 U.S.P.Q. 502 (E.D. Penn. 1976); Compact Van Equipment Co. v. Leggett & Platt, Inc., 566 F.2d 952, 196 U.S.P.Q. 721 (5th Cir. 1978).

(1) Does the movant exhibit probable success at trial on the merits?
   (a) Does the movant have title to the patent?
   (b) Is the patent valid?
   (c) Does the accused product infringe the patent?
(2) Will the movant suffer irreparable injury?
(3) Has the "balance of equities" been convincingly weighed in favor of the movant?

In the last analysis, the granting or denying of a request for preliminary relief is a matter addressed to the sound judicial discretion of the court.[9] Each of the above guidelines will be carefully reviewed in the text of this paper.

Clearly, preliminary injunctions are *never* granted where the right is *doubtful* or the wrong is *uncertain.*[10] This is especially true when obscure propositions of law are presented and intricate and disputed questions of fact are found.[11]

The results of the 25-year survey are set forth in Tables 1-4. Table 1 shows the award or denial of preliminary injunctions on a circuit-by-circuit basis. Traditionally, it has been maintained that preliminary injunctions are rarely granted.[12] As one practicing attorney has observed:

> In practice, few counsel are sufficiently optimistic concerning their chances of success to recommend an effort to secure preliminary relief, and even fewer courts are sufficiently persuaded of the merits of the claim to grant it.[13]

[9] Olsen v. Baby World Co., 120 F. Supp. 462, 101 U.S.P.Q. 143 (E.D.N.Y. 1954).

[10] Marshall Metal Products, Inc., v. Aghnides, 126 F. Supp. 850, 103 U.S.P.Q. 176, 178 (S.D.N.Y. 1954); Norwich Pharmacal Co. v. International Brokers, Inc., 296 F. Supp. 937, 159 U.S.P.Q. 417 (N.D. Ga. 1968).

[11] Pierce v. Aeronautical Communications Equipment, Inc., 223 F.2d 410, 106 U.S.P.Q. 11 (5th Cir. 1955); Uniroyal, Inc. v. Daly-Herring Co., 294 F. Supp. 754, 161 U.S.P.Q. 506 (E.D.N.C. 1968).

[12] Latman, *Preliminary Injunctions in Patent, Trademark and Copyright Cases*, 60 Trademark Rptr. 506 (1970).

[13] R.A. White, *Patent Litigation Procedure & Tactics* at 4-80 (1977).

The results found in Table 1 indicate otherwise. At the district court level, 41% of all preliminary injunction motions were granted, and, when combined with subsequent appellate decisions the overall success rate for the patentee was 32%. In light of such statistics, preliminary injunctions can hardly be termed "rarely granted."

More importantly, "where" the motion is made is significant. In the Second Circuit, with an overall allowable rate of 8%, it can safely be stated that preliminary injunctions are "rarely granted." Whereas in the Fifth Circuit, with an overall allowance rate of 86%, and in the Ninth Circuit, with an overall allowance rate of 80%, it can be contended that patent preliminary injunctions are "almost always granted." Thus, upon inspection of Table 1, it is evident that a patentee should consider "forum" the *most* important factor in deciding whether or not to seek preliminary relief.

Table 2 sets forth another surprising result. In more than half (55%) of appealed preliminary injunction cases (whether awarded or denied), the appellate court upheld the district court. In an appeal of the award of a preliminary injunction (which occurred in 9 out of 22 cases or 41% of the cases) over half (56%) *were reversed.* Hence, it would appear to be advantageous for a losing defendant to appeal the award.

Tables 2-4 set forth a statistical analysis of the various requirements and the levels of proof required to obtain preliminary relief. Discussions of these tables are found in the following sections. A listing of cases on a circuit-by-circuit basis, comprising the raw data for this survey, is available from the authors.

II. Elements of Proof

A. *Probability of Success at Trial*

In order to prevail upon this requirement, in patent cases, proof of (1) title, (2) patent validity, and (3) infringement must be presented.

1. *Title*

Proof of title in the movant is mandatory in preliminary relief requests.[14] The standard of proof in all courts requires that title in the movant be demonstrated "beyond a reasonable doubt."[15]

Title in the movant is usually demonstrated by producing a certified copy of the patent.[16] If the movant is an assignee of the patent, a certified copy of the assignment, as recorded in the U.S. Patent and Trademark Office, is necessary.[17] If the movant is a licensee of the patent, a copy of the original agreement granting the license will be required.[18] Other particulars that should be introduced to bolster an adequate showing of title include the filing of a verified complaint asserting that the movant has title, a showing that past judgments rendered on the patent acknowledge title to be in the movant, and failure by the non-movant to substantially question title.[19] An admission by the non-movant of title would also appear to be sufficient.[20] Title, however, is never proven by the submission of affidavits.[21]

Failure to prove title will result in an immediate denial of the preliminary injunction as the movant cannot establish a probability of success on the merits.[22]

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[14] The Singer Manufacturing Co. v. Better Service Sewing Machine Co., 131 F. Supp. 146, 105 U.S.P.Q. 190 (S.D.N.Y. 1955); Norwich Pharmacal Co. v. International Brokers, Inc., 296 F. Supp. 937, 159 U.S.P.Q. 417 (N.D. Ga. 1968).

[15] Schwartz, *Injunctive Relief in Patent Infringement Suits*, 112 U. Penn. L. Rev. 1025 (1964).

[16] Norwich Pharmacal Co. v. International Brokers, Inc., 296 F. Supp. 937, 159 U.S.P.Q. 417 (N.D. Ga. 1968).

[17] Schwartz, *Injunctive Relief in Patent Infringement Suits*, 112 U. Penn. L. Rev. 1025 (1964).

[18] Edaco Stahlwarenfabrik Ernst Darmann & Co. v. Hill Novelties Manufacturing Corp., 185 F. Supp. 621, 126 U.S.P.Q. 41 (S.D.N.Y. 1960).

[19] Norwich Pharmacal Co. v. International Brokers, Inc., 296 F. Supp. 937, 159 U.S.P.Q. 417 (N.D. Ga. 1968).

[20] FED. R. CIV. P. 36(b).

[21] Edaco Stahlwarenfabrik Ernst Darmann & Co. v. Hill Novelties Manufacturing Corp., 185 F. Supp. 621, 126 U.S.P.Q. 41 (S.D.N.Y. 1960).

[22] *Id.*

In this event, the defendant should move for a summary judgment based upon the movant's lack of capacity to sue.

A problem arises in licensing situations, as the right to bring and maintain a suit on a patent cannot, by contract alone, be assigned arbitrarily as between a licensor and his licensee. This "ticklish" situation has been previously discussed [23] and should be the starting point of defense by the non-movant.

In the 25-year survey, only one case was faulty due to "title" considerations.[24] However, it must again be stressed that if the court is not convinced of title in the movant, the preliminary injunction will be denied.

2. *Validity*

As set forth in Table 4, failure to adequately show patent validity is the reason most frequently pronounced by courts in denying injunctive relief. It is not surprising to find many sub-issues relating to proof of validity. In this section, these numerous sub-issues will be analyzed in relation to the burden of proof required to demonstrate validity. The burden of proof for validity is high and, as indicated for the various circuits in Table 2, the burden of proof standard varies slightly from circuit to circuit. Proof "beyond question" is the overwhelming standard employed by most circuits. Both the Sixth and Seventh Circuits require seemingly less stringent standards of proof (i.e., "very probably" and "strong probability"). "Beyond question" indicates that no reasonable doubt of validity may remain in the mind of the court.[25]

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[23] H.R. Mayers, *Drafting Patent License Agreements*, Sec. 6.04 (1971).

[24] Edaco Stahlwarenfabrik Ernst Darmann & Co. v. Hill Novelties Manufacturing Corp., 185 F. Supp. 621, 126 U.S.P.Q. 41 (S.D.N.Y. 1960), wherein an affidavit of title made by the plaintiff's attorney was dismissed as mere hearsay.

[25] Standard Paint Co. v. Reynolds, 43 F. 304, 305 (C.C.D.N.J. 1890); Norwich Pharmacal Co. v. International Brokers, Inc., 159 U.S.P.Q. 417 (N.D. Ga. 1968); Coleco Industries, Inc. v. Empire Plastic Corp., 169 U.S.P.Q. 94 (S.D.N.Y. 1971).

All circuits universally recognize that a patent duly issued by the United States Patent and Trademark Office is presumptively valid. This presumption is explicitly mandated in 35 U.S.C. §282. The weight accorded this presumption, however, varies substantially from circuit to circuit. For example, the Seventh Circuit has stated:

> On the issue of validity we start, as we must in all patent cases . . . with the presumption of validity which attaches the grant. This presumption is not an idle gesture, as Defendants would have us believe, but is *a positive factor* which must be overcome by one who asserts invalidity. . . .[26] (emphasis added)

On the other hand, the Ninth Circuit has stated:

> The presumption of validity is *too slim a reed* to support a preliminary injunction in a patent case. Moreover, the presumption of validity afforded to patents is not conclusive, but exists simply to give the grant substance and value.[27] (emphasis added)

From the above it is clear that upon presentation by the movant of an issued U.S. Letters Patent, the defendant has an opportunity to rebut this presumption.

The level of proof required for this rebuttal has been variously and contradictorily termed:

1. One who seeks to rebut the presumption bears a heavy burden.[28]
2. The presumption has no independent evidentiary value; rather, it serves to place the burden of proof on the person who asserts invalidity.[29]

The presumption of patent validity has been even further diminished by the courts in considering motions

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[26] Artmoore v. Dayless Manufacturing Co., 208 F.2d 1, 3 (7th Cir. 1953).

[27] Navy Corp. v. Rodstein, 480 F.2d 714, 178 U.S.P.Q. 449 (9th Cir. 1973); followed in Julien v. Gomez & Andre Tractor Repairs, Inc., 196 U.S.P.Q. 224 (M.D. La. 1977).

[28] Hobbs v. United States, 451 F.2d 849 (5th Cir. 1971).

[29] Rains v. Niaqua, Inc., 406 F.2d 275, 278, 160 U.S.P.Q. 370, 373-374 (2d Cir. 1969), *cert. denied*, 395 U.S. 909, 161 U.S.P.Q. 832 (1969). It is the authors' belief that the burden of proof does not shift to the defendant; rather the presumption is merely rebutted and plaintiff retains the burden of proof.

for preliminary injunctions, perhaps even to the point that there is a presumption of invalidity.[30] It is generally not difficult for the defendant to rebut the presumption of validity—such evidence as is necessary can be garnered from any of the following principles:

1. Obviousness (35 U.S.C. § 103)
2. Abandonment (35 U.S.C. § 102(c))
3. "The invention was patented . . . in this or a foreign country . . . more than one year prior to the date of the application for a patent in the United States.". (35 U.S.C. § 102(b))
4. "The invention was in public use . . . in this country more than one year prior to the date of the application for patent in the United States." (*id.*)
5. "The invention was . . . described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States." (*id.*)
6. "The invention was . . . on sale in this country more than one year prior to the date of the application for patent in the United States." (*id.*)
7. "The [inventor] did not himself invent the subject matter sought to be patented." (35 U.S.C. § 102(f))
8. "The invention was known . . . by others in this country . . . before the invention thereof by the applicant for patent." (35 U.S.C. § 102(a))
9. "The invention was . . . used by others in this country . . . before the invention thereof by the applicant for patent." (*id.*)
10. "The invention was . . . patented . . . in this or a foreign country before the invention thereof by the applicant for the patent." (*id.*)
11. "The invention was . . . described in a printed publication in this or a foreign country before the invention thereof by the applicant for patent in the United States." (*id.*)
12. "The invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent." (35 U.S.C. § 102(e))

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[30] Jungerson v. Ostby & Barton Co., 335 U.S. 560, 572, 80 U.S.P.Q. 82, 86 (1949).

13. Though "first to conceive," applicant was the "last to reduce to practice" and did not use "reasonable diligence . . . from the time prior to conception by the other." (35 U.S.C. § 102(g))
14. "Before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed or concealed it." (*id.*)
15. Fraud on the Patent Office.[31]
16. Misconduct before the Patent Office.[32]
17. "Unclean hands," resulting in a refusal by the court to enforce the patent.[33]

Only one case was found in this survey where the defendant did *not* present evidence in rebuttal to the statutory presumption of validity.[34] Of course, the preliminary injunction was granted.

Once evidence of invalidity has been presented by the defendant, the burden of proving validity returns to the movant—the presumption has run its course. Hence, it is wise at the outset for the movant to present additional evidence supportive of validity. Generically these additional factors fall into the separate categories of:

1. prior adjudication of validity;
2. public acquiescence;
3. admissions of validity; and
4. other equitable considerations.

When a patent has been previously adjudicated, courts are more disposed to grant preliminary injunctive relief.

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[31] Barr Rubber Products Co. v. Sun Rubber Co., 425 F.2d 1114, 165 U.S.P.Q. 429 (2d Cir. 1970), *cert. denied*, 400 U.S. 878, 167 U.S.P.Q. 385 (1970); Xerox Corp. v. Dennison Manufacturing Co., 322 F. Supp. 963, 968-969, 168 U.S.P.Q. 700 (S.D.N.Y. 1971); Armour & Co. v. Swift & Co., 466 F.2d 767, 175 U.S.P.Q. 70 (7th Cir. 1972); Monsanto Co. v. Rohm & Haas Co., 456 F.2d 592, 597, 172 U.S.P.Q. 323, 326-327 (3rd Cir. 1972), *cert. denied*, 407 U.S. 934, 174 U.S.P.Q. 129 (1972).

[32] Carter-Wallace, Inc., v. Davis-Edwards Pharmacal Corp., 443 F.2d 867, 169 U.S.P.Q. 625 (2d Cir. 1971); Norton v. Curtiss, 433 F.2d 778, 793, 167 U.S.P.Q. 532, 543-544 (C.C.P.A. 1970).

[33] Xerox Corp. v. Dennison Manufacturing Co., 332 F. Supp. 963, 168 U.S.P.Q. 700 (S.D.N.Y. 1971); Pfizer, Inc. v. International Rectifier Corp., 538 F.2d 180, 190 U.S.P.Q. 273 (8th Cir. 1976).

[34] Waco-Porter Corp. v. Tubular Structures Corp., 220 F. Supp. 724, 138 U.S.P.Q. 476, *modified*, 222 F. Supp. 332, 139 U.S.P.Q. 37 (S.D. Cal. 1963).

A decree or judgment of federal circuit court, after a full hearing or trial in an adversary cause sustaining a patent, is very strong evidence of its validity in an application for an injunction.[35] Indeed, where a patent has been adjudged valid and infringed by a circuit court of appeals, a district court may properly grant a preliminary injunction against infringement by another on a showing that the alleged infringing device is not materially different.[36]

The prior adjudication, however, must have been a fully contested adversary proceeding, its scope sufficient to include the present issues in suit.[37] For it has been held that a court is not required to grant a preliminary injunction simply because the validity of the patent has been sustained in a previous decision.[38] It also has been held that a prior judgment sustaining a patent, if entered by default, is not sufficient to warrant issuance of a preliminary injunction.[39] However, the decision will generally be followed unless the non-movant introduces new evidence not set forth in the previous suit,[40] or un-

[35] American Middlings Purifier Co. v. Christian, F. Cas. 307 (1877); Westinghouse Air Brake Co. v. Christensen Engineering Co., 113 F. 594 (2d Cir. 1901); Bowers Dredging Co. v. New York Dredging Co., 80 F. 119 (9th Cir. 1897); American Bell Telephone Co. v. McKeesport Telephone Co., 57 F. 661 (3rd Cir. 1893).

[36] Consolidated Rubber Tire Co. v. Diamond Rubber Co., 157 F. 677 (2d Cir. 1907), *aff'd*, 162 F. 892 (2d Cir. 1908), *aff'd*, 220 U.S. 428 (1910).

[37] Stoody v. Osage Metal Co., 95 F.2d 592, 37 U.S.P.Q. 169 (10th Cir. 1938); Pacific Cage & Screen Co. v. Continental Cage Corp., 259 F.2d 87, 119 U.S.P.Q. 338 (9th Cir. 1958); Gordon Johnson Co. v. Hunt, 109 F. Supp. 571, 96 U.S.P.Q. 92 (D.C. Ohio 1953).

[38] Diamond Match Co. v. Union Match Co., 129 F. 602 (8th Cir. 1904); Elite Pottery Co. v. Dececo Co., 150 F. 581 (3rd Cir. 1907); Westinghouse Electric & Manufacturing Co. v. Condit Electrical Manufacturing Co., 159 F. 144 (2d Cir. 1908), *aff'd*, 167 F. 546 (2d Cir. 1909).

[39] Mannie v. Everett, F. Cas. 9,039 (2d Cir. 1879).

[40] Nicholl, Inc. v. Schick Dry Shaver, 98 F.2d 511 (9th Cir. 1938); Electric Manufacturing Co. v. Edison Electric Light Co., 61 F. 834 (7th Cir. 1894). In the following cases the new evidence or defense was sufficient to warrant refusal of a preliminary injunction: Lockwood v. Faber, 27 F. 63 (2d Cir. 1886); Brunswick-Balke-Collender Co., v. Koehler & Hinrichs, 115 F. 648 (8th Cir. 1902); Western Electric Co. v. Anthracite Telephone Co., 100 F. 301 (3rd Cir. 1900);

less he raises new issues which were not fully considered in the prior litigation.[41] If the non-movant does so, the factor of prior adjudication becomes substantially less meaningful and the plaintiff must thereupon present additional proof of validity.

Obviously, if the parties in the instant suit were adversaries in a prior adjudication and if the same issues are involved, it is clear that evidence of prior judgment is "conclusive proof of validity of the patent."[42] Even interference proceedings are entitled to great weight in subsequent litigation between the same parties.[43]

Prior decrees entered on stipulation, though not indicative of a complete prior adjudication, are available as evidence of acquiescence.[44] Acquiescence has been defined as a voluntary submission against interest to an asserted right.[45] The mere issuance of a U.S. letters patent does not suffice as a legal assertion.[46] Therefore, regarding patents, the fact that a product or method is patented must be asserted to the public. Under the doc-

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Bowers v. San Francisco Bridge Co., 69 F. 640 (9th Cir. 1895); Jacobson v. Alpi, 46 F. 767 (2d Cir. 1891); Carey v. Miller, 34 F. 392 (2d Cir. 1888). In the following cases the new evidence or defense was insufficient to warrant the refusal of a preliminary injunction: Electric Manufacturing Co. v. Edison Electric Light Co., 61 F. 834 (7th Cir. 1894); Tannage Patent Co. v. Donallan, 75 F. 287 (1st Cir. 1896); Carter & Co. v. Wollsclaeger, 53 F. 573 (2d Cir. 1892); Brush Electric Co. v. Accumulator Co., 50 F. 833 (3rd Cir. 1892); MacBeth v. Braddock Glass Co., 54 F. 173 (3rd Cir. 1890); Seibert Cylinder Oil Cup Co. v. Michigan Lubricator Co., 34 F. 33 (6th Cir. 1888).

[41] Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 443 F.2d 867, 169 U.S.P.Q. 625 (2d Cir. 1971); National Electric Products Corp. v. Grossman, 70 F.2d 257 (2d Cir. 1934); Société Anonyme du Filtre Chamberland Systeme Pasteur v. Allen, 84 F. 812 (6th Cir. 1897); Page v. Holmes Burglar Alarm, 2 F. 330 (2d Cir. 1880); Parker v. Brant, F. Cas. 10,727 (3rd Cir. 1850).

[42] 3 Robinson, *The Law of Patents for Useful Inventions* 562 (1890).

[43] Automatic Weighing Machine Co. v. Pneumatic Scale Corp., 166 F. 288 (1st Cir. 1909). However, a decision in an interference proceeding cannot be invoked, as against strangers to it, as a ground for the issuance of a preliminary injunction, see Wilson v. Consolidated Store-Service Co., 88 F. 286 (1st Cir. 1898).

[44] Perkins Oil Well Cementing Co. v. Owen, 293 F. 455 (9th Cir. 1923).

[45] *Id.* at 590.

[46] *Id.* at 591.

trine of acquiescence, the public must have an opportunity to become acquainted with the invention and to be informed of the patent rights.[47] With this knowledge, the public must have voluntarily refrained from appropriating the invention and the evidence must show that the public's forebearance is a result of such knowledge and deliberation.[48] It has been stated that the significance of the duration of acquiescence is not estimated by the mere lapse of time.[49] Rather, courts look to other types of proof. These factors include the following:

1. Does the patented product enjoy tremendous commercial success? [50]
2. Have there been numerous favorable comments on the patented product in trade publications? [51]
3. Until the advent of the defendant's product, was the plaintiff the sole source of this type of product? [52]
4. Are consumers intimately familiar with plaintiff's product, and its usefulness? [53]
5. Has plaintiff's patented product been sought out by other competing manufacturers for licensing? [54]

Creative counsel should be able to substantially increase this list of factors.

The defendant can present evidence in refutation of public acquiescence by demonstrating that a number of other competitors are infringing the patent—which in-

[47] 3 Robinson, *The Law of Patents for Useful Inventions* 594 (1890); see also, Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 443 F.2d 867, 169 U.S.P.Q. 625, 628 (2d Cir. 1971).

[48] *Id.* at 594; see also, Carter-Wallace, Inc., v. Davis-Edwards Pharmacal Corp., 443 F.2d 867, 169 U.S.P.Q. 625, 628 (2d Cir. 1971).

[49] *Id.* at 593.

[50] Nuclear-Chicago Corp. v. Nuclear Data, Inc., 173 U.S.P.Q. 326, (N.D. Ill. 1972), *rev'd*, 465 F.2d 428, 174 U.S.P.Q. 384 (7th Cir. 1972); Eli Lilly & Co. v. Generix Drug Sales, Inc., 460 F.2d 1096, 1100, 174 U.S.P.Q. 65 (5th Cir. 1972).

[51] Nuclear-Chicago Corp. v. Nuclear Data, Inc., 173 U.S.P.Q. 326, 337 (N.D. Ill. 1972), *rev'd*, 465 F.2d 428, 174 U.S.P.Q. 384 (7th Cir. 1972); Teledyne Industries, Inc. v. Windmere Products, Inc., 433 F. Supp. 710, 195 U.S.P.Q. 354 (S.D. Fla. 1977).

[52] Eli Lilly & Co. v. Generix Drug Sales, Inc., 324 F. Supp. 715, 169 U.S.P.Q. 13, 20 (S.D. Fla. 1971).

[53] *Id.*

[54] Nuclear-Chicago Corp. v. Nuclear Data, Inc., 173 U.S.P.Q. 326, 336 (N.D. Ill. 1972).

fringement the plaintiff has allowed by not suing.[55] Furthermore, if the defendant can present evidence that the plaintiff himself did not use the teachings of the patent, then, due to lack of assertion, no acquiescence can be found.[56]

In the case of a pioneer patent, there appears to be a presumption of acquiescence.[57] A pioneer patent has been defined as one which provides a decided advantage over the existing state of the art thereby opening up a new field of endeavor.[58] As one commentator has stated:

> If the invention were of great importance, affecting the whole course and practice of the art, the absence of infringement can be attributed only to the compliance with the prohibitions of the patent.[59]

In addition to evidence of prior adjudication and public acquiescence, the plaintiff should also introduce any evidence relating to admissions by the defendant which acknowledge or imply the validity of the patent. Such a burden can be met by showing that the defendant applied to the plaintiff for a patent license [60] and by admissions of validity found in the defendant's pleadings.[61] Creativity by counsel should again be employed; for example, introducing statements of validity made voluntarily by the defendant to third persons is viable evidence of defendant's acquiescence.

Lastly, evidence pertaining to other equitable considerations should be presented to the court as demonstrative of acquiescence. The following are representative of such considerations:

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[55] Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 443 F.2d 867, 169 U.S.P.Q. 625 (2d. Cir. 1971).

[56] Eli Lilly & Co. v. Generix Drug Sales, Inc., 460 F.2d 1096, 174 U.S.P.Q. 65, 74 (5th Cir. 1972).

[57] Schwartz, *Injunctive Relief in Patent Infringement Suits*, 112 U. Penn. L. Rev. 1025, 1033 (1964).

[58] Id. at 1033; see United Shoe Machine Corp. v. Industrial Shoe Machine Corp., 223 F. Supp. 826, 834 (D. Mass. 1963).

[59] 3 Robinson, *The Law of Patents for Useful Inventions* 593 (1890).

[60] Id. at 597.

[61] Id. at 597.

1. Defendant's product is a copy of the patented product. As reflected by one court:
   While such copying is not only the sincerest form of flattery it is a touchstone of plaintiff's invention.[62]
2. All the pertinent prior art cited by the defendant has been previously presented to and analyzed by the United States Patent and Trademark Office. As one court stated:
   Most of the pertinent references in the record were before the Patent Office and were rejected as anticipations. This fact greatly strengthens the presumption of novelty and invention which arises from the grant of the patent.[63]
3. Plaintiff has expended a considerable amount of money in development and research of its product.[64]
4. The appearance of defendant's product with plaintiff's product is so similar that actual confusion has resulted in the marketplace.[65]
5. Defendent has acted with full knowledge of plaintiff's product.[66]
6. Plaintiff's product is a fresh, efficacious and undisclosed use and is deservant of the full amount of statutory protection.[67]

Thus, while a strong showing of patent validity is required—prior adjudication or industrial and/or public acquiescence—a preliminary presentation of validity should be supported by demonstrating that the equitable considerations rooted in the dispute are canted in favor of the movant. Such additions can only help sway the court and, indeed, may be the basis of a decision granting the preliminary injunction.

In all of the above (i.e., prior adjudication, acquiescence, admissions, and equity), the forms of proof for validity are clearly definite, easily procured, simply presentable to the court, and are generally of such nature as to preclude contradiction.

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[62] Bishman Manufacturing Co. v. Stewart-Warner Corp., 259 F. Supp. 300 (N.D. Ill. 1966).

[63] Modern Products Supply Co. v. Drachenberg, 152 F.2d 203, 205 (6th Cir. 1945), *cert. denied*, 327 U.S. 806 (1946).

[64] Eli Lilly & Co. v. Generix Drug Sales, Inc., 460 F.2d 1096, 1103, 174 U.S.P.Q. 65 (5th Cir. 1972).

[65] Eli Lilly & Co. v. Generix Drug Sales, Inc., 324 F. Supp. 715, 169 U.S.P.Q. 13, 20 (S.D. Fla. 1971).

[66] *Id.*

[67] Eli Lilly & Co. v. Generix Drug Sales, Inc., 460 F.2d 1096, 1103, 174 U.S.P.Q. 65 (5th Cir. 1972).

3. *Infringement*

After establishing title in the movant and validity of the patent, another hurdle presents itself—adequately demonstrating that the patent has been infringed by the defendant. Regarding conventional at trial patent infringement situations, the United States Supreme Court has defined infringement as follows:

> In determining whether an accused device or composition infringes a valid patent, resort must be had in the first instance to the words of the claim. If the accused matter falls clearly within the claim, infringement is made out and that is the end of it.[68]

As set forth in Table 2, the level of proof required has been variously termed "beyond question" and "reasonably clear." Indeed, conflicting standards have even existed within the same circuit. For example, in the Second Circuit, Judge Learned Hand stated that the patent in dispute must be "beyond question valid and infringed."[69] Yet while this standard has been consistently followed in Second Circuit patent infringement cases in the 1970's, some Second Circuit courts have propagated the lesser "clear and convincing" standard.[70] The showing of infringement required for preliminary injunctive purposes has been equated to the showing prescribed for summary judgment.[71] Therefore, if on a clear reading of the claims, the defendant's product or process infringes the claims, this requirement becomes easily satisfied.

If the patented configuration *is* the same as the movant's product, and the defendant's product *is* a copy of the movant's product, infringement should be clear-cut. It must be emphasized that, if possible, a visual

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[68] Graver Tank Manufacturing Co. v. Linde Air Products Co., 339 U.S. 605, 607, 85 U.S.P.Q. 328, 330 (1950).

[69] Simpson Bros. v. Blancard & Co., 22 F.2d 498, 499 (2d Cir. 1927).

[70] See Table 2, Footnote 2.

[71] Superior Electric Co. v. General Radio Co., 194 F. Supp. 339, 343, 129 U.S.P.Q. 248 (D.N.J. 1961); see 7 Moore *Federal Practice* § 65.04, at 1640 (2d ed. 1955).

demonstration of infringement should be presented to the court. For the court, upon occasion, can ascertain infringement upon physical inspection and comparison of the movant's product and the alleged infringing goods.[72]

Such clear-cut cases, however, do not generally present themselves. Rather, the defendant's alleged infringement requires the application of the doctrine of equivalents.[73] Involved in this type of situation, a movant can still prevail in his preliminary relief motion by introducing evidence of substantial identity under this well-established doctrine. Great care must be exercised by the plaintiff in presenting technical issues to the court. Simple graphic charts showing infringement, element by element, should be utilized.

The intent of the defendant may be a supporting factor. For example, if the defendant is a former licensee or a former employee, and his was a situation whereby he could gain access to the patented invention, courts will tend to find infringement even though such a determination is not based upon a clear reading of the claims.[74] For an innocent or "good faith" infringer (i.e., the product in dispute resulted from an independent conception and development), courts will lean towards the test whereby infringement is established only from a clear reading of the claims of the patent.[75]

B. *Irreparable Injury*

After showing probability of success on the merits, the movant has the obligation to demonstrate a probable wrong which has been termed "irreparable injury." Unlike trademark cases, where "likelihood of confusion" in the public is the standard used as a test for irrepar-

[72] Consolidated Rubber Tire Co. v. Diamond Rubber Co., 157 F. 677 (2d Cir. 1907), *aff'd*, 162 F. 892 (2d Cir. 1908), *aff'd*, 220 U.S. 428 (1910).

[73] Rosenberg, *Patent Law Fundamentals* at 297 (1975).

[74] See II.(C), Balancing the Equities.

[75] *Id.*

[76] Franklin Mint, Inc. v. Franklin Mint, Ltd., 331 F. Supp. 827, 169 U.S.P.Q. 403 (E.D. Penn. 1971) (Test of trademark infringement is likelihood of confusion).

able injury,[76] the evidentiary burden in patent infringement disputes appears to be more difficult to discharge.

Irreparable injury occurs when the acts of the defendant substantially destroy an existing right in the movant which cannot be adequently compensated by money damages.[77] The legal right involved is a patent right which has been generally considered to be an intangible personal property right.[78]

Although there appears to be no formal "burden of proof" standard as is required to prove probability of success at a trial on the merits, courts have variously termed an adequate demonstration of irreparable injury as:

1. Unbiased, non-speculative evidence of irreparable injury,[79] and
2. Proof of irreparable injury beyond mere conclusionary statements and affidavits.[80]

Perhaps these rather vague standards explain why the failure to show irreparable injury is a leading factor in the denial of preliminary injunctive relief (see Table 4). Hence, great care must be exercised by the plaintiff in his presentation of irreparable injury, as the defendant, being well advised, knows this to be an Achilles' heel of patent preliminary injunction motions.

The following facts have been previously considered as facts sufficient to show the irreparable injury necessary to support the grant of a preliminary injunction:

1. A permanent loss of market position,[81]
2. A loss of sales,[82]
3. The inability of the defendant to respond with damages,[83]

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[77] Nuclear-Chicago Corp. v. Nuclear Data, Inc., 173 U.S.P.Q. 326, 337 (N.D. Ill. 1972).

[78] 3 Robinson, *The Law of Patents for Useful Inventions* 96 (1890).

[79] Bose Corp. v. Linear Design Labs, Inc., 467 F.2d 304, 175 U.S.P.Q. 385, 387 (2d Cir. 1972).

[80] Nadya Inc., v. Majestic Metal Specialties, Inc., 127 F. Supp. 467, 104 U.S.P.Q. 109 (S.D.N.Y. 1954).

[81] *Id.*

[82] *Id.*

[83] Owens v. American Stereographic Corp., 116 F. Supp. 406, 99 U.S.P.Q. 157 (S.D.N.Y. 1953); Collins v. Wallin, 66 F. Supp. 687

4. The unavailability of a permanent injunction since the patent will expire prior to trial,[84]
5. Confusion in the marketplace as to the source or origin of defendant's product and plaintiff's product,[85]
6. Plaintiff is the sole source of the product,[86]
7. Use of plaintiff's product by members of the public for a number of years,[87]
8. A forcing of the plaintiff to bring a multiplicity of lawsuits against other infringers as they enter the market as well as distributors and retailers handling defendant's product.[88]

The movant, in order to prevail on the issue of irreparable injury, must use creativity in his marshalling of facts. In gathering these facts, the movant should be aware of the possible pitfalls which arise at the outset by defining his damages *with too much certainty*. In the following situations, preliminary relief has been denied on a finding of no irreparable injury:

1. The patent is about to expire.[89]
2. An established license with definite royalties exists.[90]
3. The damages are finite due to a limited market and are, therefore, easily calculated with the defendant being financially responsible for the amount.[91]
4. Only past damages are presented.[92]

(D. Mass. 1946); Eskimo Pie Corp. v. Arctic Fruit Ices, Inc., 15 F.2d 853 (E.D.N.Y. 1926). See Also Sinko v. Casco, 89 F.2d 916 (7th Cir. 1937); Penmac Corp. v. Falcon Pencil Corp., 62 F. Supp. 358 (S.D.N.Y. 1958).

[84] Freedman v. Friedman, 242 F.2d 364 (4th Cir. 1957); Jordan v. Hemphill Co., 180 F.2d 457 (4th Cir. 1950); Hughes Tool Co. v. A.F. Spengler Co., 73 F. Supp. 156 (W.D. Okla., 1947), *appeal dismissed*, 169 F.2d 166 (10th Cir. 1948).

[85] Eli Lilly & Co. v. Generix Drug Sales, Inc., 460 F.2d 1096, 174 U.S.P.Q. 65, 74 (5th Cir. 1972).

[86] Eli Lilly & Co. v. Generix Drug Sales, Inc., 324 F. Supp. 175, 169 U.S.P.Q. 13, 20 (S.D. Fla. 1971).

[87] *Id.*

[88] Eli Lilly & Co. v. Milan Pharmaceuticals, Inc., 169 U.S.P.Q. 32 (N.D. W.Va. 1968).

[89] Owens v. American Stereographic Corp., 116 F. Supp. 406, 99 U.S.P.Q. 157 (S.D.N.Y. 1953).

[90] 3 Robinson, *The Law of Patents for Useful Inventions* 603 (1890).

[91] *Id.* at 603; see Nuclear-Chicago Corp. v. Nuclear Data, Inc., 173 U.S.P.Q. 326 (N.D. Ill. 1972), *rev'd*, 465 F.2d 428, 174 U.S.P.Q. 381 (7th Cir. 1972); Tyrolean Handbag Co. v. Empress Handbag, Inc., 122 F. Supp. 299, 102 U.S.P.Q. 382 (S.D.N.Y. 1954).

[92] 3 Robinson, *The Law of Patents for Useful Inventions* 603 (1890).

5. The fact that other competitors will be entering the marketplace.[93]
6. The defendant swore to its financial responsibility in the event of a recovery by the plaintiff.[94]
7. The business of the alleged infringer is comparatively small.[95]

The trend evident from the cases denying injunctive relief based upon a lack of showing irreparable injury seems to be that the courts will weigh heavily the calculation of a finite marketplace (even when such is not apparent) and the financial responsibility of a defendant who will be able to compensate the movant at a later date. It behooves the movant to present evidence of all types setting forth the *un*certainty of damages and the perhaps shaky financial resources of the defendant based upon defendant's past performance or based upon projected economic forecasts for the defendant's business.

C. *Balancing the Equities*

Even though the movant succeeds in demonstrating favorably a probable right and a probable wrong, he may well lose upon a balancing of equities by the court. It is truly this phase where the court's discretion is the widest. Even in this area, however, certain guidelines appear.

If the movant has waited too long to bring his plea for relief, the doctrine of laches becomes applicable.[96] An unexcused delay is sufficient reason to deny preliminary injunctive relief even though the plaintiff prevailed

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[93] Eli Lilly & Co. v. Milan Pharmaceuticals, Inc., 169 U.S.P.Q. 32 (N.D. W.Va. 1968).

[94] Tyrolean Handbag Co. v. Empress Handbag, Inc., 122 F. Supp. 299, 102 U.S.P.Q. 382 (S.D.N.Y. 1954).

[95] Sommer v. Rotary Lift Co., 58 F.2d 765 (9th Cir. 1932).

[96] Uniroyal, Inc. v. Dayl-Herring Co., 294 F. Supp. 754, 161 U.S.P.Q. 506 (E.D.N.C. 1968); Klauber Brothers, Inc. v. Lady Marlene Brassiere Corp., 285 F. Supp. 806, 157 U.S.P.Q. 338 (S.D. N.Y. 1968); Pfizer, Inc. v. International Rectifier Corp., 538 F.2d 180, 190 U.S.P.Q. 273 (8th Cir. 1976); Carter-Wallace, Inc., v. Davis-Edwards Pharmacal Corp., 443 F.2d 867, 169 U.S.P.Q. 625, 629 (2d Cir. 1971).

on all other requirements.[97] Plaintiff, therefore, should promptly seek preliminary relief and serve proper notice on the defendant under Rule 65(a) of the Federal Rules of Civil Procedure.

Another equitable factor which the court will consider is whether the awarding of a preliminary injunction will result in irreparable harm to the defendant.[98] If it does, the court sometimes is faced with a difficult decision in balancing the equities. Factors which have been considered by the court include the following:

1. The brevity of the selling season of the product would harm the defendant by denying him the right to sell.[99]
2. The fact that defendants have expended nothing in research and development and will not, themselves, be irreparably harmed.[100]
3. If the defendant is bankrupt, he will not be permitted to continue infringement even though he cannot continue in business.[101]
4. Defendant would lose its business, the goodwill of its customers, and its discharged employees would suffer.[102]

While some of the above might indicate that no preliminary injunction could issue if a defendant is irreparably injured, the court must weigh the relative injuries to the parties,[103] for inconvenience and injury to an infringer resulting from a compulsory cessation of infringing activities should not dissuade a court of equity

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[97] Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 443 F.2d 867, 169 U.S.P.Q. 625, 629 (2d Cir. 1971).

[98] Heyman Manufacturing Co. v. Electrix Corp., 200 F. Supp. 217, 131 U.S.P.Q. 387 (D. R.I. 1961); Nadya Inc., v. Majestic Metal Specialties, Inc., 127 F. Supp. 467, 104 U.S.P.Q. 109 (S.D.N.Y. 1954).

[99] Coleco Industries, Inc. v. Empire Plastic Corp., 169 U.S.P.Q. 95, 96 (S.D.N.Y. 1971).

[100] Eli Lilly & Co. v. Generix Drug Sales, Inc., 324 F. Supp. 715, 169 U.S.P.Q. 13 (S.D. Fla. 1971).

[101] Carter-Wallace, Inc., v. Davis-Edwards Pharmacal Corp., 169 U.S.P.Q. 645 (E.D.N.Y. 1971), *vacated*, 443 F.2d 867, 169 U.S.P.Q. 625 (2d Cir. 1971).

[102] Uniroyal, Inc., v. Daly-Herring Co., 294 F. Supp. 754, 161 U.S.P.Q. 506 (E.D.N.C. 1968).

[103] Nuclear-Chicago Corp. v. Nuclear Data, Inc., 173 U.S.P.Q. 326 (N.D. Ill. 1972); Doe Skin Products v. United Paper Co., 195 F.2d 356, 359, 93 U.S.P.Q. 328, 329-330 (7th Cir. 1952).

from granting a preliminary injunction in a clear case.[104] This is especially true in cases of intentional copying.[105]

III. Procedural Aspects

A. *Hearing*

Some courts have held that a hearing is not necessary in that the award or denial of a patent preliminary injunction can be determined from affidavits, briefs, and pleadings.[106] On the other hand, a substantial number of courts believe reliance on such material to be insufficient.[107] Indeed, many plaintiffs have lost their preliminary injunctive requests due to insufficient evidence presented only in affidavits and pleadings. As one court stated:

> Where such an issue of fact exists, the give and take of oral examination and cross examination is particularly necessary.[108]

The presentation of oral testimony, affidavits, and the use of pleadings should be employed thoroughly by the plaintiff in setting up his arguments.[109] This is especially true as the movant wants to avoid reversal of an award upon appeal. In the absence of oral testimony and cross-examination, the appellate courts can easily re-examine the evidence as if they were in the position of the trial judge. As one appellate court stated, in the absence of oral testimony:

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[104] Schick Dry Shaver v. Motoshaver, 21 F. Supp. 722 (D. Cal. 1938).

[105] Teledyne Industries, Inc. v. Windmere Products, Inc., 433 F. Supp. 710, 195 U.S.P.Q. 354 (S.D. Fla. 1977).

[106] Norwich Pharmacal Co. v. Veterinary Corp. of America, 296 F. Supp. 937, 159 U.S.P.Q. 758 (M.D. Ga. 1968).

[107] Heyman Manufacturing Co. v. Electrix Corp., 200 F. Supp. 217, 131 U.S.P.Q. 387, 388 (D. R.I. 1961); Plaintform Foundations, Inc. v. Stafford, 96 U.S.P.Q. 231 (S.D.N.Y. 1953); Uniroyal, Inc. v. Daly-Herring Co., 294 F. Supp. 754, 161 U.S.P.Q. 506 (E.D.N.C. 1968); Burroughs v. Hardee, 126 U.S.P.Q. 471 (E.D.S.C. 1960).

[108] Marshall Metal Products, Inc. v. Aghnides, 126 F. Supp. 850, 103 U.S.P.Q. 176, 178 (S.D.N.Y. 1954).

[109] Marshall Metal Products, Inc. v. Aghnides, 126 F. Supp. 850, 103 U.S.P.Q. 176 (S.D.N.Y. 1954).

[We are] in as good a position as a trial court was to determine whether a preliminary injunction would be justified under the proper standard.[110]

B. *Consolidation*

A risk to be considered by the plaintiff in moving for preliminary relief is the threat of consolidation of his motion into a trial on the merits under Rule 65(a) (2) of the Federal Rules of Civil Procedure. The trial judge may order advancement and consolidation either on the motion of a party or on his own motion.[111] Furthermore, and most importantly, no notice to the parties need be given.[112]

The threat of consolidation can be easily avoided if the plaintiff requests a jury trial. Under such a request, the judge is not permitted to consolidate.[113]

A well prepared defendant may well want to consider a motion for consolidation especially if the plaintiff is ill-prepared and if the defendant has solid evidence of invalidity. If a plaintiff does not wish to seek a jury trial, the plaintiff should move quickly and aggressively in preparing his case in these preliminary stages in order to be prepared in the event of consolidation. Furthermore, all evidence presented in the preliminary stages is carried into the trial at its merits.[114] Therefore, it behooves the plaintiff and the defendant to

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[110] Concord Fabrics, Inc. v. Marcus Brothers Textile Corp., 409 F.2d 1315, 1317, 161 U.S.P.Q. 3, 4 (2d Cir. 1969).

[111] Singleton v. Anson County Board of Education, 387 F.2d 849 (4th Cir. 1967).

[112] FED. R. CIV. P. 65(a)(2), which provides that consolidation may be ordered "after the commencement of the hearing." However, see Puerto Rican Farm Workers v. Eatmon, 427 F.2d 210 (5th Cir. 1970), where it was held that plaintiffs were entitled to a full hearing on the merits and if there was to be a consolidation, plaintiffs were entitled to notice.

[113] FED. R. CIV. P. 65(a)(2), which states that this rule "shall be so construed and applied as to save the parties any rights they may have to trial by jury."

[114] FED. R. CIV. P. 65(a)(2), which provides that "any evidence received upon an application for a preliminary injunction which would be admissible upon the trial on the merits becomes a part of the record on the trial and need not be repeated upon the trial."

crystalize issues as quickly as possible to avoid possible issue foreclosure due to estopping statements.

C. *Bonds*

In the event the court awards a preliminary injunction to the plaintiff, the court will require a showing, under Rule 65(c) of the Federal Rules of Civil Procedure, of financial responsibility.[115] In granting an award of preliminary relief the court may take judicial notice of the fact that the plaintiff is sufficiently solvent to be held accountable for any future damages to the defendant should the plaintiff not prevail at the trial on the merits.[116] On the other hand, the court may require the posting of an actual bond.[117]

In the latter event, it is well recognized that bonds are not easy to get and bonding companies generally require of the plaintiff a dollar-for-dollar collateral basis.[118] The court may set the amount of the bond or the parties may jointly agree to a fixed amount.[119] It has been stated by an experienced litigator in this area that a preliminary injunction bond has never been collected upon.[120]

Requiring a successful plaintiff to post a bond, especially a large one, is definitely a pyschological deterrent. Furthermore, after affrontage of the direct costs of the bond, there is the resulting impact upon the

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[115] FED. R. CIV. P. 65(c).

[116] Continental Oil Co. v. Frontier Refining Co., 338 F.2d 780 (10th Cir. 1964), where it was held that under the applicable rule the judge had discretion in the matter of requiring security and no bond was necessary in the absence of likelihood of harm.

[117] Eli Lilly & Co. v. Milan Pharmaceuticals, Inc., 169 U.S.P.Q. 32 (N.D. W.Va. 1968); Buddy Systems, Inc. v. Exer-Genie (9th Cir. Sept. 27, 1976); VCR Cold Retreading v. Schelkmann, 178 U.S.P.Q. 60 (D. Mass. 1973).

[118] "[T]he surety companies require, save in exceptional cases, [negotiable securities, cash, or government bonds] . . . in an amount equal to the entire sum at risk." FIRE, CASUALTY & SURETY SECTION BONDS C-8 (3rd Printing Sept. 1948).

[119] Waterman-Bic Pen Corp. v. Beisinger Indus. Corp., 321 F. Supp. 178, 169 U.S.P.Q. 163, 165 (S.D.N.Y. 1970).

[120] Latman, *Preliminary Injunctions in Patent, Trademark and Copyright Cases*, 60 Trademark Rptr. 506 (1970), p.510.

plaintiff's credit rating. Hence, although the plaintiff may prevail and obtain preliminary relief, it may be to defendant's clear tactical advantage to have the plaintiff placed in this position. The defendant may wish to seek the highest possible bond.

If the defendant is being sued for patent infringement and the patent in dispute is obviously invalid, it may be wise to allow the patentee to obtain a preliminary injunction while only stressing the amount of damages to be covered by plaintiff's bond. In this situation, the defendant can use the award of a preliminary injunction as an investment. For example, suppose the defendant spent approximately $100,000 developing his product and he can show the court by reference to past market performance of similar products that its market value is approximately $500,000. The plaintiff is then required to post a $500,000 bond and the defendant can divert money it would have spent marketing the product into developing and marketing other product lines. The defendant can later show the patent invalid at a trial on the merits and collect damages—lost profits—which may approach the earlier $500,000 figure.

On the other hand, courts denying preliminary relief have requested, on occasion, the posting of a suitable bond by the defendant. In one case, a Ninth Circuit district court gave the plaintiff the option of posting a bond and obtaining the injunction or declining the injunction upon deposit of a bond by the defendant.[121] Hence, it may be to the plaintiff's advantage to bring a motion for preliminary relief in that even if such relief is denied, the court may require the defendant to post a substantial bond and this may, likewise, effect an early settlement of the case.

D. *Appellate Review*

Upon a ruling by the trial court, either granting or denying preliminary relief, the losing party has the

[121] Ryan v. Ideal Toy Corp., 260 F. Supp. 828, 151 U.S.P.Q. 165 (C.D. Cal. 1966).

right to appeal the award to the appropriate circuit court.[122] Appellate courts have long stated and it has been long believed by practicing attorneys that the trial court has wide discretion in this matter and will not be reversed except on a clear showing that the trial court abused the discretion.[123]

Although the above would indicate a high approval rate by appellate courts of district court preliminary awards, the results of the 25-year survey indicate that on appeal over fifty percent (55%) of those preliminary injunctions granted by the district court *were reversed* by the appeals court whereas *all* (100%) of the preliminary injunctions denied by the district court were affirmed. Clearly, when a preliminary injunction is granted, a defendant should seriously consider an appeal. On the other hand, a plaintiff denied an award is well advised *not* to appeal unless the court clearly erred or abused its discretion.

In one case, the preliminary injunction was not only reversed but an order for dismissal was issued.[124]

IV. Tactical Considerations

A host of considerations, both legal and non-legal, face the plaintiff in determining whether or not to bring a motion for a preliminary injunction at the outset. Based upon the survey and the prior analysis of the case law, the authors present their own thoughts in this section on various tactics which may be considered, depending on the situation one who considers preliminary relief finds himself in. The authors would welcome criticism, comment and suggestions of these and other tactics from the readership pertaining to this section.

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[122] 28 U.S.C. § 1292(a).

[123] Lawrence v. St. Louis San Francisco R.R. Co., 274 U.S. 588 (1927); Simms v. Green, 161 F.2d 87 (3rd Cir. 1947); American Mercury, Inc., v. Kiely Postmaster, 19 F.2d 295 (2d Cir. 1927); Huber Baking Co. v. Stroehmann Brothers Co., 208 F.2d 464, 99 U.S.P.Q. 429 (2d Cir. 1953); Packard Instrument Co. v. Ans, Inc., 416 F.2d 943, 162 U.S.P.Q. 193, 194 (2d Cir. 1969).

[124] Triumph Hosiery Mills v. Triumph International Corp., 308 F.2d 196, 135 U.S.P.Q. 45 (2d Cir. 1962).

A. *In Filing Patent Applications*

At the outset, there are several tactics that a patent attorney can consider which would place his client in a position of prevailing on a preliminary injunction motion long prior to the actual seeking of relief.

First, when initially drafting the patent application, it becomes imperative to effect a *comprehensive* validity search. It is well worth the investment for a large corporation to conduct an extremely thorough validity search prior to the filing of an application, especially on a product with anticipated high sales. While such an approach generally cannot be taken when the attorney is representing an individual, the attorney should still endeavor to provide a reasonably effective search at a cost that the client can afford.

However, in either case (whether a large corporate client or an individual), it behooves the attorney to place in the actual patent application all of the prior art which he uncovers and to distinguish the invention in the specification *of the patent application* from that prior art. This gives an obvious advantage in the subsequent motion for preliminary relief, in that if the prior art has been considered by the Patent and Trademark Office, the trial judge will accord such consideration of the art great weight. To a Court of Equity, the placing of this substantial prior art in the specification of the application would appear to manifest the good faith or "clean hands" with which the plaintiff has filed his application for patent.

The patent attorney might also delay filing the application until his client's product has reached the production stage (but prior to maturation of any statutory bars, including foreign bars if seeking patent protection abroad is anticipated). In other words, an application should be filed on the actual configuration of the product which is to be marketed. Such an application will then correspond, element for element, to the marketed product. Often, an attorney will file too early and will not

include important subsequently added features of the product nor a drawing that embodies the final product. In active fields in which early filing dates are crucial, attorneys should continue to file as soon as possible, but should also strongly consider filing continuation-in-part applications and improvement applications (especially within the one year grace period) so that the production model is not only covered by the claims but also shown in the drawings.

In a hearing for preliminary relief, if the plaintiff's *own patent* does not identically conform to the plaintiff's *own product*, he generally must explain the differences to the court in order to impress upon that court the viability of his evidence of acquiescence. This hurdle can be avoided by delayed filing. Delayed filing is also prudent as identical copying of a successful product by a defendant is becoming more prevalent.

The obvious risk, on the other hand, is that by the time the patent issues, the infringer's copying may be well established. In this situation, the patentee is given the opportunity to counter the risk by drafting claims directly on the infringing product while the application is still in prosecution. The patentee can then petition the Patent and Trademark Office to make his application special based upon defendant's infringement.[125] It is desirable that by the time the patent issues the plaintiff's own product corresponds to the configuration in the application and that as many claims as possible are directly applicable to the defendant's product. In this situation, the defendant's product will infringe the patent on a clear reading of the claims.

Furthermore, the matter of several months it takes the Patent and Trademark Office to issue the patent on a made special application provides sufficient time for the plaintiff to prepare a solid case for the award of a preliminary injunction so that upon immediate issuance of

[125] Manual of Patent Examining Procedure, Rev. 51, Jan. 1977, Sec. 708.02.

the patent the plaintiff is in a strong legal and factual position. Clearly, the plaintiff is not guilty of laches by waiting for his patent to issue.

B. *In Preparation of Filing for Preliminary Relief*

Generally, after the patent issues and the plaintiff observes an infringing product, he is wise to postpone sending a threatening letter until he has determined the strength of his preliminary relief position. Specifically, the plaintiff should proceed immediately, under counsel, to catalog the facts under the doctrines set forth in the preceding sections. This chronicling of facts should be as thorough and meaningful as possible. Simultaneously, the plaintiff would be wise to perform a *validity* search on his own patent. He knows the defendant will do this and he may as well become aware of any difficulties, so that if need be, an appropriate reissue application of the patent can be filed without necessity of complicated and expensive civil litigation.

During the time prior to filing for a preliminary relief motion, the plaintiff should embark upon a campaign of notifying the public of his patent rights in order to garner evidence of public acquiescence. It is imperative that advertisements, operating manuals, brochures, etc. all be embellished with notice of the U.S. Letters patent number and other supportive language. Existing advertising should be immediately changed to reflect such notice. Furthermore, the novelty and the originality, especially as to any break-through features and advantages covered by the patent, should be highlighted and emphasized to the public. The plaintiff should elicit favorable press and editorials. If there were ever a time to seek reviews favorable to the plaintiff's product, this would be that time.

During this period, the plaintiff should instruct members of its organization to document any instances of confusion and of doubts raised by suppliers or distributors as to the alleged infringing product and to carefully

document this with supporting affidavits in order to freeze the testimony, especially of third persons not related to plaintiff or defendant. This evidence does arise and must be preserved.

It is also imperative that the plaintiff document any and all types of irreparable injury. Such irreparable injury includes possible confusion between the plaintiff's and the defendant's products, documentation of sales and growth of plaintiff's product, and warranty problems (is defendant's product being turned into plaintiff's service centers?).

The time required to prepare a case in support of a motion for preliminary injunction may take several weeks to a month and the plaintiff should consider withholding notice to the defendant during this time. During this time, the plaintiff has been seeking information on the strength of his patent through a validity search, ascertaining his storehouse of facts (or lack thereof), and setting the stage for the motion by informing the public of the various patented features of his product and how important those features are, hopefully thereby eliciting good reviews. After the plaintiff is confident of his position, he should give prompt notice by means of an infringement letter.

As previously mentioned, the single most important factor affecting patent preliminary relief appears to be the choice of forum in which to bring suit. Therefore, prior to commencing litigation, the patentee should seek a favorable jurisdiction such as the Ninth or Fifth Circuit (see Table 1). On the other hand, the defendant anticipating the possibility of a preliminary injunction should endeavor to force the lawsuit through a declaratory judgment action into a jurisdiction not favorable to the patentee, such as the Second or Third Circuit. The plaintiff may desire to eliminate this possibility of declaratory judgment action by filing for preliminary relief in a selected forum without sending an infringement notice letter to the defendant.

C. *In Filing for Preliminary Relief*

After preparing his case and selecting a jurisdiction, the plaintiff is set to file his complaint. It appears to be advantageous to file a verified complaint, setting forth in the complaint itself as many facts as are known. In the *Teledyne* case, the complaint was 30 pages long, not including exhibits, and facts as to as many of the elements of validity and infringement were set forth at that time. Attached exhibits in the *Teledyne* case included:

1. Favorable reviews and editorial comments on the Shower Massage product;
2. Examples of advertisisng of the Shower Massage by Water-Pik,® on which Teledyne spent 72 million dollars (the number and the names of magazines were listed, examples of direct mailing, number and names of television shows on which the product was advertised, etc.);
3. Pictures comparing the two products;
4. Pictures of the plaintiff's and defendant's product in stores (where they were sold side by side);
5. Schematic diagrams showing both the plaintiff's and defendant's products broken down and how the elements correspond;
6. Documentation of the extent of product sales;
7. A list of nationwide service centers where it was documented that confused customers had brought the defendant's product to be repaired; and,
8. Product failure rates and warranty returns.

The verified complaint in the *Teledyne* case contained as many facts as could be gathered which pertained to commercial success, indefiniteness of the market, goodwill established around the plaintiff's product (as shown by nationwide surveys, etc.) and to other considerations.

After filing the verified complaint and request for preliminary relief, the court is obliged to provide priority to the case under its priority rules. In the *Teledyne* case, the judge bifurcated the presentations of evidence. Specifically, the judge first scheduled a presentation of the plaintiff's case to ascertain whether or not it would be necessary for the defendant to present its case.

In presenting its case, the plaintiff should draw forth and produce all the information it has in support of the previously stated patent preliminary injunction requirements. Title, of course, is easily proven. Validity, infringement, and irreparable harm likewise should not be difficult to prove. If they are, then plaintiff *should not* be seeking preliminary relief. A series of precise requests for admissions to the defendant may well make the plaintiff's presentation easier and less complex. For example, if the defendant admits infringement of the patent, the plaintiff may then concentrate on maintaining patent validity. Admissions of infringement in preliminary requests have occurred in the past.[126]

Conclusion

The award of preliminary injunctive relief in patent cases appears to be much more frequent than is popularly believed. Regretably, the overriding consideration in filing for preliminary relief is in the selection of the forum. Upon a review of twenty-five years of patent cases wherein preliminary injunctions were sought, it is the authors' belief that such a distinct difference between the circuits does substantial harm to the overall fairness advocated by Equity. It is also the authors' contention that the vast differences between, for example, the Second and Fifth Circuits in the percentage of decrees of preliminary relief, injures the meaning of law. There will be a race in the future between patentees who seek Fifth Circuit injunctive relief and defendants who seek Second Circuit declaratory judgments. Thus, justice will take a backseat to tactics and opportunity. Although we operate under a system of government which sought to eliminate "Balkanism," we can certainly say, based on the 25-year survey, that such a state now reigns among the circuits, at least regarding the allowance or denial of preliminary patent requests.

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[126] FED. R. CIV. P. 36(b).

In the spirit of having a single national set of standards for the analysis of patent preliminary relief, it is the authors' position that that single standard of proof should be "beyond a reasonable doubt" as to the title requirement, and "beyond question" as to validity and infringement. Such standards correspond with the majority of United States District case law. Meeting these burdens of proof should be the goal an attorney strives for, while a judge should keep them *all* at the forefront of his mind in deciding whether to award preliminary relief to enjoin patent infringement.

The results of the 25-year survey indicate that one moving for a preliminary injunction must demonstrate to the court that he has title, that the patent is valid and infringed, that he will suffer irreparable injury should the injunction not issue, and that the balance of equities tips in his favor. In the presentation of each of these elements, equities appear to be invaluable and the movant should endeavor to offer to the court *all* that can be gleaned from the facts of the dispute.

The defendant, on the other hand, must demonstrate that the balance of hardships tips against him and thus indicate that the hardship in not preventing irreparable injury to the movant is outweighed by the concomitant harm to the defendant should the preliminary injunction issue. Defenses which would move the court to declare the patent invalid or refuse to enforce the patent should also be vigorously set forth.

TABLE 1

PATENT PRELIMINARY INJUNCTIONS

A 25-Year Survey

(January, 1953—September, 1978)

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Breakdown By Circuit

	DISTRICT COURT				CIRCUIT COURT*					
					Upheld		Vacated			
Circuit	Total Pre. Inj. Cases	Pre. Inj. Granted	Pre. Inj. Denied	Percent Granted	G	D	G	D	% Aff'd	Total % Granted
1	2	1	1	50%	—	—	—	—	—	50%
2	25	3	22	12%	—	—	1	—	0%	8%
3	5	1	4	20%	—	—	—	—	—	20%
4	3	0	3	0%	—	—	—	—	—	0%
5	7	6	1	86%	2	1	—	—	100%	86%
6	1	1	0	100%	—	—	—	—	—	100%
7	4	3	1	75%	1	1	2	—	50%	25%
8	1	1	0	100%	—	—	1	—	0%	0%
9	5	5	0	100%	1	—	1	—	50%	80%
10	0	0	0	—	—	—	—	—	—	—
D.C.	1	1	0	100%	—	—	—	—	—	100%
TOTALS:	54	22	32	41%	4	2	5	0	55%**	32%

* G and D indicate the number of preliminary injunctions granted or denied which were either upheld or vacated on appeal.

** 44% of granted preliminary injunctions which were appealed were affirmed (4 of 9), while 100% of preliminary injunctions denied were affirmed on appeal (2 of 2).

TABLE 2

PATENT PRELIMINARY INJUNCTIONS

A 25-Year Survey

(January, 1953 - September, 1978)

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Burden of Proof Requirements •

Circuit	*Validity*	*Infringement*
1st	Beyond Question [1]	Beyond Question [1]
2nd	Beyond Question [2]	Beyond Question [2]
3rd	Beyond Question [3]	Reasonably Likely [4]
4th	Beyond Question [5]	Beyond Question [5]
5th	Beyond Question [6]	Beyond Question [6]
6th	Very Probably [7]	Very Probably [8]
7th	Strong Probability [9]	Strong Probability [9]
8th	———	Reasonably Clear [10]
9th	Beyond Question [11]	Beyond Question [11]
10th	Beyond Question [12]	Beyond Question [12]
D.C.	———	———

• In circuits where no cases within the 25 year period examined were found to espouse the burden of proof requirements, resort was had to pre-1953 cases.

[1] Leavitt v. The McBee Co., 124 F.2d 938, 939, 52 U.S.P.Q. 193, 194 (1st Cir. 1942); Heyman Manufacturing Co., v. Electrix Corp., 200 F. Supp. 217, 131 U.S.P.Q. 387 (D. R.I. 1961).

[2] Simpson Bros., Inc. v. Blancard & Co., 22 F.2d 498, 499 (2d Cir. 1927); Coleco Industries, Inc. v. Empire Plastic Corp., 169 U.S.P.Q. 94 (S.D.N.Y. 1971); H. Kohnstamm & Co. v. Allied Chemical Corp., 182 U.S.P.Q. 360 (S.D.N.Y. 1973). Espousing different standards are: Owens v. American Stereographic Corp., 116 F. Supp. 406, 99 U.S.P.Q. 157 (S.D.N.Y. 1953) (infringement must be *"reasonably clear"* and and patent validity must be shown by *"clear and convincing"* evidence); Tyrolean Handbag Co. v. Empress Hand Bag, Inc., 122 F. Supp. 299, 102 U.S.P.Q. 382 (S.D.N.Y. 1954) (patent validity must be shown by *"clear and convincing"* evidence); Marshall Metal Products, Inc. v. Aghnides, 126 F. Supp. 850, 103 U.S.P.Q. 176 (S.D. N.Y. 1954) (both infringment and patent validity must be shown by *"clear and convincing"* evidence); Singer Manufacturing Co., v. Better Service Sewing Machine Co., 131 F. Supp. 146, 105 U.S.P.Q. 190 (S.D.N.Y. 1955) (patent validity must be shown by *"clear and convincing"* evidence); Loctite Corp. v. B. Jadow & Sons, Inc., 177 U.S.P.Q. 410 (S.D.N.Y. 1973) (preliminary injunction will not issue in a patent infringement suit "except when the patent is clearly found to be valid and infringed").

[3] Standard Paint Co. v. Reynolds, 43 F. 304, 305 (3rd Cir. 1890) (no preliminary injunction should issue "where the answering affidavits show a reasonable doubt about the . . . validity of the . . . patent.").

[4] Knoll International, Inc. v. Continental Imports, Inc., 192 U.S.P.Q. 502 (E.D. Penn. 1976).

[5] Uniroyal, Inc., v. Daly-Herring Co., 294 F. Supp. 754, 161 U.S.P.Q. 506 (E.D.N.C. 1968), citing with approval Judge Learned Hand's statement in Simpson Bros., Inc. v. Blancard & Co., 22 F.2d 498, 499 (2d Cir. 1927), that the patent must be "beyond question valid and infringed" before a preliminary injunction will issue.

[6] Norwich Pharmacal Co., v. International Brokers, Inc., 159 U.S.P.Q. 417 (N.D. Ga. 1968); Eli Lilly and Co., v. Generix Drug Sales, Inc., 324 F. Supp. 715, 169 U.S.P.Q. 13 (S.D. Fla. 1971), *aff'd* as to granting preliminary injunctions, *vacated* as to permanent injunction, 460 F.2d 1096, 174 U.S.P.Q. 65 (5th Cir. 1972); Julien v. Gomez & Andre Tractor Repairs, Inc., 196 U.S.P.Q. 224 (M.D. La. 1977); Teledyne Industries, Inc. v. Windmere Products, Inc., 433 F. Supp. 710, 195 U.S.P.Q. 354 (S.D. Fla. 1977).

[7] Gleaned from the texts of City of Grand Rapids v. Warren Bros. Co., 196 F. 892, 894-897 (6th Cir. 1912), and Mueller v. Wolfinger, 68 F. Supp. 486, 69 U.S.P.Q. 311 (S.D. Ohio 1946).

[8] Gordon Johnson Co., v. Hunt, 109 F. Supp. 571, 96 U.S.P.Q. 92 (N.D. Ohio 1952); City of Grand Rapids v. Warren Bros. Co., 196 F. 892 (6th Cir. 1912); Crescent Specialty Co. v. National Fireworks Distributing Co., 219 F. 130 (6th Cir. 1915).

[9] Nuclear-Chicago Corp. v. Nuclear Data, Inc., 173 U.S.P.Q. 326 (N.D. Ill. 1972), *rev'd*, 465 F.2d 428, 174 U.S.P.Q. 381 (7th Cir. 1972). See also, Artmoore Co., v. Dayless Manufacturing Co., 100 F. Supp. 110, 90 U.S.P.Q. 300 (N.D. Ill. 1951) (infringement must be "reasonably clear"); Standard Elevator v. Crane Elevator Co., 56 F. 718, 719 (7th Cir. 1893) (standard used was "without reasonable doubt"); Flintkote Co., v. Philip Carey Co., 13 F.2d 850 (7th Cir. 1926) (per curiam) ("beyond question" was the standard used).

[10] Diamond Power Specialty Corp. v. Bayer Co., 95 F.2d 541, 37 U.S.P.Q. 233 (8th Cir. 1938).

[11] Pacific Cage & Screen Co. v. Continental Cage Corp., 259 F.2d 87, 119 U.S.P.Q. 338 (9th Cir. 1958); Mayview Corp. v. Rodstein, 480 F.2d 714, 178 U.S.P.Q. 449 (9th Cir. 1973).

[12] Stoody Co. v. Osage Metal Co., 95 F.2d 592, 593, 37 U.S.P.Q. 169, 170 (10th Cir. 1938), citing Simpson Bros., Inc. v. Blancard & Co., 22 F.2d 498, 499 (2d Cir. 1927) (patent must be beyond question valid and infringed).

TABLE 3

PATENT PRELIMINARY INJUNCTIONS

A 25-Year Survey

(January, 1953 - September, 1978)

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Breakdown By Age Of Patent •

Summary of Results:

Category	*Granted*	*Denied*	*Percent Granted*
A (0-5 years old)	2	23	8%
B (5-10 years old)	2	2	50%
C(10 years or older)	10	8	56%

Breakdown by Years:

Age	*Number of Patents*	*Granted*	*Denied*	*Percent Granted*
1	11	1••	10	9%
2	4	1	3	25%
3	3	0	3	0%
4	4	1	3	25%
5	1	1	0	100%
6	—	—	—	—
7	—	—	—	—
8	—	—	—	—
9	1	1	0	100%
10	1	0	1	0%
11	4	3	1	75%
12	4	3	1	75%
13	4	1	3	25%
14	1	0	1	0%
15	2	1	1	50%
16 or older	6	2	4	33%

• This table reflects the results after entire disposition of the case. For example, if the preliminary injunction was granted and then vacated on appeal, it is indicated here as denied.

•• This case was later overruled.

TABLE 4

PATENT PRELIMINARY INJUNCTIONS

A 25-Year Survey

(January, 1953 - September, 1978)

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Reasons For Denials *

Reason	*Number of Occurrences*
1. The patent was not clearly valid.	17
2. No showing of irreparable harm.	15
3. No demonstration of acquiescence by the industry or the public.	7
4. No infringement was shown.	6
5. Insufficient evidence upon which to grant or deny a preliminary injunction.	3
6. The patentee was guilty of laches.	2
7. The patentee misused the patent.	2

* This table reflects the fact that preliminary injunctions were often denied for a number of reasons. It therefore contains some overlap and the total number of reasons for denials does not equal the number of cases where preliminary injunctions were denied.

EXAMINING THE EXTRA BURDEN IMPOSED ON A PATENTEE WHO SEEKS A PRELIMINARY INJUNCTION

GERALD SOBEL*

INTRODUCTION

A patentee who seeks a preliminary injunction against an alleged infringer must satisfy a burden of unusual stringency. In addition to the elements traditionally required for a preliminary injunction,[1] the patentee must show that his patent is "beyond question valid and infringed."[2] In contrast, nonpatent litigants seeking preliminary injunctive relief must show no more than a likelihood of success on the merits.[3]

The higher standard for preliminary injunctive relief in patent infringement cases has so long been a part of the jurisprudence[4] that it is taken for granted. The rationales for maintaining the stringent standard are skepticism concerning the correctness of Patent Office determinations of patentability[5] and the desire to foster competition by ensuring that technical matter that does not truly comprise an invention remains freely available for use.[6] After reviewing the history and effect of the current standards for obtaining preliminary injunctive relief in patent and nonpatent litigation, this Article analyzes these rationales in light of conflicting considerations, including the express and implied rights of patentees reflected in the Patent Code, the policy of fostering innovation, and the jurisprudence of individual merit. This analysis indicates that the extra burden imposed on patentees should be eliminated.

I. CURRENT STANDARDS FOR OBTAINING PRELIMINARY INJUNCTIONS

A. Nonpatent Cases

The standard that most courts currently require of nonpatent litigants seeking preliminary injunctions is less stringent than that required of patentees seeking such relief. Typically courts require the movant in nonpatent cases to demonstrate a likelihood or probability of success on the merits, a likelihood of irreparable injury if relief is denied, an injury outweighing any harm to the other party from granting the injunction, and a lack of adverse effect on the public interest if the injunction is granted.[7]

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1. *See infra* text accompanying notes 7-9.

2. Simson Bros. v. Blancard & Co., 22 F.2d 498, 499 (2d Cir. 1927). *See infra* text accompanying notes 21-27.

3. *See infra* text accompanying notes 7-9.

4. *See infra* text accompanying notes 21-28.

5. *See* Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 443 F.2d 867, 871-72 (2d Cir. 1971) (noting "free rein often exercised by [Patent Office] Examiners in their use of the concept of invention") (quoting Graham v. John Deere Co., 383 U.S. 1, 18 (1966)), *cert. denied*, 412 U.S. 929 (1973). *See infra* text accompanying notes 134-36.

6. *See infra* text accompanying notes 119-26.

7. *See* Harris v. Wilters, 596 F.2d 678, 680 (5th Cir. 1979) (prisoner sought injunction to require state to pay litigation expenses); North Carolina State Ports Auth. v. Dart Containerline Co., 592 F.2d 749, 750 (4th Cir. 1979) (state sought to enjoin application of provisions of common carrier's pending tariff); Kolz v. Board of Educ., 576 F.2d 747, 748-49 (7th Cir. 1978) (school teachers sought to enjoin transfer from one school to another); Constructors Ass'n v. Kreps, 573 F.2d 811, 815 (3d Cir. 1978) (association sought to enjoin application of provisions of federal law or government contracts); UV Indus. v. Posner, 466 F. Supp. 1251, 1255 (D. Me. 1979) (corporation sought injunction to prevent purchase of its stock by another corporation). For a discussion of the four criteria required to obtain a preliminary injunction, see 7 J. MOORE, MOORE'S FEDERAL PRACTICE

Several federal circuit courts follow an even more relaxed standard. The Second Circuit, for example, like other courts, requires nonpatent movants to prove that irreparable harm will result if relief is not granted.[8] In addition, however, it requires only that the movant show either a likelihood of success on the merits, or sufficiently serious questions on the merits to establish a fair ground for litigation with the equities in favor of the party requesting preliminary relief.[9]

B. Patent Cases

In contrast to the general standard for a preliminary injunction, the standard for patentees seeking injunctive relief pendente lite is more burdensome. In order to show a likelihood of success on the merits, a patentee must prove "beyond question" the validity and infringement of the patent.[10] Only two classes of patents have proved likely to satisfy this requirement: those previously adjudicated valid and those in whose validity industry has acquiesced.[11] After meeting this requirement, a patentee must also demonstrate the remaining elements of the general standard.[12]

The "beyond question" rule, defined by the Court of Appeals for the Second Circuit,[13] has been followed in a majority of the circuits.[14] Ac-

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¶ 65.04[1], at 65-39 (2d ed. 1982) and C. WRIGHT & A. MILLER, FEDERAL PRACTICE AND PROCEDURE § 2948, at 430-66 (1973).

8. Jackson Dairy, Inc. v. H.P. Hood & Sons, 596 F.2d 70, 72 (2d Cir. 1979). Irreparable injury is "injury for which a monetary award cannot be adequate compensation." *Id.* The court noted disagreement about how likely and imminent the threatened irreparable injury must be, with alternatives ranging from "possible" to "probable"—the latter having been defined as " 'not remote or speculative but . . . actual and imminent.' " *Id.* (quoting New York v. Nuclear Regulatory Comm'n, 550 F.2d 745, 755 (2d Cir. 1977)).

9. Jackson Dairy, Inc. v. H.P. Hood & Sons, 596 F.2d 70, 72 (2d Cir. 1979). Other circuits also have reduced the standard for success on the merits when the balance of hardships favored the plaintiff. *See* Campbell "66" Express, Inc. v. Rundel, 597 F.2d 125, 127-28 (8th Cir. 1979) (preliminary injunction granted on showing of probable success on merits and possible irreparable damage); Brink's, Inc. v. Board of Governors of the Fed. Reserve, 466 F. Supp. 112, 115 (D.D.C. 1979) (preliminary injunction would issue on substantial case on merits and showing of other three factors); People v. City of South Lake Tahoe, 466 F. Supp. 527, 543-44 (E.D. Cal. 1978) (preliminary injunction denied for failure to show irreparable harm or equities favoring plaintiff).

10. *See, e.g.*, Mayview Corp. v. Rodstein, 480 F.2d 714, 717 (9th Cir. 1973); Eli Lilly & Co. v. Generix Drug Sales, Inc., 460 F.2d 1096, 1099 (5th Cir. 1972); Frommelt Indus. v. W.B. McGuire Co., 504 F. Supp. 1180, 1184 (N.D.N.Y. 1981). *See also infra* note 15 and accompanying text.

11. Rosenberg v. Groov-Pin Corp., 81 F.2d 46, 47 (2d Cir. 1936).

12. *See supra* note 7 and accompanying text. *See infra* notes 21-24 and accompanying text.

13. *See infra* notes 21-28 and accompanying text.

14. Mayview Corp. v. Rodstein, 480 F.2d 714, 717 (9th Cir. 1973) (preliminary injunction denied unless patent valid beyond question); Eli Lilly & Co. v. Generix Drug Sales, Inc., 460 F.2d 1096, 1099 (5th Cir. 1972) (preliminary injunction denied unless patent valid beyond question and infringed); Pacific Cage & Screen Co. v. Continental Cage Corp., 259 F.2d 87, 88 (9th Cir. 1958) (dicta) (same); Leavitt v. McBee Co., 124 F.2d 938, 939-40 (1st Cir. 1942) (same); Hoeme v. Jeoffroy, 100 F.2d 225, 226 (5th Cir. 1938) (same); Stoody Co. v. Osage Metal Co., 95 F.2d 592, 593 (10th Cir. 1938) (preliminary injunction denied unless patent is "clearly and convincingly" valid); Zenith Labs., Inc. v. Eli Lilly & Co., 460 F. Supp. 812, 820 (D.N.J. 1978) (preliminary injunction denied unless patent valid beyond question and infringed), *aff'd sub nom.* Eli Lilly & Co. v. Premo

cording to a 1978 survey of the standard for preliminary relief in patent infringement cases, seven circuits apply the "beyond question" test and two circuits apply standards similar to this test.[15] The Eighth Circuit has applied a "reasonably clear" standard to the issue of infringement as distinct from validity.[16] The Third Circuit recently declined to apply the "beyond question" standard, and instead applied the general test for preliminary injunctions—reasonable probability of success on the merits—to a patent infringement case.[17] Federal district courts in the Third Circuit, however, more recently have applied the "beyond question" test.[18]

With regard to the other requirements for obtaining a preliminary injunction, there is currently some disagreement about whether the mere fact of infringement of the patentee's right of exclusivity is enough to establish irreparable injury, or whether, as is more commonly held, something more need be shown to establish the inadequacy of a monetary recovery.[19] There is little in the patent cases on the issues of balancing the equities and identifying the public interest. One case that did address these questions held that the equities and public interest favored a preliminary injunction because denial of relief would encourage others to infringe, would drain the patent-holder's profits by increased litigation costs, and would discourage further research and development.[20]

Pharmaceutical Labs., Inc., 630 F.2d 120 (3d Cir.), *cert. denied*, 449 U.S. 1014 (1980); Uniroyal, Inc. v. Daly-Herring Co., 294 F. Supp. 754, 759 (E.D.N.C. 1968) (same); Heyman Mfg. Co. v. Electrix Corp., 200 F. Supp. 217, 218 (D.R.I. 1961) (same).

15. *See* Dorr & Duft, *Patent Preliminary Injunctive Relief*, 60 J. PAT. OFF. SOC'Y 598, 632-33 (1978) (25-year survey of preliminary injunctions in patent suits). The Sixth Circuit was characterized as using a "very probable" standard for determining patent validity and infringement; the Seventh Circuit, a "strong probability" standard. *Id.* at 632.

16. *See* Diamond Power Specialty Corp. v. Bayer Co., 95 F.2d 541 (8th Cir. 1938).

17. Eli Lilly & Co. v. Premo Pharmaceutical Labs., Inc., 630 F.2d 120 (3d Cir.), *cert. denied*, 449 U.S. 1014 (1980).

18. *See, e.g.*, Rohm & Haas Co. v. Mobil Oil Corp., 525 F. Supp. 1298, 1302 (D. Del. 1981) (preliminary injunction requires proof that patent valid beyond question and infringed); Jenn-Air Corp. v. Modern Maid Co., 499 F. Supp. 320, 322 (D. Del. 1980) (same), *aff'd mem.*, 659 F.2d 1068 (3d Cir. 1981). *See also* Frommelt Indus. v. W.B. McGuire Co., 504 F. Supp. 1180, 1184 (N.D.N.Y. 1981) (preliminary injunction requires proof that patent valid beyond question and infringed).

19. *Compare* Zenith Labs., Inc. v. Eli Lilly & Co., 460 F. Supp. 812, 825-26 (D.N.J. 1978) (strong showing of other requirements for preliminary injunction justifies relief based on invasion of patent rights as requisite irreparable injury), *aff'd sub nom.* Eli Lilly & Co. v. Premo Pharmaceutical Labs., Inc., 630 F.2d 120 (3d Cir.), *cert. denied*, 449 U.S. 1014 (1980) *and* Teledyne Indus. v. Windmere Prods., 433 F. Supp. 710, 739-40 (S.D. Fla. 1977) (invasion of exclusive patent right constitutes irreparable injury) *with* Nuclear-Chicago Corp. v. Nuclear Data, Inc., 465 F.2d 428, 429-30 (7th Cir. 1972) (alleged invasion of patent does not constitute irreparable injury); Signode Corp. v. Weld-Loc Sys., 216 U.S.P.Q. (BNA) 310, 312 (N.D. Ill. May 27, 1982) (patentee must meet substantially heavier burden of proving irreparable injury); Frommelt Indus. v. W.B. McGuire Co., 504 F. Supp. 1180, 1184-85 (N.D.N.Y. 1981) (irreparable harm not shown where monetary damages ascertainable and available) *and* Heyman Mfg. Co. v. Electrix Corp., 200 F. Supp. 217, 218 (D.R.I. 1961) (alleged invasion of patent not irreparable harm if monetary damages available).

20. Zenith Labs., Inc. v. Eli Lilly & Co., 460 F. Supp. 812, 826 (D.N.J. 1978), *aff'd sub nom.* Eli Lilly & Co. v. Premo Pharmaceutical Labs., Inc., 630 F.2d 120 (3d Cir.), *cert. denied*, 449 U.S. 1014 (1980). The dispute in *Zenith* involved the validity and infringement of the patents on two antibi-

II. HISTORY OF THE CURRENT STANDARDS

The leading case law on the standard for preliminary injunctive relief in patent cases consists of *Simson Bros. v. Blancard & Co.*[21] and *Rosenberg v. Groov-Pin Corp.*,[22] two decisions written by Judge Learned Hand for the Court of Appeals for the Second Circuit. In *Simson,* decided in 1927, the court articulated the classic statement of the rule: a preliminary injunction should be granted only when the patent is "beyond question valid and infringed."[23] In *Rosenberg,* decided nine years later, the court stated that "in the absence of long acquiescence or adjudication [a preliminary] injunction will not go."[24] Notwithstanding the presumption of validity generally granted to an issued patent,[25] the court noted that a competitor has a greater incentive than a patent examiner to exhaust prior art references.[26]

The standard for preliminary injunctions in patent suits that emerged from *Simson* and *Rosenberg,* therefore, required proof beyond doubt of the validity and infringement of the patent. These decisions identified two classes of patents likely to satisfy this test: those previously adjudicated valid and those in whose validity the industry had acquiesced.[27] The

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otic drugs. *Id.* at 814. Eli Lilly established the patents' validity by presenting evidence of industry acquiescence. *See id.* at 822. The court viewed Zenith's admissions that it solicited orders and sold the disputed antibiotics as admissions of infringement. *See id.* at 825. The court found that the invasion of Eli Lilly's patents constituted irreparable harm. *See id.* In support of its decision to grant a preliminary injunction, the court in *Zenith* cited public interest factors, including the following: Eli Lilly's initial development and continued testing of the antibiotics; Eli Lilly's potential lost profits if Zenith were allowed to continue its infringement; the common practice of drug companies entering the market with similar products while the original patent is being challenged; and the costs of continued litigation, which would deplete Eli Lilly's resources, and thereby hinder research and development. *See id.*

21. 22 F.2d 498 (2d Cir. 1927).

22. 81 F.2d 46 (2d Cir. 1936).

23. Simson Bros. v. Blancard & Co., 22 F.2d 498, 499 (2d Cir. 1927). The court reviewed prior art references, questioned whether the jewelry setting patent in issue had in fact been invented, and held that preliminary relief was unwarranted. *Id.*

24. Rosenberg v. Groov-Pin Corp., 81 F.2d 46, 47 (2d Cir. 1936). Of the two patents for metal pins allegedly infringed, one had previously been adjudicated valid. The question of infringement, however, hinged on whether the disputed material had the same performance capability as the patented material. *Id.* at 46. Because the court was not willing to decide this factual issue on the affidavits, a trial was necessary and preliminary injunctive relief was denied. *Id.* at 48.

25. *Id.* at 47.

26. *Id.* The court in *Rosenberg* stated that industry acquiescence was the equivalent of adjudication. *Id.* According to Judge Hand, the rationale for equating acquiescence with adjudication is that industry competitors would naturally have contested a patent of doubtful validity. *Id.* at 48. In this case, the new prior art reference introduced by the alleged infringer on appeal cast doubt on the validity of the patent and injunctive relief was denied. *Id.* at 46.

Perhaps another explanation for the courts' reluctance to grant preliminary relief in patent cases is the difficulty of the subject matter. Focusing on the question of infringement, one nineteenth century court referred to the difficult legal questions involved, and the "painful necessity of spending our whole vacations in anticipating and duplicating these long and difficult investigations, and trying the merits of every case on these preliminary motions." Parker v. Sears, 18 F. Cas. 1159, 1160-61 (E.D. Pa. 1850) (No. 10,748).

27. *See supra* note 11 and accompanying text.

requirements for preliminary injunctions enunciated in these cases were reaffirmed in 1971 by the Second Circuit in *Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp.*[28]

The court in the *Simson* and *Carter-Wallace* decisions relied on nineteenth and early twentieth century cases to support the stringent rule on patent validity.[29] The earliest case cited[30] refers to an 1880 decision in which a district court noted that for more than half a century a movant in a patent case had been required to show that his patent had been in use, and undisputed, for long enough to establish prima facie its validity.[31] In fact, even earlier cases had required that preliminary injunctive relief be denied "if there were any real doubts" concerning the patent's validity.[32] Courts also recognized that exclusive possession of the patent right for a considerable time warranted the issuance of a preliminary injunction without the need to adjudicate the validity of the patent.[33]

The stringent test for infringement is found in early twentieth century cases as well. A "fair" doubt regarding infringement has precluded injunctive relief.[34] Without addressing the standard for establishing infringement as a separate element, one court stated that a case wholly free from reasonable doubt was necessary for a grant of preliminary injunctive relief.[35]

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28. 443 F.2d 867 (2d Cir. 1971), *cert. denied*, 412 U.S. 929 (1973). Citing Judge Hand's rationale in *Rosenberg* that competitors are better investigators of patent validity than Patent Office examiners, the court in *Carter-Wallace* noted that "more than 80% of patent infringement actions on appeal result in a determination that the patent sued upon is invalid." *Id.* at 872.

29. *See* Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 443 F.2d 867, 871 (2d Cir. 1971), *cert. denied*, 412 U.S. 929 (1973); Simson Bros. v. Blancard & Co., 22 F.2d 498, 499 (2d Cir. 1927).

30. Dickerson v. De la Vergne Refrigerating Mach. Co., 35 F. 143 (C.C.S.D.N.Y. 1888).

31. Kirby Bung Mfg. Co. v. White, 1 F. 604, 606 (C.C.E.D. Mo. 1880), *cited in id.* at 144.

32. *See* Thomas v. Weeks, 23 F. Cas. 978, 980 (C.C.S.D.N.Y. 1827) (No. 13,914). *See also* Grover & Baker Sewing Mach. Co. v. Williams, 11 F. Cas. 83, 87 (C.C.D. Mass. 1860) (No. 5,847) (substantial doubts as to validity of plaintiffs' right or defendants' alleged infringement precluded grant of preliminary injunction); Winans v. Eaton, 30 F. Cas. 262, 264 (C.C.N.D.N.Y. 1854) (No. 17,861) (reasonable doubt surrounding originality of improvement precluded issuance of preliminary injunction); Isaacs v. Cooper, 13 F. Cas. 153 (C.C. Pa. 1821) (glaring defects in patent precluded grant of preliminary injunction against alleged infringer). *Cf.* Irwin v. Dane, 13 F. Cas. 116, 117 (C.C.N.D. Ill. 1871) (No. 7,081) (given greater likelihood of substantial or irreparable injury to complainant than to defendant, showing of "prima facie case of infringement" sufficient for preliminary injunction). Nineteenth century courts also noted that preliminary injunctive relief could be denied on a "clear" showing of infringement. *See* Hodge v. Hudson River R.R., 12 F. Cas. 276, 278 (C.C.S.D.N.Y. 1868) (No. 6,560); Potter v. Muller, 19 F. Cas. 1170, 1170 (C.C.S.D. Ohio 1864) (No. 11,334); Poppenhusen v. New York Gutta Percha Comb Co., 19 F. Cas. 1056, 1057 (C.C.S.D.N.Y. 1858) (No. 11,281).

33. Thomas v. Weeks, 23 F. Cas. 978, 980 (C.C.S.D.N.Y. 1827) (No. 13,914); Sullivan v. Redfield, 23 F. Cas. 357, 360 (C.C.D.N.Y. 1825) (No. 13,597).

34. Newhall v. McCabe, 125 F. 919, 921 (2d Cir. 1903) (citing Dickerson v. De la Vergne Refrigerating Mach. Co., 35 F. 143 (C.C.S.D.N.Y. 1888)).

35. George Cutter Co. v. Metropolitan Elec. Mfg. Co., 275 F. 158, 164 (2d Cir. 1921). *See* Hildrith v. Norton, 159 F. 428, 429 (2d Cir. 1908) (injunction denied because validity and infringement vigorously disputed).

The principal rationale offered by the courts in the earliest patent cases for the burdensome test for injunctive relief was not peculiar to patent law: rather, it derived from basic principles of equity. Courts of equity granted injunctive relief in aid of the common law under which the patentee's legal right was being infringed.[36] Courts of law admonished courts of equity not to grant an injunction upon a doubtful right, or upon an assumption that the right had been infringed.[37] The Supreme Court stated the rule concerning the issuance of injunctions in *Alexander v. Pendleton*,[38] an early quiet title case. The Court stated that a court of equity should quiet title only in a clear case and should deny relief if the right were doubtful.[39] The Supreme Court applied the same principle in a later case dealing specifically with a preliminary injunction, stating that relief would issue only upon the plaintiff's showing of a clear, firm case of right.[40] State courts of equity also applied this test in the early nineteenth century.[41]

In essence, therefore, early courts of equity required proof of a clear, firm case of right for preliminary or final injunctive relief for nonpatentees and patentees alike. Since then, the standard for preliminary relief outside the patent area has been relaxed until in the Second Circuit preliminary relief is available even without proof of a likelihood of success on the merits.[42] The present requirements,[43] which include a showing of likely irreparable injury in all cases, were fixed in 1976 in *Triebwasser & Katz v. American Telephone & Telegraph Co.*[44] In the patent

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36. *See, e.g.*, Thomas v. Weeks, 23 F. Cas. 978, 980 (C.C.S.D.N.Y. 1827) (No. 13,914) (equity will aid law only absent doubt that patent infringed). In Dickerson v. De la Vergne Refrigerating Mach. Co., 35 F. 143 (C.C.S.D.N.Y. 1888), the court observed that courts continually declined to recognize the presumption of validity attendant on letters patent because of distrust of patent officials. *Id.* at 144.

37. Dickerson v. De la Vergne Refrigerating Mach. Co., 35 F. 143, 144 (C.C.S.D.N.Y. 1888).

38. 12 U.S. (8 Cranch) 462, 468 (1814).

39. *Id.* at 468.

40. Parker v. Winnipiscogee Lake Cotton & Woolen Co., 67 U.S. (2 Black) 545, 552 (1862) (nuisance suit).

41. *See, e.g.*, Charles River Bridge v. Warren Bridge, 24 Mass. (7 Pick.) 344 (1829), *aff'd*, 36 U.S. (11 Pet.) 420 (1837); Morris Canal & Banking Co. v. Society for Establishing Useful Manufactures, 5 N.J. Eq. 202, 221-22 (N.J. Ch. 1845); Hart v. Mayor of Albany, 3 Paige Ch. 213, 214 (N.Y. Ch. 1832); Scott v. Burton, 2 Ashm. 312, 330 (1st Jud. D. Pa. 1840).

42. *See supra* notes 8-9 and accompanying text. The Second Circuit came to hold that the standard for demonstrating probable success on the merits was less stringent in cases in which the balance of hardships favored the movant. *See, e.g.*, Dino DeLaurentiis Cinematografica, S.p.A. v. D-150, Inc., 366 F.2d 373, 375 (2d Cir. 1966). At one point the Second Circuit held that the party seeking the injunction did not have to show irreparable injury if the balance of hardships tilted decidedly in its favor. *See* Sonesta Int'l Hotels Corp. v. Wellington Assoc., 483 F.2d 247, 250 (2d Cir. 1973). In *Sonesta* the court held that a preliminary injunction could be granted upon either a clear showing of probable success on the merits and possible irreparable injury, or sufficiently serious questions on the merits to establish a fair ground for litigation and equities favoring the movant.

43. *See supra* text accompanying notes 8-9.

44. 535 F.2d 1356 (2d Cir. 1976). In *Triebwasser & Katz*, the court held that a satisfactory

area, however, the stringent standard for preliminary relief has not been relaxed.[45] The clear case of right, in the form of the "beyond doubt" test, still is required of patentees seeking preliminary injunctions.

III. Effect of the Extra Burden on Patentees

The extra burden imposed on patentees makes it difficult to obtain a preliminary injunction. A twenty-five-year survey of patent actions for preliminary injunctions indicates a success rate of 41% at the district court level and 32% at the appellate level.[46] These figures are inflated because they include the exceptions to the "beyond doubt" rule: instances of prior adjudication and industry acquiescence.[47] Furthermore, they do not reflect the instances in which motions for preliminary relief were never brought because of the stringent standard. Although statistics are not available, it is reasonable to infer that preliminary injunc-

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showing of irreparable injury was always necessary for a preliminary injunction because equity could not act when money damages would compensate for an injury. *Id.* at 1359.

45. The standard of proof of irreparable injury has become stricter as well. Originally, a patentee had only to demonstrate, with the requisite proof, an interference with his right to exclusive use, assumed to be irreparable for purposes of preliminary relief. *See* Gibson v. Van Dresar, 10 F. Cas. 329, 334 (C.C.N.D.N.Y. 1850) (No. 5,402) (injunction granted with no discussion of irreparable injury). As the 19th century progressed, some courts examined the issue of irreparable injury in relation to the balance of hardships in patent cases. *See* Bowers Dredging Co. v. New York Dredging Co., 77 F. 980, 984 (C.C.W.D. Wash. 1896) (burden on complainant to prove irreparable injury); Potter v. Whitney, 19 F. Cas. 1191, 1192 (C.C.D. Mass. 1860) (No. 11,341) (in unique circumstances, decision to issue injunction should consider balance of equities); Morris v. Lowell Mfg. Co., 17 F. Cas. 822, 823 (C.C.D. Mass. 1866) (No. 9,833) (before issuing injunction, court considers situation of parties and potential harm to defendants). *See also, e.g.*, Silver & Co. v. J.P. Eustis Mfg. Co., 130 F. 348, 350 (C.C.D. Mass. 1904) (balance of hardships in favor of defendant); Hockholzer v. Eager, 12 F. Cas. 269, 270 (C.C.D. Nev. 1873) (No. 6,556) (same). By the time Judge Hand wrote his opinions on the subject, however, some courts still granted preliminary relief without inquiring into the particular hardships involved. *See, e.g.*, Hilditch v. American Bumper Corp., 15 F.2d 451, 452 (E.D.N.Y. 1926). Some courts continued to regard the loss of exclusivity as irreparable injury. *See id.*; General Elec. Co. v. Wise, 119 F. 922, 924 (N.D.N.Y. 1903).

Irreparable injury was one of the requirements for a preliminary injunction in the early 19th century outside the patent area. *See* Charles River Bridge v. Warren Bridge, 24 Mass. (7 Pick.) 344, 401 (1829), *aff'd*, 36 U.S. (11 Pet.) 420 (1837). Conversely, when there was an adequate remedy at law, equity had to stay its hand. *See, e.g.*, Hart v. Mayor of Albany, 3 Paige Ch. 213, 214 (N.Y. Ch. 1832). Further, preliminary injunctions were available to prevent interference with exclusive rights generally, without proof of inability to calculate monetary losses. *See* Osborn v. Bank of the United States, 22 U.S. (9 Wheat.) 738 (1824) (government suit to prevent enforcement of state tax that would have destroyed national bank). In *Osborn* the Supreme Court observed that injunctions were often used to prevent interference with exclusive franchises. "The injury done, by denying to the bank the exercise of its franchise in the state of Ohio, is as difficult to calculate, as the injury done by participating in an exclusive privilege." *Id.* at 841-42. *See also* Livingston v. Ogden, 4 Johns. Ch. 48 (N.Y. Ch. 1819) (injunction granted to protect steamboat's exclusive right to navigate). Thus, it is evident that the irreparable injury requirement of the preliminary injunction standard has been made harsher as well.

46. Dorr & Duft, *supra* note 15, at 631.

47. *Id.* at 608-11. A federal court decree sustaining a patent after a full hearing constitutes very strong evidence of a patent's validity. *Id.* at 608. The prior adjudication, however, must have been fully contested and must have encompassed the issues of the present suit. *Id.* A prior decree entered by default is insufficient proof of a patent's validity. *Id.*

tions are more often sought and obtained in other causes of action not burdened by the "beyond doubt" standard.

According to the survey, the most common ground for denial of preliminary relief in patent cases is a finding that the patent is not clearly valid.[48] The second most frequent ground is a failure to show irreparable harm.[49] In most patent cases, therefore, a preliminary injunction against patent infringement does not issue unless there is a history of acquiescence respecting the relevant patent or a prior adjudication upholding its validity—the exceptions built into the "beyond question" rule. In one notable case, however, the absence of the requirement of acquiescence or prior adjudication was not determinative.[50] The court concluded that, after six months of litigation, it was in a position to determine whether the patents were "probably" valid and "probably" infringed and granted a preliminary injunction under this less strict test.[51]

The relative inability of a patentee to obtain preliminary relief puts a patentee who wishes to stop infringement in a difficult position. For the year ending June 30, 1982, the median length of litigation in the federal district courts of patent cases proceeding to trial was thirty-six months.[52] Ten percent of these cases lasted longer than seventy-seven months.[53] Figures for preceding years are not significantly different.[54] A determined infringer, consequently, often can use the patent for more than three years until trial and judgment. During this period an alleged in-

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48. *Id.* at 599.

49. *Id.*

50. Teledyne Indus. v. Windmere Prods., 433 F. Supp. 710 (S.D. Fla. 1977). In *Teledyne* a showerhead manufacturer sought a temporary injunction against the marketing of a similar imported device that allegedly infringed Teledyne's patent rights. The patents in question were obtained in 1973, 1974, and 1976—too recently, in the eyes of the court, to support a finding of a history of industry acquiescence. The court stated, however, that long acquiescence and prior adjudication were not the only means of ensuring that all prior art had been brought before the court. *Id.* at 713.

51. *Id.* at 713-14. The court relied on evidence that it was likely that Teledyne would succeed on the merits and would suffer irreparable harm if relief were not granted. *Id.* at 714. In Ryan v. Ideal Toy Corp., 260 F. Supp. 828 (C.D. Cal. 1966), *overruled in* Mayview Corp. v. Rodstein, 480 F.2d 714 (9th Cir. 1973), the court issued a preliminary injunction without acquiescence, prior adjudication, or a beyond doubt showing that the patent was valid and infringed, requiring only a "strong probability" of validity and infringement. *Id.* at 832. The court in *Ryan*, however, relied upon two Supreme Court holdings that dealt with permanent injunctions granted after a trial on the merits, not with preliminary relief. *See* Mumm v. Jacob E. Decker & Sons, 301 U.S. 168 (1937); Radio Corp. of Am. v. Radio Eng'g Labs., Inc., 293 U.S. 1 (1934). Moreover, the *Ryan* decision was expressly overruled in Mayview Corp. v. Rodstein, 480 F.2d 714, 717-18 (9th Cir. 1973). *See also* Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 443 F.2d 867, 872 n.5 (2d Cir. 1971) (noting that Ninth Circuit should decide whether decision in *Ryan* stated relaxed rule too emphatically), *cert. denied*, 412 U.S. 929 (1973).

52. ADMINISTRATIVE OFFICE OF THE U.S. COURTS, 1982 ANNUAL REPORT OF THE DIRECTOR 253.

53. *Id.*

54. ADMINISTRATIVE OFFICE OF THE U.S. COURTS, 1981 ANNUAL REPORT OF THE DIRECTOR A-32.

fringer enjoys the fruits of the patentee's inventive and developmental effort, and perhaps the higher-than-average profit that a patentee exploiting his invention alone might receive. In short, the alleged infringer is the beneficiary of a de facto compulsory license.

IV. Analysis of the Extra Burden on Patentees

A. Conflict with the Patentee's Statutory and Implied Rights

1. The presumption of validity

Section 282 of the Patent Code[55] states that "[a] patent shall be presumed valid."[56] This section, first enacted in 1952,[57] codified the presumption of validity recognized by the courts.

The Supreme Court defined the presumption of patent validity in *Radio Corp. of America v. Radio Engineering Laboratories, Inc.*[58] In rejecting arguments concerning priority of invention that had been made unsuccessfully by a patent applicant in other litigation, Justice Cardozo stated:

> A patent regularly issued, and even more obviously a patent issued after a hearing of all the rival claimants, is presumed to be valid until the presumption has been overcome by convincing evidence of error. The force of that presumption has found varying expression in this and other courts. . . . Through all the verbal variances, however, there runs this common core of thought and truth, that one otherwise an infringer who assails the validity of a patent fair upon its face bears a heavy burden of persuasion, and fails unless his evidence has more than a dubious preponderance.[59]

Three years later, in *Mumm v. Jacob E. Decker & Sons,*[60] the Supreme Court held that an equity bill was sufficient even though it did not negate prior publication or use in asserting a claim for infringement because those were matters of affirmative defense.[61] Chief Justice Hughes explained that the heavy burden of proving that a particular invention

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55. 35 U.S.C. § 282 (1976).

56. Section 282 provides that:

> A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim. The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity.

According to the legislative history, § 282 proposed to enact the presumption of patent validity recognized by the courts but never expressed in a statute. S. Rep. No. 1979, 82d Cong., 2d Sess. (1952), *reprinted in* 1952 U.S. Code Cong. & Ad. News 2394, 2402-03.

57. Act of July 19, 1952, ch. 950, 66 Stat. 812 (codified as amended at 35 U.S.C. § 282 (1976)).

58. 293 U.S. 1 (1934).

59. *Id.* at 7-8.

60. 301 U.S. 168 (1937).

61. *Id.* at 171.

is not novel required that every reasonable doubt be resolved against the alleged infringer.[62]

Prior to 1952, courts generally treated the presumption of patent validity as a procedural matter. Once a plaintiff presented a duly issued patent to the court, the alleged infringer assumed the burden of demonstrating the patent's invalidity. Following the decision in *Radio Corp. of America v. Radio Engineering Laboratories, Inc.*,[63] courts required the alleged infringer to introduce "clear" or "convincing" evidence of invalidity to overcome the presumption.[64]

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62. *Id.* (quoting Coffin v. Ogden, 85 U.S. 120, 124 (1873)). One district court read these decisions as requiring it to disregard dictum in its own circuit imposing the "beyond doubt" test on a patentee seeking a preliminary injunction, and instead to apply only a "strong probability" test. Ryan v. Ideal Toy Corp., 260 F. Supp. 828, 831-32 (C.D. Cal. 1966), *overruled in* Mayview Corp. v. Rodstein, 480 F.2d 714 (9th Cir. 1973). In overruling *Ryan*, however, the Court of Appeals for the Ninth Circuit in Mayview Corp. v. Rodstein, 480 F.2d 714, 717-18 (9th Cir. 1973), considered the presumption of validity "too slim a reed" to justify a preliminary injunction in a patent case. *Id.*

The Second Circuit, in Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 443 F.2d 867 (2d Cir. 1971), *cert. denied*, 412 U.S. 929 (1973), declined to follow the reasoning of *Ryan* on the ground that the *Radio Corp. of Am.* and *Munn* cases did not involve preliminary injunctions. *Id.* at 871 n.4. The court also noted that *Ryan* had never been cited. *Id.* The Second Circuit relied instead on its own rule that the presumption of validity served only to shift the burden of proof to the party asserting invalidity and to resolve reasonable doubt on the issue of validity in favor of the patentee. *Id.* at 867 (citing Rains v. Niaqua, Inc., 406 F.2d 275, 278, *cert. denied*, 395 U.S. 909 (1969)). The court noted that the presumption carried no "independent evidentiary" weight and had no effect on the standard of evidence that determines the issue. *Id.* The *Rains* standard is based on Lorenz v. F.W. Woolworth Co., 305 F.2d 102, 105 (2d Cir. 1962), in which the court elaborated on the test as follows:

> The [statutory] presumption of validity relieves the patent holder of the burden of establishing that validity as a requisite for the successful maintenance of an infringement action, and places the burden of establishing invalidity on the alleged infringer who asserts it . . . . More than that, the most that can be said of the presumption is that it requires that reasonable doubt on the question of validity be resolved in favor of the patent holder. . . . The statute does not require that the presumption be accorded the weight of actual evidence or that the use of the presumption should affect a decision of invalidity that would otherwise be reached with confidence. This court has recognized the unavoidable obstacles to an accurate and impartial decision that are inherent in ex parte proceedings in the patent office . . . . We cannot properly allow decisions of that office to alter the preponderance of the evidence on the question of validity . . . . In the present case, defendant satisfied his burden of coming forward with evidence of invalidity and we have no such doubts on the question as would bring the presumption further into play.

Id. at 105-06.

63. 293 U.S. 1, 7 (1934) (only clear and cogent evidence overthrows presumption of patent validity).

64. *See, e.g.*, Charles Peckat Mfg. Co. v. Jacobs, 178 F.2d 794, 801 (7th Cir. 1949) (clear and convincing evidence necessary to overcome presumption of validity), *cert. denied*, 339 U.S. 915 (1950); Insul-Wool Insulation Corp. v. Home Insulation, Inc., 176 F.2d 502, 505 (10th Cir. 1949) (more than dubious preponderance of evidence required to overcome presumption that patented item not anticipated by prior knowledge and use); Crosley Corp. v. Westinghouse Elec. & Mfg. Co., 152 F.2d 895, 904 (3d Cir. 1945) (clear and convincing proof required to overcome presumption of validity); F.E. Myers & Bros. Co. v. Goulds Pumps, Inc., 91 F. Supp. 475, 479 (W.D.N.Y. 1950) (clear and satisfactory proof necessary to overcome issuance of patent as prima facie evidence of validity); Cohen v. Western Auto Supply Co., 33 F. Supp. 25, 27 (N.D. Ga. 1940) (only clear and satisfactory proof overthrows presumption of validity), *aff'd*, 131 F.2d 109 (5th Cir. 1942).

Following the enactment of the Patent Act of 1952,[65] the Supreme Court examined the presumption of validity reflected in the new statute. The Court upheld the presumption, citing its strength as a "buttress" to the licensor's case.[66] Lower courts handing down decisions after 1952 continue to treat the statutory presumption of validity as requiring the alleged infringer to offer more than a mere preponderance of evidence that a patent is invalid.[67] Even the Second Circuit test currently requires that reasonable doubt be resolved in favor of the patent holder, although it acknowledges that the presumption cannot affect a decision reached with confidence.[68] Moreover, the Second Circuit recognizes the presumption of patent validity despite the alleged inadequacies of the ex parte process in the Patent Office.[69]

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65. Act of July 19, 1952, ch. 590, 66 Stat. 792 (codified as amended at 35 U.S.C. §§ 1-376 (1976 & Supp. V 1981)).

66. Lear, Inc. v. Adkins, 395 U.S. 653, 670 (1969). In Blonder-Tongue Labs., Inc. v. University of Ill. Found., 402 U.S. 313 (1972), the Court also recognized the effect of the presumption of validity. *Id.* at 335.

Courts agree that a challenger can weaken the presumption of validity by demonstrating that the patent examiner did not review all references to the relevant prior art at the time the patent issued. *See, e.g.*, Sidewinder Marine, Inc. v. Starbuck Kustom Boats & Prods., 597 F.2d 201, 206 (10th Cir. 1979) (presumption diminished or dissipated when Patent Office failed to account for all relevant prior art); Santa Fe-Pomeroy, Inc. v. P & Z Co., 569 F.2d 1084, 1092 (9th Cir. 1978) (presumption weakened when patent examiner did not consider pertinent instances of prior art); Reynolds Metals Co. v. Acorn Bldg. Components, Inc., 548 F.2d 155, 160 (6th Cir. 1977) (same); Forbro Design Corp. v. Raytheon Co., 532 F.2d 758, 761-62 (1st Cir. 1976) (presumption weakened when Patent Office conducted incomplete examination of prior art); Parker v. Motorola, Inc., 524 F.2d 518, 521 (5th Cir. 1975) (reason for presumption dissipated by issuance of patent without review of pertinent prior art), *cert. denied*, 425 U.S. 975 (1976). One court has stated that proof of an incomplete examination of pertinent art requires courts to "scrutinize the patent claims in suit more closely than when the presumption is at full force." Parker v. Motorola Inc., 524 F.2d 518, 521 (5th Cir. 1975), *cert. denied*, 425 U.S. 975 (1976). There appears to be no reason why courts could not consider prior art on the preliminary injunction motion.

67. *See, e.g.*, Gaddis v. Calgon Corp., 506 F.2d 880, 885 (5th Cir. 1975) (clear and convincing evidence required to overcome presumption of validity); Moore v. Schultz, 491 F.2d 294, 298 (10th Cir.) (clear and convincing evidence required to defend against claim of patent infringement), *cert. denied*, 419 U.S. 930 (1974); Laser Alignment, Inc. v. Woodruff & Sons, Inc., 491 F.2d 866, 871 (7th Cir.) (clear and convincing proof necessary to overcome presumption of validity), *cert. denied*, 419 U.S. 874 (1974); National Research Dev. Corp. v. Great Lakes Carbon Corp., 410 F. Supp. 1108, 1115 (D. Del. 1975) (clear and convincing evidence required to overcome presumption of validity); Minnesota Mining & Mfg. Co. v. Berwick Indus., 393 F. Supp. 1230, 1233 (M.D. Pa. 1975) (clear and convincing evidence needed to prove patent's invalidity), *aff'd*, 532 F.2d 330 (3d Cir. 1976).

Several other courts, however, have required only that the alleged infringer overcome the presumption of validity by a preponderance of the evidence. *See, e.g.*, Dickstein v. Seventy Corp., 522 F.2d 1294, 1297 (6th Cir. 1975) (preponderance of evidence sufficient to establish invalidity), *cert. denied*, 423 U.S. 1055 (1976); Jack Winter, Inc. v. Koratron Co., 375 F. Supp. 1, 29-30 (N.D. Cal. 1974) (preponderance of evidence standard adequate to protect patentee from need to establish affirmative validity). This minority view appears incompatible with *Radio Corp. of Am.* *See supra* note 63 and accompanying text.

68. Lorenz v. F.W. Woolworth Co., 305 F.2d 102, 105 (2d Cir. 1962). *See* Gross v. JFD Mfg. Co., 314 F.2d 196, 198 (2d Cir.) (quoting *Lorenz*, 305 F.2d at 105), *cert. denied*, 374 U.S. 832 (1963). *See supra* note 62.

69. The allegations of inadequacies in the ex parte process at the Patent Office derive from the view that the Patent Office is deluged with applications and, accordingly, is unable to give full consideration to the prior art references or to demand full disclosure of all relevant information in each proceeding. Judge Mansfield commented on the defects in this argument in his dissent in

Although the cases that recognize the presumption of patent validity have not involved preliminary injunctions,[70] the Patent Code does not limit the applicability of the presumption to trials. Nevertheless, courts have ignored the presumption in the preliminary injunction context. In fact, by requiring patentees to carry the extra burden for preliminary relief, courts have invoked a *negative* presumption—a presumption of *in*validity that is inherent in the "beyond question" standard. The "beyond doubt" test, therefore, is inconsistent with the statutory presumption.[71]

2. Right of unabridged access to the courts

By erecting a barrier to preliminary relief for patentees, the courts are abridging the remedies available to patentees,[72] thus limiting their access to the courts. A patentee's right of access to the courts, however, enjoys a high priority not reached even by the antitrust laws, except in very limited circumstances.[73]

Carter-Wallace, pointing out that the patent examiner has at his disposal a wealth of scientific and technical information that encompasses the prior art references in any given field. Moreover, the examiner is an expert in the field in which he issues patents. Finally, despite the fact that the proceeding is ex parte, the patent examiner acts as an adversary, not simply as an administrator, by demanding that the applicant introduce all relevant prior art and examining each reference before deciding to issue a patent. Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 443 F.2d 867, 886 (2d Cir. 1971) (citation omitted) (Mansfield, J., dissenting), *cert. denied*, 412 U.S. 929 (1973).

70. In *Carter-Wallace* the Second Circuit distinguished the *Radio Corp. of Am.* and *Mumm* cases on the ground that they involved motions for preliminary relief, not full hearings on the merits. *See id.* at 872 n.5.

71. *See supra* notes 55, 65-66 and accompanying text.

72. The Patent Code authorizes actions for patent infringement, 35 U.S.C. § 281 (1976), actions for damages due to infringement, 35 U.S.C. § 284 (1976), and actions to enjoin infringement, 35 U.S.C. § 283 (1976). Section 283 provides that the courts "may grant injunctions in accordance with the principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable."

Federal patent law has contained an injunction provision since 1819, when Congress first gave the circuit courts authority to grant injunctions in patent cases "according to the course and principles of courts of equity . . . on such terms and conditions as the said courts may deem fit and reasonable." Act of Feb. 15, 1819, ch. 19, 3 Stat. 481 (1819), *amended by* Act of July 19, 1952, ch. 950, § 283, 66 Stat. 792, 812 (1952); Act of Aug. 1, 1946, ch. 726, § 1, 60 Stat. 778 (1946); Act of Feb. 18, 1922, ch. 58, § 8, 42 Stat. 389, 392 (1922); Act of March 3, 1897, ch. 391, § 6, 29 Stat. 692, 694 (1897); Act of July 8, 1870, ch. 230, § 55, 16 Stat. 198, 206 (1870); Act of July 4, 1836, ch. 357, § 17, 5 Stat. 117, 124 (1836). The Senate report concerning the 1952 revisions of the Patent Code, which established the current provision, states that § 283 merely "replace[s] present statutes on suits, with a good deal of reorganization in language to clarify the statement of the statutes." S. REP. NO. 1979, 82d Cong., 2d Sess., *reprinted in* 1952 U.S. CODE CONG. & AD. NEWS 2394, 2403.

Although the statute does not address, and never has addressed, preliminary injunctions specifically, it is reasonable to infer that the statute covers preliminary as well as final injunctions. The principles of equity, therefore, should govern both areas. Because equitable principles have long applied a "beyond doubt" standard to the granting of injunctions in the patent area, the "beyond doubt" test arguably is consistent with the statute. On the other hand, the statutory reference to equitable principles evokes the general, typical preliminary injunction rules applicable to all kinds of cases.

73. *See* Handgards, Inc. v. Ethicon, Inc., 601 F.2d 986 (9th Cir. 1979), *cert. denied*, 444 U.S. 1025 (1980).

The Supreme Court recognized the general doctrine that underlies the right of access to the courts in *Eastern Railroad Presidents Conference v. Noerr Motor Freight, Inc.*[74] The Court held that the Sherman Act protected private parties' concerted efforts to injure their competitors by influencing the passage of legislation because the Act did not preclude the "mere solicitation of governmental action with respect to the passage and enforcement of laws."[75] The Court recognized that construing the antitrust laws to proscribe the challenged conduct would interfere with the right to petition guaranteed by the first amendment.[76] The Court stated, however, that "a mere sham to cover what is actually nothing more than an attempt to interfere directly with the business relationships of a competitor" would justify the application of the Sherman Act.[77] The Supreme Court later extended the protection accorded efforts to influence legislation to concerted approaches to administrative and judicial tribunals,[78] reasoning that the right of access to the courts is an element of the right to petition.[79]

In the patent litigation area, the courts have specifically recognized patentees' right of access to the courts. Patents can be asserted and litigated in good faith, free from antitrust liability, even though they are ultimately held invalid.[80] The controlling principle was articulated

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74. 365 U.S. 127 (1961).

75. *Id.* at 138.

76. *Id.* at 139 (such construction would deprive government of information and people of right to petition).

77. *Id.* at 144. *See* United Mine Workers v. Pennington, 381 U.S. 657, 676 (1965) (*Noerr* exemption extended to concerted efforts to influence government officials in executive branch). In *Pennington* the Supreme Court immunized joint attempts by certain larger coal mine operators and the United Mine Workers Union to destroy smaller mines by inducing the Secretary of Labor to extend minimum wage requirements to certain small companies. *Id.* at 660-61.

78. *See* California Motor Transp. Co. v. Trucking Unlimited, 404 U.S. 508 (1972).

79. *Id.* at 510-11. The Court added, however, that the right of access to the courts does not necessarily grant immunity from antitrust regulation. *Id.* at 513.

80. *See* Rex Chainbelt, Inc. v. Harco Prods., 512 F.2d 993, 1000-07 (9th Cir.) (counterclaiming infringer not entitled to damages if patentee believed patent was valid and was not misusing patent or violating antitrust laws), *cert. denied*, 423 U.S. 831 (1975); Bendix Corp. v. Balax, Inc., 471 F.2d 149, 159 (7th Cir. 1972) (patentee permitted to sue on assumption that patent was valid), *cert. denied*, 414 U.S. 819 (1973); American Potato Dryers, Inc. v. Peters, 184 F.2d 165, 173 (4th Cir. 1950) (patentee's threats of suit for patent infringement were good faith efforts to protect rights believed to be secured by patent, not unlawful attempt to extend patent monopoly), *cert. denied*, 340 U.S. 930 (1951); Virtue v. Creamery Package Mfg. Co., 179 F. 115, 120 (8th Cir. 1910) (patentees who had right to bring suits for infringement had right to issue warnings in good faith), *aff'd*, 227 U.S. 8 (1913); Koratron Co. v. Lion Uniform, Inc., 409 F. Supp. 1019, 1030 (N.D. Cal. 1976) (no damages to alleged infringer despite patentee's antitrust violation because insufficient evidence that suit initiated in bad faith and as part of plan to violate antitrust laws); Crown Mach. & Tool Co. v. D & S Indus., 270 F. Supp. 271, 279 (D. Ariz. 1967) (belief that patent is valid precludes charge of bad faith or knowledge of invalidity), *aff'd per curiam*, 409 F.2d 1307 (9th Cir.), *cert. denied*, 396 U.S. 824 (1969); Morny v. Western Union Tel. Co., 40 F. Supp. 193, 201-02 (S.D.N.Y. 1940) (patentee can bring suits and give warnings based on good faith and honest belief in infringement). *Cf.* United States Galvanizing & Plating Equip. Corp. v. Hanson-Van Winkle-Munning Co., 104 F.2d 856, 862 (4th Cir. 1939) (unfair competition cannot be sustained if patentee believed patents were being infringed and gave notice accordingly); Alliance Sec. Co. v. De Vilbiss Mfg. Co., 41 F.2d 668,

more than a half century ago: access to the courts cannot be denied or penalized, even though only debatable questions are presented.[81] The principle was reiterated recently in a decision in which the court stated that a patentee who had reasonable grounds for believing that his patent was valid and was being infringed was authorized to bring an action for infringement, notwithstanding the perpetuation of the effects of other antitrust violations.[82]

The Court of Appeals for the Ninth Circuit discussed this principle most incisively in *Handgards, Inc. v. Ethicon, Inc.*[83] The Ninth Circuit recognized the interrelationship of the patent doctrine, the *Noerr* principle, and the presumption of patent validity. The court of appeals noted that the doctrine permitting patent owners to seek enforcement of their patents in good faith required the courts to shield the honest patentee who brought an infringement action to protect his legal monopoly from counterclaims for antitrust violations by reason of such enforcement.[84]

In sustaining patentees' right to test the validity of their patents in court, the court observed that patentees' "status as alleged possessors of a legal monopoly does not cause them to be pariahs before the law."[85] Accordingly, the court held that a suit for patent infringement was presumed to be in good faith and that only clear and convincing evidence could rebut the presumption.[86] The court reasoned that the presumption of good faith was consistent with the statutory presumption of patent validity.[87] The imposition of an extra burden on patentees seeking preliminary relief, therefore, indirectly undermined the patentee's right to seek redress in the courts.

3. Compulsory licensing

The near impossibility of preliminary relief and the duration of litigation on the merits in patent cases ensures alleged infringers several years

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670-71 (6th Cir. 1930) (patentee's claims of infringement not considered legal wrong unless made in bad faith or with malice).

81. *See* Straus v. Victor Talking Mach. Co., 297 F. 791, 798-99 (2d Cir. 1924).

82. Ansul Co. v. Uniroyal, Inc., 448 F.2d 872, 882-83 (2d Cir. 1971), *cert. denied*, 404 U.S. 1018 (1972). *Accord* Solvex Corp. v. Freeman, 459 F. Supp. 440, 451 (W.D. Va. 1977) (patent infringement suit is usual means of enforcing patent, without which patent rights may be useless); Cameron Iron Works, Inc. v. Edward Valves, Inc., 175 F. Supp. 423, 426 (S.D. Tex. 1959) (bringing and maintaining suit for patent infringement alone cannot violate Sherman Act), *aff'd*, 286 F.2d 933 (5th Cir.), *cert. denied*, 368 U.S. 833 (1961).

83. 601 F.2d 986 (9th Cir. 1979), *cert. denied*, 444 U.S. 1025 (1980).

84. *Id.* at 996. The court reversed a jury award of damages to the alleged infringer, who had brought a treble damage action against the patentee claiming bad faith litigation as part of a plan to monopolize. *Id.* at 987.

85. *Id.* at 993.

86. *Id.* at 996. This rule was adopted in order to safeguard infringement actions from the sanction of treble damages, unless the action had been identified with certainty as being brought in bad faith. *Id.* at 993.

87. *Id.*

of freedom to infringe, notwithstanding injury to the patentee. The effect is equivalent to compulsory licensing for which there is no legal basis. The Patent Code does not include any provision for compulsory licensing, and proposals for such a provision have been rejected by Congress.[88] Moreover, the Supreme Court has adhered to the congressional view by repeatedly rejecting arguments for compulsory licensing of unpatented articles that satisfy the criteria of contributory infringement, and by declining to manufacture forfeiture or compulsory licensing out of the language of the Patent Code.[89] Such emphatic rejection of the principle of compulsory licensing by Congress and the Supreme Court leaves the compulsory licensing equivalent that results from placing preliminary relief outside the reach of patentees without legal foundation.

B. Conflict with the Synthesis of the Applicable Competing Policies

Although the ultimate goals of patent policy are similar to those of antitrust policy, the patent right is exempted from the antitrust laws. Cases considering the interface of the two legislative schemes indicate respect for the patent right and an effective presumption of validity.

The patent system is intended to encourage invention,[90] commercialization of inventions,[91] and disclosure of inventions.[92] The broader benefits that result from patent policy's fostering of industrial invention and innovation include economic vitality, improved quality of life, and the ability to solve pressing problems concerning such matters as health care, food and energy supplies, and natural resources.[93] Similarly, antitrust law attempts to ensure "the best allocation of our economic re-

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88. For example, in 1957 the Senate Subcommittee on Patents, Trademarks, and Copyrights considered a suggestion to make licensing compulsory. After assessing the importance of the public interest and the benefits of the patent system in encouraging innovation, the subcommittee concluded that compulsory licensing would be detrimental to the public interest and ineffectual in achieving the objectives sought. SUBCOMM. ON PATENTS, TRADEMARKS, AND COPYRIGHTS, PROPOSALS FOR IMPROVING THE PATENT SYSTEM, S. DOC. NO. 21, 85th Cong., 1st Sess. 29 (1957).

89. *See* Dawson Chemical Co. v. Rohm & Haas Co., 448 U.S. 176, 215 (1980) (construing 35 U.S.C. § 271(d) (1976)). *See also* Special Equip. Co. v. Coe, 324 U.S. 370, 379 (1945) (observing lack of congressional authority for compulsory licensing); Hartford Empire Co. v. United States, 323 U.S. 386, 432 (1945) ("Congress has repeatedly been asked, and has refused, to change the statutory policy by imposing a forfeiture or by a provision for compulsory licensing").

90. *See* Sears, Roebuck & Co. v. Stiffel Co., 376 U.S. 225, 229 (1964) (patents meant to encourage invention by reward of right to exclusive use); Mitchell v. Tilgham, 86 U.S. (19 Wall.) 287, 418 (1873) (principle purpose of patents to encourage useful inventions); Grant v. Raymond, 31 U.S. (6 Pet.) 94, 97 (1832) (patent is reward intended as stimulus to individual exertions).

91. *See* SCM Corp. v. Xerox Corp., 645 F.2d 1195, 1206 n.9 (2d Cir. 1981) (investors indispensable to inventions and commercialization of inventions), *cert. denied*, 455 U.S. 1016 (1982).

92. *See* Universal Oil Prods. v. Globe Oil & Ref. Co., 322 U.S. 471, 484 (1944) (patent is reward for inventions and their disclosure by inventor who refrains from keeping invention a trade secret).

93. *See* President's Message to Congress Transmitting Industrial Innovation Initiatives, 15 WEEKLY COMP. PRES. DOC. 2069 (Oct. 31, 1979) (inventive process is key to increased production, international competition, reduced unemployment, and improved quality of life).

sources, the lowest prices, the highest quality and the greatest material progress" by fostering competition.[94] Patent law promotes the progress of science and the practical arts by providing an exclusive right for a limited time to offset the risks—involving much effort, time, and cost—of research, development, and commercialization undertaken by the inventor and those providing funding.[95] Issuance of the patent results in the publication of knowledge which might otherwise have been withheld as trade secrets. Furthermore, after the patentee has reaped the benefits of the invention for the statutory period of years, the patent expires and the public receives the right to use the invention commercially.[96]

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94. Northern Pac. Ry. v. United States, 356 U.S. 1, 4 (1958).

95. Kewanee Oil Co. v. Bicron Corp., 416 U.S. 470, 480 (1947). In *Kewanee* the Court noted that the introduction of new products and processes fostered by the patent system would have positive effects on society, such as increased employment and better lives. *Id. See also* SCM Corp. v. Xerox Corp., 645 F.2d 1195, 1206 n.9 (2d Cir. 1981) (investment in commercialization and investment in basic research of comparable value), *cert. denied,* 455 U.S. 1016 (1982).

Without the statutory monopoly provided by the patent system, certain unique innovations not readily adaptable to industrial technology might never be developed. "[G]reater technological and market uncertainties, higher development costs, and longer inception-to-commercialization lags" could inhibit entrepreneurial investment where there is no assurance that a successful invention could be exploited to the fullest through exclusive patent rights. F.M. SCHERER, INDUSTRIAL MARKET STRUCTURE AND ECONOMIC PERFORMANCE 448 (2d ed. 1980). For example, patent protection evidently hastened the development of xerography. *Id.* The inventor of an electrophotographic process later named xerography had great difficulty convincing business machine companies to fund his research. *See* SCM Corp. v. Xerox Corp., 463 F. Supp. 983, 992 (D. Conn. 1978), *aff'd,* 645 F.2d 1195 (2d Cir. 1981), *cert. denied,* 102 S. Ct. 1708 (1982). It was not until 1946—eight years after the original invention—that Xerox agreed to sponsor the research in exchange for a license. *Id.* It was another fourteen years before the introduction of a xerox copier suitable for office use. *Id.*

It appears that among the great benefits of the patent system is stimulation of investment. *See* Picard v. United Aircraft Corp., 128 F.2d 632, 643 (2d Cir.) (Frank, J., concurring), *cert. denied,* 317 U.S. 651 (1942). Judge Frank stressed the procompetitive effects of the patent system's stimulus to investors, particularly when small new companies are provided with the means to compete against large corporations. This threat of competition has prodded larger corporations to expend more resources on research and development. *Id.* "The David Co. v. Goliath, Inc. kind of competition is dependent on investment in David Co.—the small new competitor. And few men will invest in such a competitor unless they think it has a potential patent monopoly as a slingshot." *Id.* Xerox is an example of such a "David." By virtue of its willingness to invest in and develop an untried *invention, Haloid Company of Rochester, New York, as Xerox was known in 1946, created new* competition for existing suppliers of copying and duplicating equipment. Many of these companies, such as Eastman Kodak, 3M and Addressograph-Multigraph, had resources that far exceeded those of Haloid. *Id. See also* United States v. Parker-Rust-Proof Co., 61 F. Supp. 805, 808 (E.D. Mich. 1945) (meritorious patent may lie unused for years until enterprising person takes promotional risk); Application of Anthony, 414 F.2d 1383, 1398 (C.C.P.A. 1969) (fundamental purpose of patent system is to stimulate investment of capital needed for further development and marketing of inventions); Application of Herr, 377 F.2d 610, 619 (C.C.P.A. 1967) (Rich, J., concurring) (grant of patent rights encourages investment of risk capital).

96. An inventor has no legal obligation to disclose his invention. *See, e.g.,* Lear, Inc. v. Adkins, 395 U.S. 653, 677 (1969) (Black, J., concurring in part and dissenting in part) (discoveror may keep discovery secret if he wishes); United States v. American Bell Tel. Co., 167 U.S. 224, 250 (1897) (inventor not bound to disclose invention—his "absolute property"—to public); Berkey Photo, Inc. v. Eastman Kodak Co., 603 F.2d 263, 281 (2d Cir. 1979), *cert. denied,* 444 U.S. 1093 (1980) (company may keep its innovations from rivals, forcing them to catch up through their own efforts).

In order to secure to the public the benefits of full knowledge of innovative ideas and the right to

The patent right, however, seems to conflict with antitrust doctrines. The Sherman Act[97] prohibits monopolization and attempts to monopolize.[98] Monopoly is customarily defined to include the power to exclude.[99] A patent, on the other hand, grants the power to exclude.[100] Assuming a relevant market co-extensive with the patent, therefore, the issuance of a patent constitutes a grant of a seventeen-year monopoly.[101]

Consequently, one body of law outlaws an illegally obtained monopoly while another body of law grants a form of legal monopoly. As the Supreme Court stated in *Dawson Chemical Co. v. Rohm & Haas,*[102] "the policy of stimulating invention that underlies the entire patent system runs no less deep" than the antitrust policy of free competition.[103] Pat-

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implement them in the future, Congress created the patent system to allow the inventor a limited opportunity to gather material rewards for his invention. *See* Special Equip. Co. v. Coe, 324 U.S. 370, 378 (1945). *See also* Kewanee Oil Co. v. Bicron Corp., 416 U.S. 470, 484 (1974) (disclosure *quid pro quo* of right to exclude); F.M. SCHERER, *supra* note 95, at 440 (governments grant exclusive patent rights on inventions to promote invention and encourage their commercial utilization and disclosure to public).

97. Ch. 647, §§ 1-8, 26 Stat. 210 (1890) (current version at 15 U.S.C. §§ 1-7 (1976)).

98. 15 U.S.C. § 2 (1976). Section 2 provides: "Every person who shall monopolize, or attempt to monopolize, or combine or conspire with any other person or persons, to monopolize any part of the trade or commerce among the several States, or with foreign nations, shall be deemed guilty of a felony . . . ."

99. United States v. Grinnell Corp., 384 U.S. 563, 576 (1966).

100. Dawson Chem. Co. v. Rohm & Haas Co., 448 U.S. 176 (1980). In *Rohm & Haas* the Court acknowledged "the long-settled view that the essence of a patent grant is the right to exclude others from profiting by the patented invention." *Id.* at 215.

101. 35 U.S.C. § 154 (1976). Section 154 provides in pertinent part: "Every patent shall contain . . . a grant to the patentee, his heirs or assigns, for the term of seventeen years, . . . of the right to exclude others from making, using, or selling the invention throughout the United States . . . ." The patent code authorizes actions for patent infringement, 35 U.S.C. § 281 (1976), actions to enjoin infringement, 35 U.S.C. § 283 (1976), and actions for damages due to infringement, 35 U.S.C. § 284 (1976). Infringement is defined in § 271. 35 U.S.C. § 271 (1976).

The authority to grant patents derives from the Constitution, which gives Congress the right to "make all Laws which shall be necessary and proper for carrying into Execution" its enumerated powers. U.S. CONST., art. I, § 8, cl. 18. Among those enumerated powers is the power "[t]o promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." *Id.* cl. 8.

102. 448 U.S. 176 (1980).

103. *Id.* at 221. In *Rohm & Haas* the Court held that under the language of 35 U.S.C. § 271(d) (1976), a patentee did not misuse his patent by refusing to license the patent except on the condition that the licensees purchase from him an unpatented nonstaple article having no significant use except in the patented process. *Id.* at 223.

The dissent would have construed § 271(d) to permit suit against unlicensed contributory infringers—persons selling the unpatented product that constituted a material part of the patented process—but would have required the patentee to offer to license those persons. *Id.* at 230-40 (White, J., dissenting). In that way, the patentee could sue for contributory infringement, but could not reserve to himself the entire market for the unpatented nonstaple article. *See id.*

The Court rejected the dissent's construction of § 271(d) on the ground that it permitted sellers of an unpatented item to await the outcome of the patentee's efforts and then to capitalize on the patentee's success by demanding licenses to sell the unpatented item in the newly developed process. *Id.* at 222. The Court noted that "[t]he incentive to await the discoveries of others might well prove sweeter than the incentive to take the initiative oneself." *Id.* Such a result, the Court reasoned, would conflict with the essence of the patent right to exclude and the absence of a statutory provision for compulsory licensing. *Id.* at 215. The Court did not decide, however, whether such a regime was either "workable" or consistent with "the principles of free competition." *Id.* at 223.

ent law therefore confers an "exemption from the antitrust laws."[104] Thus, although exploitation within the patent monopoly is protected, extension of the patent monopoly beyond its legitimate scope will result in a forfeiture of the right to enforce the patent.[105] Consistent with the patent misuse doctrine,[106] overreaching the scope of a patent will subject the patentee to the rigors of the antitrust law.[107]

In a close choice between the patentee's right to exclude and the alleged infringers' interest in competition, several recent decisions have concluded that the patentee should prevail. For example, in *Rohm & Haas* the Supreme Court held that a patentee who refused to license others to sell an unpatented product that satisfies the criteria of contributory infringement had not misused his patent.[108] In effect, the Court permitted the patentee to compel those wishing to practice its patented method to purchase from it the unpatented material necessary to practice that method, although this practice usually is treated as an illegal tie-in under the antitrust laws.[109] The Court, recognizing the risks involved in and the need to encourage research,[110] rejected a construction

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104. Walker Process Equip., Inc. v. Food Mach. & Chem. Corp., 382 U.S. 172, 177 (1965).

105. *See* Morton Salt Co. v. G.S. Suppiger Co., 314 U.S. 488, 494 (1942) (misuse of patent disqualifies patentee from suing for infringement because of adverse effect of misuse on public interest); Ethyl Gasoline Corp. v. United States, 309 U.S. 436, 459 (1940) (extension of patent monopoly to exploit unpatented article not permitted); Sylvania Indus. Corp. v. Visking Corp., 132 F.2d 947, 955-58 (4th Cir.) (injunction against patent infringement denied until patentee stopped monopolizing sale of unpatented product), *cert. dismissed*, 319 U.S. 777 (1943).

106. Under the misuse doctrine, a patent owner forfeits the right to exclude as long as the misuse and its effects continue. Once effective curative measures have been taken and any anticompetitive effects dissipated, infringement can be enjoined. *See* Performed Line Prods. v. Fanner Mfg. Co., 328 F.2d 265, 276-79 (6th Cir.) (misuse of patent by tie-in of unpatented goods to patented items to expand monopoly purged by widely enforced "unrestricted sales" policy), *cert. denied*, 379 U.S. 846 (1964).

The doctrine of patent misuse denies relief against infringement where the patentee has sought to extend unlawfully the scope of his patent; the doctrine of contributory infringement, however, provides protection for the patent right against attempts to infringe the patent indirectly by facilitating acts of third persons. *See, e.g.*, Dawson Chem. Co. v. Rohm & Haas Co., 448 U.S. 176 (1980) (judgment in favor of patentee inventor of herbicide application process against those seeking licenses from patentee for sale of unpatented herbicide); Aro Mfg. Co. v. Convertible Top Replacement Co., 377 U.S. 476 (1964) (direct infringement where convertible top combinations sold without valid license from patentee; contributory infringement where replacement fabrics specially cut for use in infringing repair supplied). *But see* Deepsouth Packing Co. v. Laitram Corp., 406 U.S. 518 (1972) (patent not infringed when unpatented elements assembled into combination outside United States); Mercoid Corp. v. Mid-Continent Inv. Co., 320 U.S. 661 (1944) (patentee's attempt to control market for unpatented goods constituted patent misuse even where goods had no use outside patented invention).

107. *See* Mercoid Corp. v. Mid-Continent Inv. Co., 320 U.S. 661, 666 (1944) (patentee who moves beyond scope of patent monopoly enters area where antitrust or other laws define public policy); United States v. CIBA GEIGY Corp., 508 F. Supp. 1118, 1150 (D.N.J. 1976) (patentee who expands monopoly beyond that reasonably implicit in patent collides with antitrust laws).

108. Dawson Chem. Co. v. Rohm & Haas Co., 448 U.S. 176, 221 (1980). *See supra* note 103.

109. Dawson Chem. Co. v. Rohm & Haas Co., 448 U.S. 176, 223 (1980). *See also* Fortner Enter. v. United States Steel Corp., 394 U.S. 495 (1969) (advantageous credit terms used to extend seller's economic power and foreclose competition in tied product illegal).

110. *See supra* notes 90-96 and accompanying text.

of the contributory infringement statute that would have compelled the patentee to license others to sell the unpatented chemical for use in the patented method.[111] The Supreme Court observed that, under such a rule, competing sellers could readily "free-ride" by awaiting the outcome of the patentee's research efforts and then reap substantial profits by demanding licenses to sell the unpatented chemical essential to the newly developed process.[112]

The Court of Appeals for the Second Circuit, by holding that patents that later confer monopoly power can be acquired under the antitrust laws,[113] emphasized the importance of patents as an incentive to development that should be protected from antitrust exposure if the development succeeds commercially.[114] Similarly, the Court of Appeals for the Third Circuit determined that the public interest favored the patentee and not the creation of competition through infringement,[115] and granted a preliminary injunction against the defendant's patent infringement even though the defendant was selling the infringing drug "at a significantly lower price" than the patentee.[116] The court observed that, unless the investment of human and capital resources required by chemical research is rewarded by some form of patent protection, major drug manufacturing companies might forego such large expenditures and divert their resources from the socially beneficial development of new drugs.[117] The courts therefore have adhered to the congressional mandate of encouraging patented developments over the

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111. Dawson Chem. Co. v. Rohm & Haas Co., 448 U.S. 176, 221 (1980). The Court's decision rested on the construction of 35 U.S.C. § 271 (1976), which codifies the patent infringement doctrine. The statute provides that:

> (c) Whoever sells a component of a patented . . . composition . . . constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.
>
> (d) no patent owner otherwise entitled to relief for infringement or contributory infringement of a patent shall be denied relief or deemed guilty of misuse or illegal extension of the patent right by reason of his having done one or more of the following: (1) derived revenue from acts which if performed by another without his consent would constitute contributory infringement of the patent; (2) licensed or authorized another to perform acts which if performed without his consent would constitute contributory infringement of the patent; (3) sought to enforce his patent rights against infringement or contributory infringement.

See supra note 103.

112. Dawson Chem. Co. v. Rohm & Haas Co., 448 U.S. 176, 222 (1980).

113. SCM Corp. v. Xerox Corp., 645 F.2d 1195 (2d Cir. 1981), *cert. denied*, 455 U.S. 1016 (1982).

114. *Id.* at 1206 (threat of treble damage liability for refusal to license patented invention should not deter commercial exploitation of invention).

115. Eli Lilly & Co. v. Premo Pharmaceutical Labs., Inc., 630 F.2d 120 (3d Cir. 1980), *cert. denied*, 449 U.S. 1014 (1980).

116. *Id.* at 137.

117. *Id.* (patent is means of inducing investment in research instead of in "production process improvement programs, advertising, increased customer service, or the like")

policy of free competition.[118]

On the other hand, the philosophy favoring removal of unwarranted interferences with competition has resulted in two significant developments in the law in the last fifteen years. In *Lear, Inc. v. Adkins*,[119] the Supreme Court abolished the doctrine of licensee estoppel to hold a patent invalid on the grounds that the public interest in permitting full and free competition in the use of ideas outweighed the equities of the licensor.[120] The Court concluded that a licensee could question the validity of a patent—which represents a determination by the Patent Office made without the aid of adversary arguments—particularly because the licensor's case was supported by the presumption of validity.[121]

Soon thereafter, the Supreme Court swept away the doctrine of mutuality of estoppel in *Blonder-Tongue Laboratories, Inc. v. University of Illinois Foundation*.[122] The Court overturned the rule that a patentee whose patent had been adjudged invalid could assert it against other defendants, holding that such a patentee was estopped from relitigating the validity of his patent.[123] Although the Court conceded the "extreme intricacy" of patent issues, it reasoned that patentees would be able to present all relevant evidence in the first litigation.[124] Furthermore, given that the presumption of patent validity favors patentees, the Court concluded that the high costs of repeated patent litigation were wasteful and that the patentee could put its funds to better uses, such as further research and development.[125]

The Supreme Court's holdings in these cases encourage challenges to patents in order to free the channels of competition from invalid patents. The Court expressed the "consistent view" that a patentee should not be insulated from suit if the patented idea is in fact not patentable or is exploited in a manner beyond the scope of the patent monopoly.[126] These decisions increase the number of potential challengers of patents and reduce the patentee's chances for success because although one loss will be dispositive, the patentee must win on validity against every infringer. This result, however, does not nullify valid patents; nor does it require a higher standard of proof for protection of valid patents. Indeed, the Court observed that patentees were "heavily favored as a class

118. *Id.* at 138.
119. 395 U.S. 653 (1969).
120. *Id.*
121. *Id.* at 670.
122. 402 U.S. 313 (1971).
123. *Id.*
124. *Id.* at 330-34.
125. *Id.* at 335.
126. *Id.* at 349-50.

of litigants" by the presumption of validity.[127] The cases weighing patents in the balance with competitive policy clearly indicate respect for the patent right and the presumption of validity, and, therefore, favor treating patentees equally with other plaintiffs in preliminary injunction proceedings.

C. Conflict with the Standard in Analogous Areas of Law

Imposition of the extra burden under the statutory presumption of patent validity does not comport with the respect accorded the presumptions of validity for copyrights[128] and trademarks.[129] In the latter areas, the traditional standard for preliminary relief prevails: a party seeking a preliminary injunction must demonstrate only a likelihood of success on the merits. In copyright cases, therefore, a preliminary injunction will be granted once the plaintiff makes a prima facie showing of his right.[130] Presenting the certificate of registration usually is sufficient.[131] Similarly, courts deciding cases arising under the Lanham

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127. *Id.* at 335.

128. The relevant portion of the 1976 Copyright Act states that "in any judicial proceedings the certificate of a registration . . . shall constitute prima facie evidence of the validity of the copyright and of the facts stated in the certificate. The evidentiary weight to be accorded the certificate of a registration made thereafter shall be within the discretion of the court." 17 U.S.C. § 410(c) (1976 & Supp. V 1981).

129. The Trademark Act of 1946 (the Lanham Act) provides in pertinent part: "A certificate of registration of a mark upon the principal register provided by this chapter shall be prima facie evidence of validity of the registration . . . ." 15 U.S.C. § 1057(b) (1976).

130. Novelty Textile Mills, Inc. v. Joan Fabrics Corp., 558 F.2d 1090, 1094 (2d Cir. 1977) (quoting Houghton Mifflin Co. v. Stackpole Sons, Inc., 104 F.2d 306, 307 (2d Cir.), *cert. denied*, 308 U.S. 597 (1939)). The rationale underlying the issuance of a preliminary injunction upon a showing of a certificate of registration is that a court may presume that a copyright holder has suffered irreparable injury when another has invaded his exclusive use of the copyrighted material. *Id.* (incidentally relying on plaintiff's independent evidence of irreparable injury). *Accord* Martin Luther King, Jr. Center for Social Change, Inc. v. American Heritage Prods., 508 F. Supp. 854, 861 (N.D. Ga. 1981) (proof of valid copyright and prima facie case of infringement entitles plaintiff to preliminary injunction without proof of irreparable harm), *rev'd on other grounds*, 694 F.2d 674 (11th Cir. 1983); Northwestern Bell Tel. Co. v. Bedco, Inc., 501 F. Supp. 299, 303 (D. Minn. 1980) (irreparable injury presumed if plaintiff shows copyright infringement); Metro-Goldwyn-Mayer, Inc. v. Showcase Atlanta Coop. Prods., 479 F. Supp. 351, 362 (N.D. Ga. 1979) (proof of copyright infringement invokes presumption of irreparable injury for purpose of preliminary injunction); Miller Brewing Co. v. Carling O'Keefe Breweries of Canada, Ltd., 452 F. Supp. 429, 437 (W.D.N.Y. 1978) (copyright infringement raises presumption of irreparable harm); Encyclopaedia Britannica Educ. Corp. v. Crooks, 447 F. Supp. 243, 247 (W.D.N.Y. 1978) (prima facie case of infringement raises presumption of irreparable harm); Walt Disney Prods. v. Air Pirates, 345 F. Supp. 108, 110 (N.D. Cal. 1972) (irreparable injury presumed from showing of valid copyright), *aff'd in part and rev'd in part*, 581 F.2d 751 (9th Cir. 1978), *cert. denied sub nom.* O'Neill v. Walt Disney Prods., 439 U.S. 1132 (1979); Universal Athletic Sales Co. v. Salkeld, 340 F. Supp. 899, 902 (W.D. Pa. 1972) (proof of prima facie case of infringement and likelihood of success on merits obviates need for detailed evidence of irreparable harm). For a departure from the norm in copyright cases, see Warner Bros. v. Film Ventures Int'l, 403 F. Supp. 522, 525 (C.D. Cal. 1975) (preliminary injunction requires showing of "reasonable certainty [not just likelihood] that plaintiffs will prevail at a trial on the merits").

131. *See, e.g.*, Herbert Rosenthal Jewelry Corp. v. Grossbardt, 428 F.2d 551, 553 (2d Cir. 1970) (certificate of registration prima facie evidence of copyright validity); Dollcraft Indus. v. Well-Made Toy Mfg. Co., 479 F. Supp. 1105, 1114 (E.D.N.Y. 1978) (same).

Act[132] require only that the trademark owner satisfy the general criteria for a preliminary injunction; courts presume the validity of the trademark right from the registration.[133] The construction of the presumption of validity in this manner in trademark and copyright cases suggests that a similar meaningful presumption should apply in patent preliminary injunction matters.

D. Conflict with the Jurisprudence of Individual Merit

One rationale for the stringent rule is that the validity of patents issued by the Patent Office is statistically so unreliable that a harsh standard is compelled in actions for preliminary relief. In a 1971 case, Judge Friendly cited a study showing that "more than 80% of patent infringement actions on appeal result in a determination that the patent sued upon is invalid."[134] Two recent five-year studies conducted by the Patent and Trademark Office[135] showed overall invalidity rates of 49% for the years 1968-1972 and 55% for 1973-1977. The invalidity rates in appellate determinations were 69% and 70%, respectively.[136]

Norms of invalidity, however, do not justify imposition of an extraordinary standard of proof on an individual litigant for a preliminary injunction. A particular patentee may be able to prove the likelihood of prevailing on the merits, despite the fact that one patent in two is found invalid. The logic of the stringent rule is that because a relatively high proportion of a sample of patents were held invalid at the appellate level, all other patents that will be litigated are likely to be held invalid. This logic is inconsistent with the basic precept of our jurisprudence that each case should be decided on its own merits, and not by reference to norms for cases of particular kinds.

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132. Ch. 540, 60 Stat. 427 (1946) (codified as amended at 15 U.S.C. §§ 1051-1127 (1976)).

133. *See* Keebler Co. v. Rovira Biscuit Corp., 624 F.2d 366, 373 (1st Cir. 1980) (trademark registration shifts burden of proof from plaintiff to defendant, who must rebut presumption of plaintiff's right to exclusive use).

The Lanham Act provides in pertinent part:

> (a) Any registration issued under the Act of March 3, 1881, or the Act of February 20, 1905, or of a mark registered on the principal register provided by this chapter and owned by a party to an action shall be admissible in evidence and shall be prima facie evidence of registrant's exclusive right to use the registered mark in commerce on the goods or services specified in the registration subject to any conditions or limitations stated therein, but shall not preclude an opposing party from proving any legal or equitable defense or defect which might have been asserted if such mark had not been registered.

Ch. 540, § 33, 60 Stat. 427, 438 (1946) (current version at 15 U.S.C. § 1115(a) (1976)).

134. Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 443 F.2d 867, 872 (2d Cir. 1971), *cert. denied*, 412 U.S. 929 (1973).

135. PATENT & TRADEMARK OFFICE, U.S. DEP'T COMMERCE, 989 OFFICIAL GAZETTE, Dec. 4, 1979, at OG 2. The statistics were compiled from notices filed by court clerks pursuant to statute and also from reported decisions. The rates were calculated by examining the status of the patent at the end of the litigation, whether in the district court, court of claims, or court of appeals.

136. *Id.*

Nor should the stringent rule be a guise for avoiding the technical difficulty of patent subject matter. Courts have proved themselves capable of considering the substance of validity issues on motions for preliminary injunctions,[137] and the Supreme Court has noted that patent cases present "difficulties comparable to those encountered daily by the courts in such frames of reference as negligence and scienter."[138] If the alleged infringer can cite pertinent new art against the patent, a district court should consider it on a motion for preliminary injunction and determine whether the patentee, nevertheless, has a reasonable likelihood of success on the merits, without simply resorting to the equivalent of an automatic rule of rejection.

Conclusion

The competing policies at work in the patent arena are sympathetic to patent rights and to encouraging innovation by according legal respect to such rights. At a minimum, they warrant treatment for patentees equal to that accorded other plaintiffs in the preliminary injunction context. Patentees should not start a preliminary injunction proceeding with an extra burden in the form of a presumption of invalidity.

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137. *See, e.g.*, Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 443 F.2d 867 (2d Cir. 1971), *cert. denied*, 412 U.S. 929 (1973); Simson Bros. v. Blancard & Co., 22 F.2d 498 (2d Cir. 1927).

138. Blonder-Tongue Labs., Inc. v. University of Ill. Found., 402 U.S. 313, 331 (1971); Graham v. John Deere Co., 383 U.S. 1, 18 (1966).

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The Decline in Effective Patent Life of New Drugs

Martin M. Eisman and William M. Wardell

The effective patent life for new chemical entity drugs has fallen sharply in recent years as a result of an increase in the clinical testing period, later starting of clinical testing after the patent application, and quicker issue of patents.

In a recent statement of concern about the state of domestic industrial innovation, the President recommended strengthening the patent system (*1*). That statement implied that the historical role of patent protection as a major stimulus for innovation had weakened. To determine the extent to which the problem affects pharmaceuticals, this paper examines the state of patent protection afforded new drugs.

The Patent Act of 1836 was adopted because of a perceived need to encourage innovation by eliminating the reluctance to disclose an invention. As incentive for disclosure, the Patent Act granted the inventor a 17-year exclusive right to his invention. As the innovative process became uncertain, lengthy, and expensive, patent protection acquired even greater importance.

In the research-based prescription pharmaceutical industry, patents play an important role. Approximately one out of 10,000 compounds initially examined survives the intense scrutiny and demonstrates the potential to justify marketing. The Pharmaceutical Manufacturers' Association surveyed its member companies in 1962, 1967, and 1970 asking for "an estimate of the number of chemicals, compounds, mixtures, filtrates, or other substances obtained, prepared, extracted or isolated for a medical research purpose, and subjected to biological tests or screens." This included material obtained from outside the company. The estimates were 144,559 for 1962, 175,760 for 1967 and 126,060 for 1970, averaging 148,793 items tested per year.

Our studies showed that an average of 15.3 New Chemical Entities (NCEs) were introduced annually from 1962 to 1978. Using these averages, the ratio of chemicals tested per year to NCEs introduced per year is 9725:1.

Bringing that single drug to market has been estimated to cost $54 million in 1976 dollars (*2*). Because of this uncertainty and high cost, patent protection is a necessary incentive for the infusion of capital to stimulate research and development. Since drugs are technically easy to copy, the patent provides the primary protection against imitation and competition.

Another form of protection against competition — one probably not intended by Congress is afforded by the regulatory system of the Food and Drug Administration. The expense involved in seeing a new drug through the demanding system of regulatory review to demonstrate safety and efficacy creates a substantial barrier to entry into the industry.

However, while certain aspects of the regulatory process may offer some protection against competition, other aspects reduce the duration of patent protection that is of commercial value to the original patent holder. Most drug patents are filed when biological activity is first observed (*3,4*). Since this occurs long before the drug receives regulatory approval for marketing, the "effective" patent life will be reduced considerably from its nominal period of 17 years. We will now examine the extent of this reduction, and its change with time.

Time Trend in Effective Patent Life (EPL)

Effective Patent Life (EPL) is defined as the period of patent protection remaining for a drug at the time of U.S. NDA approval (i.e., the time from NDA approval to expiration of the patent). Recent studies (*3,5,6*) show that EPL has declined substantially over the past 15 to 20 years. This trend is generally attributed to the concomitant increase in the time required for human investigation and NDA approval (*3,5*). To examine this hypothesis, we need to analyze the time trends in both EPL and the period from the start of clinical investigation to U.S. NDA approval.

Dr. Eisman is an Associate in the Department of Pharmacology and Toxicology, University of Rochester School of Medicine and Dentistry. Dr. Wardell is an Associate Professor of Pharmacology; Toxicology and of Medicine, and Director of the Center for the Study of Drug Development, at the University of Rochester School of Medicine and Dentistry. He is also Chairman of the Committee on Government Affairs of the American Society for Clinical Pharmacology and Therapeutics.

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Methods — The analysis is based on all patented new chemical entities (NCEs) receiving NDA approval from 1966 through 1979 (*a*). The information needed to determine EPL included dates of the start of clinical testing in the U.S., NDA approval, and patent application and issue (*b*).

Data were available for nearly all variables from 1966 through 1979 (*c*).

Sources for the patent data included the patent consultant Louis Leaman, SmithKline Corporation, direct surveys of individual pharmaceutical companies, and various reference sources, including *Chemical Abstracts* and *Official Gazette of the U.S. Patent Office*. For multi-source drugs (i.e., the same drug marketed under different brand names by different companies) only the drug of the original patent holder was included in the averages. Of all 191 NCEs approved from 1966 through 1979, 168 had patents. The data from those 168 drugs were used to calculate EPL.

Of the three types of drug patents (new compound, medical use, and chemical process), a patent on the new compound provides the most reliable protection. To calculate EPL, we used the earliest compound patent listed for a drug. If no compound patent existed, we used the earliest patent, regardless of type.

Data are grouped according to year of NDA approval. For each variable (e.g., time from start of clinical testing to NDA approval), the time difference was calculated for each drug, and those differences averaged for all drugs approved during that year. The averages were plotted and the raw plots smoothed (Figures 1 and 3) according to the "moving median of three" technique of Tukey (*7*).

Drugs tested before 1963: Length of clinical investigation phase — The IND filing dates assigned retrospectively to drugs in clinical trial before August 1962 do not represent the start of clinical testing in the U.S. (*d*).

Thus, the true period of clinical investigation for pre-1963 drugs began earlier than the date represented by retrospective IND filings. Of the 168 patented NCEs approved from 1966 through 1979, 43 had been assigned retrospective IND filing dates. We were able to obtain the date of first U.S. clinical testing in man in the U.S. for 21 of the 43 retrospective filing dates. From this information, we have derived a standard value of 24 months to apply as a correction to the remaining 22 drugs for which this information was unobtainable (*e*).

Effective Patent Life — Figure 1 displays the relationship between the patent and drug development processes, showing the times of NDA approval and the start of clinical testing in relation to the time of patent issue. The data are plotted according to year of NDA approval. EPL, the time from NDA approval to patent expiration, can be read directly from the right-hand ordinate. As shown in the Figure, EPL for pharmaceuticals was

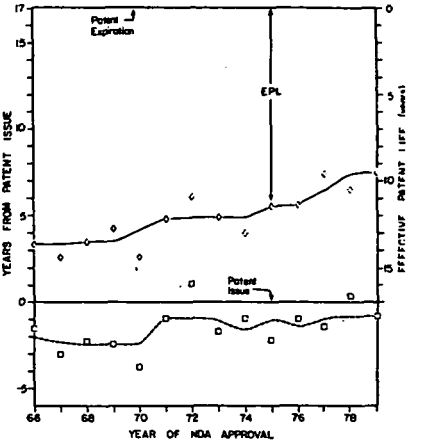

Figure 1. NDA approval (averaged ⊙; smoothed ——) and start of clinical testing (averaged □; smoothed – – –), corrected for retrospective IND filings, are plotted in relation to patent issue. Smoothing was done by Tukey's "moving median of three" technique (7).

considerably less than 17 years, even at the beginning of the 14-year study period. It declined from 13.6 years in 1966 to 9.5 years in 1979, a decrease of 4.1 years.

Time from start of U.S. clinical investigation to NDA approval — Figure 1 also shows the pattern (after smoothing (*7*)) of the period from the start of clinical testing to NDA approval during the 14 years from 1966 to 1979. During the 12-year period from 1968 to 1979, EPL dropped by 4.0 years, from 13.5 years to 9.5 years (*f*). The time from the start of U.S. clinical testing to NDA approval increased by 2.4 years (i.e., from 5.9 to 8.3 years) from 1968 to 1979, accounting for 60% of the decrease in EPL (*g*).

Thus the increase in the period from the start of clinical testing to NDA approval accounted for only slightly more than half of the decline in EPL. Therefore, we need to examine the components of EPL in more detail to determine where the remainder of its decline occurred.

Effective Patent Life and the Drug Drug Development Process

From our data (presented later in this paper) we know that the sequence of events in the process of drug development is generally as shown in Figure 2. The sequence begins with the filing of a patent application during the preclinical phase, and continues

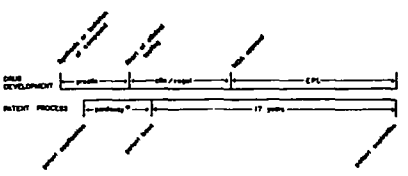

Figure 2/ *Effective Patent Life (EPL) is a function of the timing of the patent application, the pendency period, and the duration of the clinical and regulatory period, as well as the 17-year period of patent protection. *The pendency period is the time from patent application to patent issue.*

with the start of clinical testing, patent issue, NDA approval, and finally patent expiration.

From this pattern and Figure 2, we see that EPL (i.e., the period from NDA approval to patent expiration) is a function of the timing of the patent application, the pendency period, and the duration of the clinical and regulatory periods, as well as the 17-year period of patent protection.

Thus, in addition to its dependence on the duration of the clinical and regulatory periods, EPL depends on two other important factors. It decreases if clinical testing is begun later in relation to the patent application, and conversely will increase if the patent pendency period increases. The final EPL depends on the algebraic sum of the changes in the components.

The changes that occurred in the two additional components of EPL are shown in Figure 3. For the years 1968 and 1979, the two years most representative of the general trend during the study period, the time from patent application to the start of U.S. clinical testing increased 0.5 years (accounting for 13% of the decrease in EPL). The time from earliest patent application to patent issue decreased 1.1 years (accounting for 27% of the decrease in EPL) (h). Coupled with the 2.4 year increase in the period from the start of clinical testing to NDA approval, these changes account for the entire 4.0 year decrease in EPL from 1968-1979. (i)

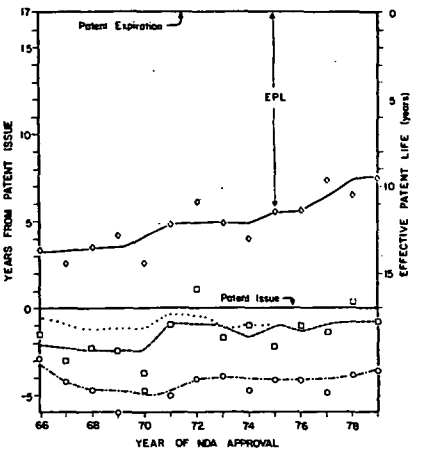

Figure 3/*Averaged and smoothed values for NDA approval, start of clinical testing, and patent application are plotted in relation to patent issue. The symbols and smoothing are defined as in Figure 1, with the addition of earliest patent filing (averaged ⊙; smoothed — · —) and start of clinical testing, uncorrected for retrospective IND filings (· · · ·).*

Discussion/Conclusions

EPL was 13.6 years at the beginning of our study period, 1966. This is considerably less than the 17-year nominal period of patent protection. As time progressed, EPL fell further. This trend is similar to that reported by other investigators (3,5,6). The decrease over time has generally been attributed entirely to an increase in the time between the beginning of clinical testing and NDA approval (3,5), although Statman suggests that this may be responsible for only part of the decrease (6).

Our analysis shows that in the specific sample of NCEs analyzed, almost half of the decline in EPL was caused by two additional factors: An increase in the time between patent filing and clinical testing and a reduction in the pendency period. It should be noted, as seen in the Figures, that the relative contribution of each of the three components depends to some extent on the years compared.

For the 12-year period from 1968 to 1979, the declining EPL can be explained by two trends. The clinical/regulatory period increased (with all of the increase being in the clinical period), and more of the clinical/regulatory period fell within the period of patent protection (i.e., after the date of patent issue). This latter trend was caused by quicker issue of the patent by the Patent Office (thereby starting the patent clock sooner in the drug development process), and by later starting of the clinical testing.

It should be clearly understood that the "start of clinical testing" being described in this analysis is clinical testing *in the U.S. only.* Although approximately half of the drugs approved in the U.S. originate abroad (10), and a significant fraction of U.S.-originated NCEs are now also first tested clinically abroad (8,9), this study is limited to the U.S. component of the drug development process.

Although a decrease in the pendency period results in earlier issue of patents, it contributes to the erosion of EPL by placing a greater proportion of the clinical/regulatory process within the period of patent protection.

It is not clear why U.S. clinical testing is starting

later in the drug development process realtive to the date of patent application, although one possible reason is the increase in preclinical data requirements prior to first human testing. Related factors, such as compliance with the Good Laboratory Practice (GLP) regulations, could also require more time. Another possibility is that more prolonged initial clinical testing is being done overseas — either by U.S. firms, or because a greater proportion of foriegn-originated drugs are getting U.S. INDs now than previously, either by licensing to U.S. firms, or through foreign-owned sponsoring firms. Further refinement of the data into subsets for self-originated and licensed drugs of U.S. and foreign-owned firms will enable us to examine the latter possibility.

Thus it is clear that tbe decline in EPL is a result of factors in both the drug development and patent processes. Taking the preclinical and clinical components together, a possible 73% (2.9 years) of the decline in EPL between 1968 and 1979 was accounted for by an increase in components influenced by the IND-NDA regulations, with the remainder of the decline influenced by the Patent Office.

Acknowledgement

This material is based in part upon work supported by the National Science Foundation under grant #DAR79—17602. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of the National Science Foundation.

Footnotes

(a) In this study we define NCEs as compounds of molecular structure not previously marketed in the U.S., excluding new salts or esters, vaccines, antigens, antisera, immunoglobins, surgical products, and diagnostic agents.

(b) For NCEs with INDs filed after 1963, we used the date of IND filing as the start of clinical testing in the U.S. The 30-day waiting period required since August 1970 has a conservstive influence on our testing of the hypothesis. As described later, for NCEs that preceded the 1963 IND requirement, we used the actual date of first human administration in the U.S., where available.

(c) All data are complete for NCEs approved from 1966 to 1979, except for the following. Data on start of clinical testing are based on 81% (13 of 16) of patented NCEs for 1977, and 69% (11 of 16) for 1978. Two drugs were excluded from the pendency averages because their pendencies were excessive compared to all other drugs approved during the same years (i.e., 1978 and 1979).

(d) The final IND regulations (Procedural and Interpretive Regulations, New Drugs for Investigational Use) printed in the *Federal Register* of January 8, 1963 required all drug sponsors to submit completed INDs by June 9, 1963 for all drugs in clinical trials as of August 10, 1962. Approximately 1100 drugs were assigned 1963 (i.e., retrospective) IND filing dates during the initial period.

(e) The value of 24 months was obtained by calculating the mean of the available values after eliminating two outlier drugs.

(f) The general trends over the study period are better represented by comparing 1979 with 1968 rather than with 1966. This is shown more clearly in Figure 3.

(g) This period is made up of two components, the IND phase and the NDA phase, which we have examined in detail in other publications (8,9). For the specific set of drugs used in this paper, the mean value of the period from NDA submission to approval was 2.4 years from 1966 to 1972, and 2.2 years from 1973 to 1979. The period of clinical testing increased from a mean of 3.3 years in 1966-1972, to a mean of 4.8 years in 1973-1979.

(h) She used the date of earliest patent filing (including date of foreign claims priority) as an indicator of the company's initial active interest in the NCE.

(i) The dotted line in Figure 3 represents the start of clinical testing, uncorrected for retrospective IND filings. Failing to correct for the retrospective IND filings would substantially underestimate the period of clinical testing and regulatory review (by more than one year from 1966 to 1970). Thus, the uncorrected estimate of the increase in the clinical/regulatory period would be artifactually high by that amount. This could account for the apparent agreement previous authors observed between the decline in EPL and the increase in clinical/regulatory time for the period 1966 to 1976 (9).

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March 18, 1981

MEMORANDUM

TO: Members of the Subcommittee on Courts, Civil Liberties and the Administration of Justice

FROM: Bruce Lehman, Chief Counsel, Subcommittee on Courts, Civil Liberties and the Administration of Justice

SUBJECT: The Patent Term Restoration Issue

You may have been contacted recently by persons seeking your cosponsorship of H.R. 1937, relating to patent term restoration.

You or your staff may find the enclosed article from Research Management Magazine helpful in independently evaluating the issue.

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Research Management, 21 (1): 18-21
1981.

The Decline in Effective Patent Life of New Drugs

Martin M. Eisman and William M. Wardell

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The Patent Act of 1836 was adopted because of a perceived need to encourage innovation by eliminating the reluctance to disclose an invention. As incentive for disclosure, the Patent Act granted the inventor a 17-year exclusive right to his invention. As the innovative process became uncertain, lengthy, and expensive, patent protection acquired even greater importance.

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(Our studies showed that an average of 15.3 New Chemical Entities (NCEs) were introduced annually from 1962 to 1978. Using these averages, the ratio of chemicals tested per year to NCEs introduced per year is 9725:1.)

Bringing that single drug to market has been estimated to cost $54 million in 1976 dollars (*2*). Because of this uncertainty and high cost, patent protection is a necessary incentive for the infusion of capital to stimulate research and development. Since drugs are technically easy to copy, the patent provides the primary protection against imitation and competition.

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Data are grouped according to year of NDA approval. For each variable (e.g., time from start of clinical testing to NDA approval), the time difference was calculated for each drug, and those differences averaged for all drugs approved during that year. The averages were plotted and the raw plots smoothed (Figures 1 and 3) according to the "moving median of three" technique of Tukey (*7*).

Drugs tested before 1963: Length of clinical investigation phase — The IND filing dates assigned retrospectively to drugs in clinical trial before August 1962 do not represent the start of clinical testing in the U.S. (*d*).

Thus, the true period of clinical investigation for pre-1963 drugs began earlier than the date represented by retrospective IND filings. Of the 168 patented NCEs approved from 1966 through 1979, 43 had been assigned retrospective IND filing dates. We were able to obtain the date of first U.S. clinical testing in man in the U.S. for 21 of the 43 retrospective filing dates. From this information, we have derived a standard value of 24 months to apply as a correction to the remaining 22 drugs for which this information was unobtainable (*e*).

Effective Patent Life — Figure 1 displays the relationship between the patent and drug development processes, showing the times of NDA approval and the start of clinical testing in relation to the time of patent issue. The data are plotted according to year of NDA approval. EPL, the time from NDA approval to patent expiration, can be read directly from the right-hand ordinate. As shown in the Figure, EPL for pharmaceuticals was

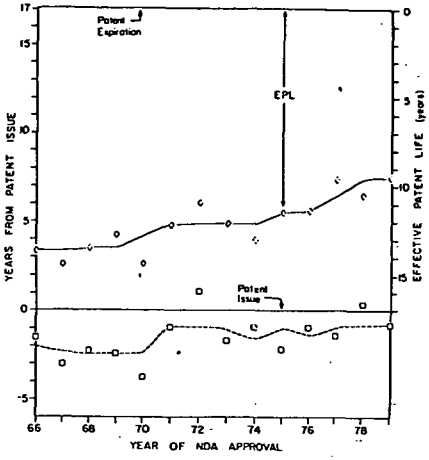

Figure 1/*NDA approval (averaged ◇; smoothed ———) and start of clinical testing (averaged □; smoothed – – –), corrected for retrospective IND filings, are plotted in relation to patent issue. Smoothing was done by Tukey's "moving median of three" technique (7).*

considerably less than 17 years, even at the beginning of the 14-year study period. It declined from 13.6 years in 1966 to 9.5 years in 1979, a decrease of 4.1 years.

Time from start of U.S. clinical investigation to NDA approval — Figure 1 also shows the pattern (after smoothing (*7*)) of the period from the start of clinical testing to NDA approval during the 14 years from 1966 to 1979. During the 12-year period from 1968 to 1979, EPL dropped by 4.0 years, from 13.5 years to 9.5 years (*f*). The time from the start of U.S. clinical testing to NDA approval increased by 2.4 years (i.e., from 5.9 to 8.3 years) from 1968 to 1979, accounting for 60% of the decrease in EPL (*g*).

Thus the increase in the period from the start of clinical testing to NDA approval accounted for only slightly more than half of the decline in EPL. Therefore, we need to examine the components of EPL in more detail to determine where the remainder of its decline occurred.

Effective Patent Life and the Drug Development Process

From our data (presented later in this paper) we know that the sequence of events in the process of drug development is generally as shown in Figure 2. The sequence begins with the filing of a patent application during the preclinical phase, and continues

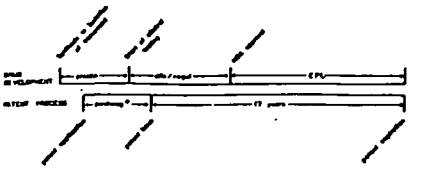

*Figure 2/ Effective Patent Life (EPL) is a function of the timing of the patent application, the pendency period, and the duration of the clinical and regulatory period, as well as the 17-year period of patent protection. *The pendency period is the time from patent application to patent issue.*

with the start of clinical testing, patent issue, NDA approval, and finally patent expiration.

From this pattern and Figure 2, we see that EPL (i.e., the period from NDA approval to patent expiration) is a function of the timing of the patent application, the pendency period, and the duration of the clinical and regulatory periods, as well as the 17-year period of patent protection.

Thus, in addition to its dependence on the duration of the clinical and regulatory periods, EPL depends on two other important factors. It decreases if clinical testing is begun later in relation to the patent application, and conversely will increase if the patent pendency period increases. The final EPL depends on the algebraic sum of the changes in the components.

The changes that occurred in the two additional components of EPL are shown in Figure 3. For the years 1968 and 1979, the two years most representative of the general trend during the study period, the time from patent application to the start of U.S. clinical testing increased 0.5 years (accounting for 13% of the decrease in EPL). The time from earliest patent application to patent issue decreased 1.1 years (accounting for 27% of the decrease in EPL) (*h*). Coupled with the 2.4 year increase in the period from the start of clinical testing to NDA approval, these changes account for the entire 4.0 year decrease in EPL from 1968-1979. (i)

Discussion/Conclusions

EPL was 13.6 years at the beginning of our study period, 1966. This is considerably less than the 17-year nominal period of patent protection. As time progressed, EPL fell further. This trend is similar to that reported by other investigators (*3,5,6*). The decrease over time has generally been attributed entirely to an increase in the time between the beginning of clinical testing and NDA approval (*3,5*), although Statman suggests that this may be responsible for only part of the decrease (*6*).

Our analysis shows that in the specific sample of NCEs analyzed, almost half of the decline in EPL was caused by two additional factors: An increase in the time between patent filing and clinical testing,

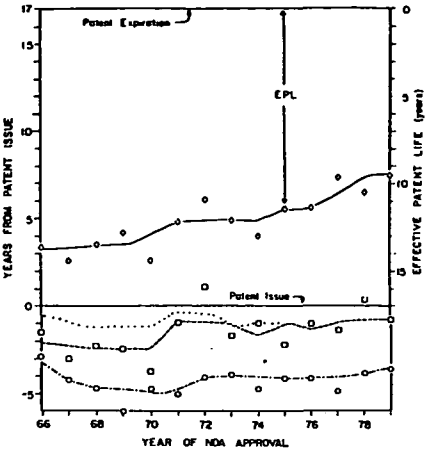

Figure 3/Averaged and smoothed values for NDA approval, start of clinical testing, and patent application are platted in relation to patent issue. The symbols and smoothing are defined as in Figure 1, with the addition of earliest patent filing (averaged ⊙; smoothed — · —) and start of clinical testing, uncorrected for retrospective IND filings (· · · ·).

and a reduction in the pendency period. It should be noted, as seen in the Figures, that the relative contribution of each of the three components depends to some extent on the years compared.

For the 12-year period from 1968 to 1979, the declining EPL can be explained by two trends. The clinical/regulatory period increased (with all of the increase being in the clinical period), and more of the clinical/regulatory period fell within the period of patent protection (i.e., after the date of patent issue). This latter trend was caused by quicker issue of the patent by the Patent Office (thereby starting the patent clock sooner in the drug development process), and by later starting of the clinical testing.

It should be clearly understood that the "start of clinical testing" being described in this analysis is clinical testing *in the U.S. only*. Although approximately half of the drugs approved in the U.S. originate abroad (*10*), and a significant fraction of U.S.-originated NCEs are now also first tested clinically abroad (*8,9*), this study is limited to the U.S. component of the drug development process.

Although a decrease in the pendency period results in earlier issue of patents, it contributes to the erosion of EPL by placing a greater proportion of the clinical/regulatory process within the period of patent protection.

It is not clear why U.S. clinical testing is starting

later in the drug development process realtive to the date of patent application, although one possible reason is the increase in preclinical data requirements prior to first human testing. Related factors, such as compliance with the Good Laboratory Practice (GLP) regulations, could also require more time. Another possibility is that more prolonged initial clinical testing is being done overseas — either by U.S. firms, or because a greater proportion of foriegn-originated drugs are getting U.S. INDs now than previously, either by licensing to U.S. firms, or through foreign-owned sponsoring firms. Further refinement of the data into subsets for self-originated and licensed drugs of U.S. and foreign-owned firms will enable us to examine the latter possibility.

Thus it is clear that the decline in EPL is a result of factors in both the drug development and patent processes. Taking the preclinical and clinical components together, a possible 73% (2.9 years) of the decline in EPL between 1968 and 1979 was accounted for by an increase in components influenced by the IND-NDA regulations, with the remainder of the decline influenced by the Patent Office.

Acknowledgement

This material is based in part upon work supported by the National Science Foundation under grant #DAR79—17602. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of the National Science Foundation.

Footnotes

(a) In this study we define NCEs as compounds of molecular structure not previously marketed in the U.S., excluding new salts or esters, vaccines, antigens, antisera, immunoglobins, surgical products, and diagnostic agents.

(b) For NCEs with INDs filed after 1963, we used the date of IND filing as the start of clinical testing in the U.S. The 30-day waiting period required since August 1970 has a conservative influence on our testing of the hypothesis. As described later, for NCEs that preceded the 1963 IND requirement, we used the actual date of first human administration in the U.S., where available.

(c) All data are complete for NCEs approved from 1966 to 1979, except for the following. Data on start of clinical testing are based on 81% (13 of 16) of patented NCEs for 1977, and 69% (11 of 16) for 1978. Two drugs were excluded from the pendency averages because their pendencies were excessive compared to all other drugs approved during the same years (i.e., 1978 and 1979).

(d) The final IND regulations (Procedural and Interpretive Regulations, New Drugs for Investigational Use) printed in the *Federal Register* of January 8, 1963 required all drug sponsors to submit completed INDs by June 9, 1963 for all drugs in clinical trials as of August 10, 1962. Approximately 1100 drugs were assigned 1963 (i.e., retrospective) IND filing dates during the initial period.

(e) The value of 24 months was obtained by calculating the mean of the available values after eliminating two outlier drugs.

(f) The general trends over the study period are better represented by comparing 1979 with 1968 rather than with 1966. This is shown more clearly in Figure 3.

(g) This period is made up of two components, the IND phase and the NDA phase, which we have examined in detail in other publications (8,9). For the specific set of drugs used in this paper, the mean value of the period from NDA submission to approval was 2.4 years from 1966 to 1972, and 2.2 years from 1973 to 1979. The period of clinical testing increased from a mean of 3.3 years in 1966-1972, to a mean of 4.8 years in 1973-1979.

(h) We used the date of earliest patent filing (including date of foreign claims priority) as an indicator of the company's initial active interest in the NCE.

(i) The dotted line in Figure 3 represents the start of clinical testing, uncorrected for retrospective IND filings. Failing to correct for the retrospective IND filings would substantially underestimate the period of clinical testing and regulatory review (by more than one year from 1966 to 1970). Thus, the uncorrected estimate of the increase in the clinical/regulatory period would be artifactually high by that amount. This could account for the apparent agreement previous authors observed between the decline in EPL and the increase in clinical/regulatory time for the period 1966 to 1976 (3).

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The Journal of LAW & ECONOMICS

ESTIMATING THE EFFECTS OF REGULATION ON INNOVATION: AN INTERNATIONAL COMPARATIVE ANALYSIS OF THE PHARMACEUTICAL INDUSTRY*

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INNOVATION in the U.S. ethical drug industry in recent years has been characterized by a number of adverse developments. In particular, there has been a sharp decline in the rate of new product introductions and the incentive for engaging in research and development (R & D) activity has been negatively influenced by rapid increases in the costs and risks of developing new products. While there is little debate about the exist nce of these adverse trends, there is considerable controversy about the factors producing them.

Briefly, we list below five hypotheses that have been discussed as explanations for the declining rate of innovation.

(1) Tighter regulation of the industry by the Food and Drug Administration (FDA) has been largely responsible for the declining rate of innovation.
(2) The decline is illusory—while there has been a decline in the *total* number of new drugs being introduced, the number of "important" new drugs introduced annually has not declined.
(3) There has been a "depletion of research opportunities" brought about by the rapid rate of new drug development in the 1950s.
(4) The tragic thalidomide episode in the early 1960s made drug firms and physicians much more cautious in their decisions concerning the marketing and prescribing of new drugs.
(5) Advances in pharmacological science have led to increased safety testing and, therefore, higher costs of developing new drugs.

In this paper, we present some new evidence on these hypotheses. Our

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new evidence is based primarily on a comparative analysis of developments in the United States and United Kingdom. In particular, we attempt to separate the impact of increased regulatory controls in the United States (stemming from the 1962 amendments to the 1938 Federal Food, Drug, and Cosmetic Act)[1] from other factors by using the U.K. industry as a control. Since firms in the latter country have been governed by a very different regulatory system but are similar to U.S. firms in most other ways, we feel that comparative analysis is a very fruitful way of approaching this question.

The paper has the following plan. First, as background to our analysis, we briefly describe the structural changes that have characterized new product innovation in ethical drugs, as well as the hypothesized relations which account for these trends. We then review two past empirical studies that have attempted to explain the most important and controversial of such structural changes: declining levels of new product introductions in the United States. Finally, a model previously developed by Martin Baily[2] is reformulated and employed in a comparative analysis of the U.S. and U.K. industries.

I. Structural Changes in Pharmaceutical Innovation: Trends and Hypotheses

Evidence from a number of studies indicates that the American pharmaceutical industry has undergone some fundamental shifts in innovational structure and performance over recent years. This section briefly documents these basic trends and more systematically considers the proliferating hypotheses which have been advanced to explain these structural changes.

A. *Trends in Pharmaceutical Innovation*

In the post-1962 period, the U.S. pharmaceutical industry has experienced the following.

i) *Declining Rates of New Product Introductions.* This decline is illustrated in Figure I. It shows the total new chemical entities (NCEs) introduced annually into the United States over the period 1954-1974, as well as the subset of each year's introductions that were discovered in the United States by the pharmaceutical industry.[3] NCEs are the most important cate-

[1] Federal Food, Drug, and Cosmetic Act of 1938, 52 Stat. 1040, c. 675 as amended by Pub. L. No. 80-625, 21 U.S.C. §§ 1-517 (1964).

[2] Martin N. Baily, Research and Development Costs and Returns: The U.S. Pharmaceutical Industry, 80 J. Pol. Econ. 70 (1972).

[3] Data on NCEs and their years of introduction were obtained from Paul de Haen, Inc. See note 54 *infra*. Biologicals and diagnostics were deleted from the analysis. Information on the country of discovery was also obtained from de Haen, as well as supplementary sources. An NCE is regarded as discovered in a particular country if the research laboratory producing the

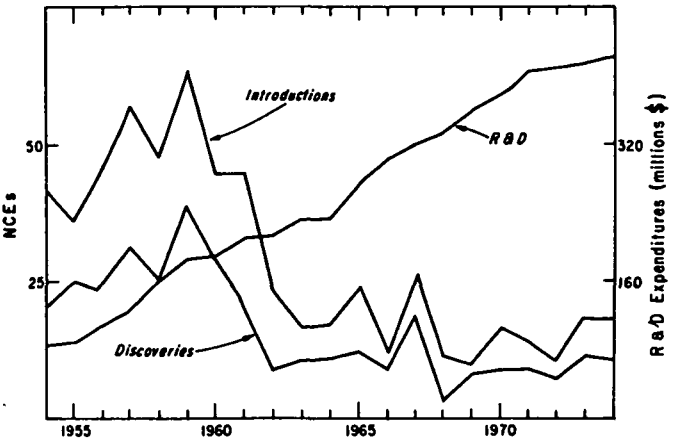

FIGURE I

Introductions and Discoveries of New Chemical Entities by Domestic Firms and Constant (1958) Dollar Expenditures on Pharmaceutical Research and Development, the United States (1954-1974).

gory of new products because they represent compounds not previously marketed and include all significant new therapeutic advances. Thus NCEs form a reasonable index of innovative output. Other new products involve combinations of existing products, new dosage forms, or new brand names.

In Table 1 data on NCE introductions are grouped into five-year periods beginning in 1957.[4] The table shows that the rate of introductions over the most recent five-year period is less than one-third the rate prevailing in a similar period a decade ago. The third column of Table 1, which shows the total market shares captured by new NCEs over these three periods, underscores the extent to which new product innovation has declined as a competitive factor in the ethical drug market.

ii) *Increasing Costs of Innovation.* Over the same time frame in which introductions and discoveries of NCEs have significantly declined, industry R & D expenditures have increased severalfold. These trends imply a rather

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entity was located in that country, irrespective of the nationality of laboratory ownership. See the Appendix for details on the procedures used in the text in this regard.

[4] The choice of period here was dictated by the availability of sales data (no data were available prior to 1957) and the three-year average sales measure employed in Table 1. The sales data were obtained from Intercontinental Medical Statistics, Inc. See note 63 *infra*. The nature of these data is discussed in the Appendix.

TABLE 1
NUMBER AND SALES OF NEW CHEMICAL ENTITIES
IN THE PRE- AND POSTAMENDMENT PERIOD IN THE UNITED STATES

Period	Total Number of New Chemical Entities (NCEs)	Average Annual Sales per NCE (during first 3 years)	Sales of NCEs as a Percentage of Total Ethical Drug Sales[a]
1957-1961	233	$1,745,000.	20.0
1962-1966	93	$2,657,000.	8.6
1967-1971	76	$3,187,000.	5.5

[a] Average annual sales of all NCEs introduced during this period as a percentage of total ethical drug sales in the last year of the period.

Sources: Lists of new chemical entities in each year were obtained from Paul de Haen, Annual New Product Parade, various issues; all information on ethical drug sales were obtained from Intercontinental Medical Statistics, various years.

formidable increase in the costs of producing an NCE, an increase which has been documented in studies by Clymer, Mund, and Sarett.[5] In particular, Sarett suggests that over the decade 1962 to 1972, development costs per NCE rose from 1.2 to 11.5 million dollars.

iii) *Increasing Risks for Innovation.* In addition, there appears to be a corresponding increase in the risks and uncertainty associated with innovational activity. One measure of risk in this industry is the attrition rates for compounds that undergo clinical testing but fail to become commercial products. Clymer[6] estimates that in the 1950s, the attrition rate of drugs undergoing clinical tests was two out of three. The best estimate of the current situation appears to be that less than one of every ten new compounds entering clinical trials become new products.[7]

In short, the decline in new product outputs in the drug industry has been accompanied by a number of adverse structural trends on the input side of the innovational process. Total development time and costs have increased severalfold. Furthermore, innovation has become subject to greater risks and uncertainty. These adverse structural trends in both innovational inputs and outputs appear related to more fundamental underlying changes in the

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[5] Harold A. Clymer, The Changing Costs and Risks of Pharmaceutical Innovation, in The Economics of Drug Innovation 109 (Joseph D. Cooper ed. 1970); Vernon A. Mund, The Return on Investment of the Innovative Pharmaceutical Firm, in the Economics of Drug Innovation 125 (Joseph D. Cooper ed. 1970); L. H. Sarett, FDA Regulations and Their Influence on Future R & D, 17 Int'l J. Research Management 18 (1974).

[6] Harold A. Clymer, *supra* note 5, at 152.

[7] In particular, Louis Lasagna & William M. Wardell, The Rate of New Drug Discovery, in Drug Development and Marketing 155 (R. B. Helms ed. 1975) (Am. Enterprise Inst.), present data (from a questionnaire survey of 15 large firms accounting for 80% of U.S. research) that indicate only 7.1% of all new drug investigational plans (INDs) filed by these firms between 1963 and 1967 had become approved NCEs by April 1974 (the date of their study).

innovational process. A review of the hypothesized causes of these adverse trends follows.

B. *The Hypotheses*

i) *Increased FDA Regulation.* Of the five hypotheses mentioned in the introduction, the role of increased regulation associated with the 1962 Kefauver-Harris amendments has received the most prominent attention in explaining declining pharmaceutical innovation. The antecedent 1938 Food, Drug, and Cosmetic Act required all new drugs to undergo a premarket approval process based on safety. Under this law, the FDA also had to reject a new drug compound within a period of sixty days or the new compound was automatically approved for marketing by the manufacturer.

The 1962 Kefauver-Harris amendments extended the regulatory controls of the FDA in several ways. First, it required firms to submit documented scientific evidence on a new drug's *efficacy* as well as its safety. This led to a substantial increase in the number of tests that had to be performed and submitted to the FDA. Second, the FDA was given discretionary power over the clinical research process. Thus, prior to any testing in humans, firms must now submit a new drug investigational plan (IND) that provides the results of animal tests and plans for human testing. Third, the new regulations provided for FDA approval of advertising claims. Finally, the provision of automatic approval of a new drug application (NDA) after sixty days unless the FDA took specific action was effectively repealed.

Over the post-1962 period, therefore, there has been a significant increase in both the scope and intensity of regulatory controls on ethical drugs. As a consequence, it has been postulated that the costs of discovering and developing a new drug, along with the risks and uncertainty of drug innovation, have increased; and that this, in turn, has been a major factor in the observed decline in innovational output.

ii) *Fewer Marginal and Ineffective Drugs.* The initial response of the FDA to hypothesis (i) was to argue that the observed decline in pharmaceutical innovation is in fact illusory:

> The relevant question is not and never has been how many new drugs are marketed each year, but rather how many significant, useful and unique therapeutic entities are developed. . . . The rate of development and marketing of truly important, significant, and unique therapeutic entities in this country has remained relatively stable for the past 22 years.[8]

Unfortunately, it is difficult to substantiate this FDA claim as there is no list of important new drugs upon which there is general agreement by medi-

[8] Speech by Alexander Schmidt, The FDA Today: Critics, Congress, and Consumerism (Oct. 29, 1974 before the Nat'l Press Club, Wash., D.C.).

cal experts. Most lists from academic sources, for example, show a significant downward trend in important therapeutic advances, as does at least one prior FDA ranking of important new drugs.[9] Furthermore, measures of pharmaceutical innovation based on economic criteria strongly suggest that a significant decline in real terms has occurred. The data presented in Table 1, in particular, indicate that the total market shares captured by NCEs have declined over time in comparable fashion to the total number of NCE introductions.[10]

Sam Peltzman has analyzed a related drug quality issue as to whether the large decline in NCE introductions could be explained by fewer ineffective drugs entering the marketplace after the 1962 amendments were passed. His analysis of data from three groups of experts—hospitals, panels employed by state public-assistance agencies, and the American Medical Association's Council on Drugs—does not support this view. These data suggest only a small fraction of the pre-1962 *and* post-1962 NCE introductions could be classified as ineffective.[11]

In sum, the hypothesis that the observed decline in new product introductions has largely been concentrated in marginal or ineffective drugs is not generally supported by empirical analyses. Moreover, these data analyses show no real tendency for more recently introduced drugs to have either significantly higher average market shares or efficacy rates than those introduced in earlier periods.

iii) *Depletion of Research Opportunities.* More recently, the FDA (along with some prominent members of the biomedical community) have emphasized a very different hypothesis—that the decline in pharmaceutical innovation is real, but that it is due to a depletion of research opportunities rather than increased regulation. This hypothesis has been described by former FDA Commissioner Schmidt as follows:

[9] Henry G. Grabowski, Drug Regulation and Innovation: Empirical Evidence and Policy Options (Am. Enterprise Inst. 1976).

[10] Market measures are premised on the notion that drugs which obtain the largest shares do so because they offer consumers the most overall utility per dollar. One can argue, however, that some drugs which have important therapeutic properties, but for relatively rare diseases, will tend to obtain low market shares. In addition, market shares are presumably influenced not only by the therapeutic advance of a new drug but also by the innovating firm's market power, promotional strategies, and so forth. However, for the broad aggregate comparison presented above, these qualifications are not as important as they might be in other situations. This is because there is no reason to believe that these factors have changed markedly over time, especially not in a direction so as to produce the lower market shares for new drugs shown above. For example, it seems unlikely that the lower market shares can be plausibly accounted for by a shift toward the production of a relatively greater number of drugs for rare diseases.

[11] In particular, these data suggest the incidence of ineffective new drugs was less than 10% in the pre- and post-1962 period. Peltzman also analyzes the growth rate patterns of NCEs in the pre- and post-1962 periods and argues they also support the findings of expert evaluations in this regard. See Sam Peltzman, An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments, 81 J. Pol. Econ. 1049, 1086 (1973).

Today's world includes a great number of important therapeutic agents unknown a generation ago. These include antibiotics, antihypertensive drugs, diuretics, antipsychotic drugs, tranquilizers, cancer chemotherapeutic agents, and a host of others. . . . In many of these important drug groups there are already a large number of fairly similar drugs. As the gaps in biomedical knowledge decrease, so do the opportunities for the development of new or useful related drugs. As shown by the declining number of new single entity drugs approved in the U.S., England, France, and Germany, this is an international phenomenon. This does not reflect a loss of innovative capacity, but rather reflects the normal course of a growth industry as it becomes technologically more mature.[12]

Adherents of the research-depletion hypothesis therefore are suggesting that in many major therapeutic areas we have reached a point where the probability that a new discovery will be an advance over existing therapies is quite low. Furthermore, they argue we are on a research plateau because the major disease areas left to conquer are the ones where we have the least adequate scientific understanding of the underlying biological processes. Hence, they suggest that considerable investments of basic research may be necessary before a new cycle of increased drug discoveries is likely to occur. They further point to the lower levels of drug introductions in other developed countries (where regulation has been less stringent than the United States) as important supportive evidence that a worldwide depletion of scientific opportunities has occurred in the pharmaceutical industry.

This hypothesis has been received with considerable skepticism in many scientific quarters. Some have challenged the hypotheses on conceptual grounds.[13] Others have pointed to the vast expenditures on basic biomedical research by the National Institutes of Health and other organizations as creating a renewed pool of basic knowledge which should offset any tendency toward a depletion of opportunities from prior drug discoveries.[14]

iv) *The Consequences of Thalidomide.* In addition to increased regulation and research depletion, Lebergott has pointed to the effects of the thalidomide tragedy on the behavior and expectations of physicians and drug firms as further confounding factors. In particular, he argues:

Do any of us believe that after that catastrophe, consumers were quite as likely as before to prefer new drugs to ones tested by experience? Were physicians henceforth quite as likely to prescribe new drugs—with the prospect of acute toxicity (and

[12] Examination of the Pharmaceutical Industry, 1973-74, Part 1: Hearings on S. 3441 and S. 966 Before the Subcomm. on Health of the Comm. on Labor and Public Welfare, 93rd Cong., 2nd Sess. 272 (1973-74) (statement of Alexander Schmidt).

[13] See, for example, statements by J. E. S. Parker and Harold Demsetz in Impact of Public Policy on Drug Innovation and Pricing (S. A. Mitchell & E. A. Link eds. 1976) (Am. Enterprise Inst.).

[14] B. M. Bloom, Socially Optimal Results from Drug Research, in Impact of Public Policy on Drug Innovation and Pricing 355 (S. A. Mitchell & E. A. Link eds. 1976) (Am. Enterprise Inst.).

malpractice suits) when the one chance of 10,000 ran against them? Which of our leading pharmaceutical firms would henceforth endanger its reputation (and its entire existing product line) on behalf of a new drug on quite the same terms as it did in the days when biochemists could do no wrong? . . . . Such massive changes in the U.S. perspective on drugs—we call them shifts in both supply and demand curves—had to cut the number of more venturesome drugs put under investigation since 1962. It would have done so if the entire FDA staff had gone fishing for the next couple of years.[15]

Thus, Lebergott argues that after thalidomide strong shifts occurred in the incentives facing physicians and manufacturers, which would operate independently to increase R & D costs and lower new drug introductions. His analysis points up the difficulties in trying to identify the effects of regulatory and nonregulatory factors that changed simultaneously as a result of the thalidomide incident.

v) *Advances in Pharmacological Science.* Finally, Dr. Pettinga of Eli Lilly and others have pointed to scientific advances in pharmacological science over the past few decades as another potentially important factor. In particular, he suggests that these advances, which have made teratology and toxicological studies much more sophisticated and costly in nature, would have been incorporated into drug firm testing procedures even in the absence of regulatory requirements to do so.[16] That is, drug firms would undertake many of these tests in their own self-interest, in order to reduce the likelihood of future losses in goodwill and potential legal liabilities.

In sum, while our primary objective in this paper is to identify the effects of increased regulation on declining levels of pharmaceutical innovation, a number of plausible alternative factors to regulation must also be considered. After briefly reviewing prior empirical work in the next section, we will turn to an international comparative approach to analyze these hypotheses.

C. *Prior Empirical Work*

i) *Sam Peltzman's Study.* Sam Peltzman's cost-benefit analysis of the 1962 amendments has received considerable attention in both economic and policy circles. We shall restrict our review here to only his analysis of the effects of the amendments on the rate and character of drug innovation.[17]

[15] Competitive Problems in the Drug Industry. Part 23: Development and Marketing of Prescription Drugs. Hearings Before the Subcomm. on Monopoly of the Select Comm. on Small Business, 93rd Cong., 1st. Sess. 9843 (1973) (statement of Stanley Lebergott).

[16] See remarks of Dr. Pettinga, in Regulation, Economics, and Pharmaceutical Innovation 288 (J. D. Cooper ed. 1975).

[17] Sam Peltzman, *supra* note 11.

Peltzman employs a "demand pull" model of new drug introductions by the pharmaceutical industry.[18] In particular, the supply of new drugs in his model responds with a lag to shifts in demand side factors (for example, the number of out-of-hospital prescriptions and expenditures on physician services). The model is estimated on pre-amendment data (1948-1962) and the estimated equation is then employed to forecast what the number of NCEs would have been in the post-1962 period in the absence of regulation. The effects of the 1962 amendments are then computed as the residual difference between the predicted and actual flow of NCEs.

Using this approach, Peltzman concludes that "all of the observed difference between pre- and post-1962 NCE flows can be attributed to the 1962 amendments."[19] However, his approach never formally includes or considers any of the supply side factors in the hypotheses cited above. All of the observed residual difference after 1962 is simply assigned to increased regulation. Since this residual difference can plausibly reflect the effects of a number of the other factors cited above (that is, research depletion, changing expectations, and scientific factors), it probably encompasses various nonregulatory phenomena as well.

ii) *Martin Baily's Study.* Martin Baily employs a production function model of drug development which does try explicitly to separate the effects of regulation from the depletion of scientific opportunities. He postulates that the number of new chemical entities introduced by the industry in any period is a function of lagged-industry R & D expenditures and that both regulation and research depletion operate to shift this R & D production function over time.

After experimenting with various functional forms and distributed lag relations, he estimates the following production function equation using time series data for the period 1954 to 1969:[20]

$$\log\left[\frac{N_t}{E_t}\right] = \underset{(15.96)}{4.708} - \underset{(6.13)}{1.337}\, D_t - \underset{(3.71)}{0.03854}\, P_t;$$

(t-statistics in parentheses) $R^2 = .95, \rho = -.3, DW = 1.98,$ (1)

where N_t = number of NCEs introduced and discovered by U.S. firms in year t

E_t = average industry deflated R & D expenditures for ethical drugs

[18] The analysis builds on the approach of Jacob Schmookler, Invention and Economic Growth (1966), who postulated that technological innovation generally followed demand rather than vice-versa.

[19] Sam Peltzman, *supra* note 11, at 1055.

[20] Martin N. Baily, *supra* note 2, at 77.

in the United States in years $t-4$, $t-5$, and $t-6$ (it is assumed there is a fixed five-year lag from R & D outlays to introduction)

D_t = a zero-one dummy variable representing the effect of regulation (it equals 0 through 1961 and 1 afterward)

$P_t = \frac{1}{7}\sum_{v=7}^{13} M_{t-v}$ where M_t is total number of new drugs introduced from all sources (this seven-year moving average of past introductions is Baily's proxy variable for depletion).

In this formulation, R & D productivity (or NCEs per dollar of R & D invested) is related in a statistically and quantitatively significant manner to proxy variables for both regulation and research depletion. For example, the estimated coefficient on D_t implies that the annual expenditures required to develop a constant number of new drugs more than tripled in the post-amendment period.[21]

The Baily model therefore appears to perform well and suggests that both the regulation and research depletion hypotheses are valid. Nevertheless, it should also be noted that this specification does embody a number of strong assumptions. First, the model implies a fixed lag as well as constant returns to scale in the relation of NCE introductions to R & D expenditures. Second, the seven-year moving average formulation for the depletion variable has a somewhat arbitrary character; it also does not formally allow for additions to the stock of knowledge. Third, the zero-one dummy variable formulation for regulatory effects imposes the same shift factor on the entire post-amendment period (rather than a differential response over time). Finally, no attempt is made to consider additional factors such as those presented in hypotheses (iv) and (v) above.[22]

[21] Baily presents the estimated regulatory effect on costs only implicitly in a table showing the annual expenditure required to develop a constant number of drugs, before and after the 1962 change in regulation. This table indicates that costs increased by a factor of 2.35 beginning in 1962. However, these cost figures confound regulatory and depletion effects, and further embody the rather dubious property that the effect of depletion on costs after 1962 has only about half the magnitude of pre-1962 effects. This property follows from the assumption that the flow of drugs from non-U.S.-industry sources is lower in the post-1962 period and Baily's formulation of the depletion variable.

The direct regulatory effect, holding depletion constant, is calculated from the coefficient on the dummy variable, which, given Baily's specification, implies an increase in costs by a factor of 3.8. Martin N. Baily, *supra* note 2.

[22] Additional Baily assumptions include: (a) All R & D expenditures are allocated to discovery and development of NCEs. To the degree that the proportion of R & D expenditures devoted to NCEs falls to exhibit systematic shifts over the period of analysis, this assumption should not affect results. It should be remembered that relative or before-and-after effects are the focus of concern. (b) The gross national product deflator adequately represents price trends for R & D

Since the Baily model was published, several years of additional data have become available. In order to test the stability of his estimated regression equation, we reestimated it using more recent data. Baily used data covering 1954-1969, while we employ data for the longer period 1954-1974. Our reestimation of the Baily model yields the following equation:

$$\log\left[\frac{N_t}{E_t}\right] = \underset{}{-0.88} - \underset{(2.40)}{2.26\, D_t} - \underset{(8.63)}{0.003\, P_t} \qquad \underset{(0.23)}{} \qquad (1')$$

$$R^2 = .88 \qquad DW = 1.60.$$

Hence, the main finding of our reanalysis is that the coefficient of the depletion variable has become statistically insignificant, though it does continue to have the expected negative sign. The explanatory power of our reestimated equation also has declined substantially from that obtained by Baily (the R^2 declined from 0.95 to 0.88). Furthermore, a number of other functional specifications were analyzed and the research depletion variable performed poorly in each instance.[23]

Thus, neither the studies of Peltzman nor Baily would seem to provide completely satisfactory approaches for isolating the effects of increased regulation on pharmaceutical innovation from other confounding factors. Although Baily's production function model does provide a conceptual basis for separating regulatory factors from other supply side factors like research depletion, his proxy variable for research depletion is obviously highly unstable when extended forward in time.

In the next section, we present our own methodological approach for empirically isolating the effects of regulation from other factors. It is based on an international comparative analysis of developments in the United States and United Kingdom which we believe offers some important advantages over the time series analysis of a single country.

II. A Comparative Analysis of the U.S. and the U.K. Industries

Under ideal laboratory conditions, one would wish to observe the behavior of innovation in the United States in two states of the world: one with the

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inputs in the pharmaceutical industry. There is some evidence to indicate that the movements of the two trends are highly correlated so that the gross national product deflator is an adequate proxy. See Nat'l Science Foundation, NSF72-310, A Price Index for the Deflation of Academic R & D Expenditures (May 1972).

[23] In particular, we examined both the multiplicative and linear functional specification and a number of formulations that relaxed various strong assumptions embodied in equation (1) (for example, fixed lag, regulatory dummy shift variable, and so forth). These generalizations are discussed in Table 3, in the context of our international analysis. However, the research depletion variable employed by Baily was never statistically significant in any of these alternative specifications.

1962 amendments in effect and one where they were not in effect. Given the impossibility of this experiment, a "second-best" experiment would be to find another country which was as similar to the United States as possible, and in which the regulatory pattern before and after 1962 was similar to that of the United States prior to 1962. The United Kingdom appears to be the best candidate for such an experiment.

In the analysis which follows, we specifically compare changes in R & D productivity in the United States and the United Kingdom. Our ultimate objective is to analyze the effects of regulation on R & D productivity in the United States, using the United Kingdom experience as a control for non-regulatory factors.

An international comparative analysis is of course subject to some inherent problems and biases as well as advantages. In what follows, we set out an analytical strategy designed to exploit the strengths of comparative analysis while minimizing or avoiding the problems.

A. *The U.K. Regulatory Environment*

As in the case of the United States, the United Kingdom experienced some basic changes in regulatory procedures governing drugs as a result of the thalidomide incident. Prior to 1963, the laws in the United Kingdom required registration of all new drug substances with the Ministry of Health. The main control on safety, however, came into play *after* a drug was marketed. Each registered new drug was referred to a Committee of the National Health Services for classification of its therapeutic properties.[24] Their evaluation of each drug was then disseminated to physicians. Some sanctions were available to the National Health Services to discourage physicians from prescribing drugs classified as being of "unproven value."

In 1963, the Committee on Safety on Drugs was established in the United Kingdom to undertake premarket safety reviews of drugs. Hence, the U.K. system after 1963 incorporated the basic requirement of premarket safety reviews that had been in effect in the United States for many years before 1962. At the same time, the United Kingdom did not institute most of the requirements associated with the 1962 amendments. Specifically, the United Kingdom did not require formal proof of efficacy until the Medicines Act was implemented in 1971;[25] before this act, the task of evaluating a drug's efficacy was essentially left to the market mechanism. In addition, the U.K. IND procedure was on a voluntary basis until 1971. Finally, the British

[24] See W. D. Reekie, The Economics of the Pharmaceutical Industry ch. 7, at 100-12 (1975), for a more detailed discussion of this and other historical developments with respect to the U. K. regulatory system.

[25] Medicines Act, 1968, c. 67.

system apparently relied more on outside committees of medical experts and emphasized postmarket surveillance compared with the United States.[26]

Aside from these differences in regulatory procedures after 1962, the two countries share a number of important similarities. Firms in the U.K. ethical drug industry are also characterized by high levels of R & D intensity and have produced a number of important drugs adopted on a worldwide basis.[27] In addition, both countries have high standards of medical training and practice.

Firms in the U.K. ethical drug industry should also be similarly affected by the nonregulatory factors cited in hypotheses (iii) to (v) above. First, the factor receiving the most attention—research depletion—certainly should not operate only in one particular country, but should be worldwide in scope. This is especially so given the rapid diffusion of knowledge concerning new drug discoveries throughout all developed countries. Secondly, the thalidomide incident as a factor making drug firms and prescribing physicians more cautious and thereby leading to higher costs of innovation would also be expected to operate abroad as well as in the United States. Indeed, since the United Kingdom was a country directly affected by thalidomide, one might expect it to play a greater role there than in the United States. Third, technical advances in the detection of adverse effects of new drugs would also be available to foreign firms who wished to use them for reasons of self-interest in the absence of any regulatory prodding.

A comparison of the United States and the United Kingdom therefore, would seem insightful because the regulatory environment of each country after 1962 was very different in character, while the other hypothesized nonregulatory factors for the decline in innovation in the United States would tend to operate in a similar (but not necessarily identical) manner across the two countries. Two basic problems do arise, however, which must be considered: first, the U.K. regulatory environment has not been static during the period of analysis, but rather has also experienced regulatory change, culminating in the important Medicines Act of 1971; second, there are multinational linkages across the two countries.

To deal with the former problem we will structure our analysis as follows. First, to avoid confounding the effects of depletion, thalidomide, and techni-

[26] Derrick Dunlop, The British System of Drug Regulation, in Regulating New Drugs 229 (Richard L. Landau ed. 1973). For a more detailed comparison of the two systems which reaches similar conclusions, see Louis Lasagna & William M. Wardell, *supra* note 7, Part II at 51. In particular, see ch. 10, at 109-23, for a further discussion and analysis of U.K. developments since enactment of the Medicines Act.

[27] See the comparative analysis of innovational outputs in G. Teeling-Smith, Comparative International Sources of Innovation, in Regulation, Economics, and Pharmaceutical Innovation 57 (J. D. Cooper ed. 1975); and also the material in W. D. Reekie, *supra* note 24, at 50-70 & 84-99.

cal change with the regulatory effects associated with the Medicines Act, we will focus on the period prior to 1971 in the United Kingdom. Secondly, we will make the strong assumption that all variations in U.K. trends in R & D productivity before 1971 are due to nonregulatory factors.[28] The other major U.K. regulatory change occurred, as discussed above, in 1963. In order to gauge the significance of this regulatory change for U.K. rates of innovation, we regressed R & D productivity of the United Kingdom on time and an intercept dummy for 1962 and 1963. These failed to yield statistically significant coefficients on the regulatory shift dummies, even at the 10 per cent level.[29] This is in sharp contrast to the U.S. situation and suggests the regulatory changes enacted in 1963 in the United Kingdom had far less impact on innovation in that country compared to the effects in the United States of the 1962 Kefauver amendments.

Nevertheless, there may be significant negative side effects of increased U.K. regulation on R & D productivity over this period that are not adequately captured in this model. To the extent that this is so, our strong assumption that all of the observed U.K. decline in R & D productivity before 1971 is due to nonregulatory factors will impart a *conservative* bias to our estimates of regulatory effects in the United States (since we employ these U.K. trends in innovation as a control for nonregulatory factors in the United States).

We will follow the general strategy in this paper of consciously structuring our analysis so that errors and biases operate to yield an *underestimate* of the effects of regulation on innovation.

[28] It is recognized that additional health policy changes occurred in the United Kingdom during the period of analysis. For example, beginning in 1961, the Ministry of Health was empowered to negotiate price directly on any patented drug with large sales, and the prices for such drugs repeatedly changed. (M. A. Shankerman, Common Costs in Pharmaceutical Research and Development: Implications for Direct Price Regulation, in Impact of Public Policy on Drug Innovation and Pricing 3 (S. A. Mitchell & E. A. Links eds. 1976). Quite probably these alterations of policy affected the incentives for U.K. pharmaceutical firms to invest in R & D activities. However, there is little reason to believe that policy changes other than those occurring in 1963 and 1971 and discussed above would affect the productivity of whatever R & D expenditures were undertaken. And it is only productivity which will be an object of analysis here.

[29] The least squares regression equations for the U.K., 1960 to 1970, using the intercept dummy in 1963 (D_t) were:

$$\operatorname{Log}\left(\frac{N_t}{E_t}\right) = \underset{(3.19)}{1.19} - \underset{(1.14)}{.35}\, D_t - \underset{(2.62)}{.11}\, T_t$$

$$R^2 = .72 \qquad \rho = -.55 \qquad F = 9.57 \qquad DW = 2.48$$

$$\operatorname{Log}\left(\frac{N_t}{E_t}\right) = \underset{(2.59)}{3.24} - \underset{(.69)}{.25}\, D_t - \underset{(2.37)}{1.41} \log T_t$$

$$R^2 = .71 \qquad \rho = .53 \qquad F = 8.49 \qquad DW = 2.43.$$

A second class of problems which arise in an international comparative analysis are associated with multinational linkages between the U.K. and the U.S. industries. An outline of these problems and a comparable strategy for dealing with them is presented in the section which follows.

B. *The Problems Posed by Multinational Interdependence*

In Figure II, we present trends on total NCE introductions in the United Kingdom, the subset of NCE introductions discovered by the U.K. pharmaceutical industry, and this industry's R & D expenditures on ethical drugs for the period 1960-1974.[30] Clearly the trends depicted for the United Kingdom in Figure II are qualitatively similar in nature to those shown for the United States in Figure I. That is, total NCE introductions and discoveries in each country decline over time, while R & D expenditures increase.

FDA Commissioner Schmidt has argued that the downward trend on total NCE introductions in the United Kingdom (and other Western European countries)—paralleling the U.S. trend—provides evidence for a worldwide

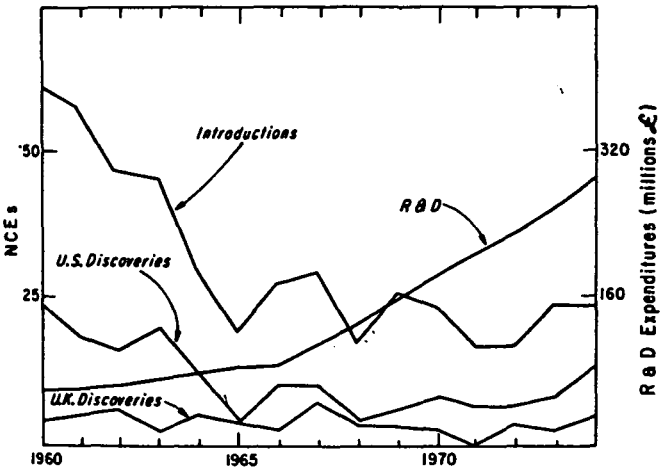

FIGURE II

Introductions of New Chemical Entities (Total Discoveries by U.K. Firms and by U.S. Firms) and Constant (1958) Pound Expenditures on Pharmaceutical Research and Development, the United Kingdom (1960-1974).

[30] These variables are defined in comparable fashion to those for the U.S. case. See the Appendix for further details.

phenomenon of research depletion.[31] However, this line of reasoning is subject to at least two major qualifications. First, as noted above, the United Kingdom increased the scope of their regulatory controls over ethical drugs during the 1960s. Second, U.S. firms historically have been prominent in the U.K. market. Given this, it is plausible to expect that more stringent regulations in the United States after 1962 would have some negative "spillover" or "echo" effects on NCE introductions in the United Kingdom.

Relevant to this second point, we have plotted in Figure II the annual number of NCE introductions in the United Kingdom that were discovered in the United States.[32] This plot shows that U.S. discoveries introduced into the United Kingdom, exhibited a strong downward trend over the decade of the 1960s. Indeed this decline in U.S.-discovered introductions is a major factor underlying the downward trend in total U.K. introductions over this period. The observed pattern of U.S.-discovered NCEs in the United Kingdom is, therefore, quite consistent with the hypothesis of an echo effect from U.S. regulation postulated above.[33]

In order to minimize the biases associated with this interdependence phenomenon, we focus our analysis on domestically discovered NCE introductions. R & D productivity, the dependent variable of our analysis, is formulated as the number of NCE introductions originating in and developed by the pharmaceutical industry in each country relative to its R & D expenditures.

This procedure does not remove all of the bias associated with multinational interdependence, however. In particular, another problem arises from

[31] See his remarks as quoted at note 8 *supra*.

[32] The definition of a U.S.-discovered drug is the same one employed previously; that is, a drug discovered in a U.S. research laboratory, irrespective of the nationality of the laboratory ownership. See note 3 *supra*.

[33] It is interesting to note that the percentage of U.K. introductions accounted for by U.S. discoveries starts increasing during the seventies. In this regard, there are plausible reasons for expecting "echo" effects to be much greater in the short run (that is, the initial post-1962 period). This is because of the institutional procedures and strategies followed by U.S. firms in the preamendment period. In an earlier paper we found that, prior to 1962, most U.S.-discovered drugs were introduced in foreign markets, such as the United Kingdom, only after being introduced in the United States. Furthermore, many NCEs were initially manufactured here and exported abroad, in accordance with the product-life-cycle theory. Thus, at the time when regulatory conditions became more stringent in 1962, the rate of foreign introductions was quite directly tied to the level of U.S. introductions. In other words, foreign countries were generally treated as secondary markets by the U.S. firms.

As one might expect, the increased regulatory controls instituted in the United States after 1962 created strong incentives for firms to alter many of these traditional practices. Consistent with this viewpoint, we found a steady increase after 1962 in the percentage of U.S.-discovered drugs introduced in the United Kingdom before (or in lieu of) their introduction in the United States. Henry G. Grabowski & John M. Vernon, Innovation and Invention: Consumer Protection Regulation in Ethical Drugs, 67 Am. Econ. Rev. 359, tab. 2, at 363 (Papers & Proceedings, Feb. 1977). Nevertheless, this shift apparently took years to become fully effective—in part because of some significant legal barriers associated with the exporting of new drugs under review by the FDA. Henry G. Grabowski, *supra* note 9, at 51.

the participation of U.K. firms in the U.S. market. U.K. multinational firms obviously develop many of their products with the U.S. and other foreign markets in mind. As a consequence, increased costs of entry in the United States after 1962 would be expected to cause higher R & D costs and lower R & D productivity for many drugs discovered and developed wholly within the United Kingdom.

We hope this bias is second order in effect.[34] In any event, it will be similar in direction to the bias that comes from ignoring the effects of pre-1971 U.K. regulatory changes. In particular, our assumption that all changes of R & D productivity in the United Kingdom over the period 1960-1971, the control nation, are due to nonregulatory factors (and not due to increased regulation in the United Kingdom or the United States) will operate to produce an underestimation of U.S. regulatory effects.

In summary, a comparative international analysis does not provide an independent control like that of a laboratory experiment for two basic reasons. First, the regulatory environments in foreign countries like the United Kingdom have not remained completely fixed over time but have become more stringent in nature. Second, the drug industry has a significant multinational nature, so that increased regulatory controls in the United States would be expected to have some negative spillover effects on foreign country introductions and R & D activity. Although neither problem can be completely avoided, we hope to minimize the biases from spillover effects by focusing on R & D productivity (rather than total introductions) in each country. With regard to the biases which remain, we structure our analysis so that we obtain conservative estimates of regulatory effects. Thus, we wish to see whether a significant effect of regulation can be observed from our comparison of the United States and United Kingdom, even when the analysis is deliberately structured to produce an underestimate of regulatory effects.

C. *Simple Comparative Productivity Trends*

In this section, we present the basic comparative trends of the dependent variable for our analysis, R & D productivity. As discussed above, we use the term "productivity" to refer to the variable Baily defined as N_t/E_t, that is, the number of new chemical entities discovered and introduced in a country per effective R & D dollar. Following this, we present regression results,

[34] One reason for expecting this might be so is that our data suggest a much greater tendency for U.K. firms to license U.S. firms to develop and market drugs in the United States compared to the reverse situation involving U.S. introductions in the United Kingdom. One apparent reason for this is the unwillingness of the FDA historically to accept foreign trials as acceptable proof of safety and efficacy and its requirement that all applicable clinical trials be performed in the United States before considering a new drug application. (See Louis Lasagna & William M. Wardell, *supra* note 7, at 156.)

where the estimated U.K. time trend of productivity decline is used to represent the effect of all factors except regulation on U.S. productivity.

In Table 2, we show the productivity of R & D in the United States and the United Kingdom. Our initial calculations embody two of the strong assumptions made by Baily in his analysis. Specifically, 1) *all* R & D expenditures in each country are allocated to discovery of new NCEs[35] and 2) a five-year lag is assumed between R & D expenditures and the actual introduction of an NCE. These have been applied uniformly to the data for both countries. Since we are primarily interested at this point in the relative trend in R & D productivities of the two countries rather than the absolute value of R & D productivity at a point in time, these assumptions are less limiting than they might first appear. Furthermore, in our regression analysis in the next section, we relax the five-year lag assumption and allow for an increasing lag structure.

Because of U.K. data limitations, we were able to obtain productivities for only two years prior to 1962. However, for the later period we have measured productivity in five-year periods. These particular periods (1962-1966, 1966-1970, and 1970-1974) were selected because of the increased U.K. regulation which began in 1971. In addition, there has been a significant increase in R & D performance by U.S. firms in the United Kingdom and other countries in the 1970s, making the assumption of independence in the discovery process less tenable.[36]

TABLE 2
COMPARATIVE PRODUCTIVITY OF UNITED STATES AND UNITED KINGDOM IN DISCOVERED NCEs PER DOLLAR OF R & D INPUT

	United States		United Kingdom	
	Actual Value[a]	Index	Actual Value[b]	Index
1960-61	.232	594	.408	283
1962-66	.054	138	.232	160
1966-70	.039	100	.144	100
1970-74	.029	74	.061	42

Sources: See Appendix.

Notes:

[a] Number of NCEs discovered and introduced in the United States per R & D input (R & D is measured in millions of constant 1963 dollars).

[b] Number of NCEs discovered and introduced in the United Kingdom per R & D input. (U.K. data measured in millions of constant 1963 dollars where pounds are converted to dollar basis here at exchange rate of $2.80/pound).

[35] David Schwartzman, The Expected Return from Pharmaceutical Research 26-28 (Am. Enterprise Inst. 1975), has estimated that approximately 50% of the U.S. industry's ethical drug R & D expenditures over the period 1961-1967 were for the discovery and development of new NCEs as opposed to the development of other drug products (combinations, new dosage forms, and so forth). Thus, the assumption that all R & D is for new NCEs tends to somewhat understate R & D productivity in absolute terms (for both countries).

[36] See Henry G. Grabowski, *supra* note 9, at 44-48, for an analysis of the amount of R & D activity performed abroad by U.S. firms in recent years.

The productivities calculated in Table 2 should ideally be adjusted for any systematic differences in the quality of NCE introductions discovered in the United States and the United Kingdom. Teeling-Smith[37] has performed an analysis of the relative quality of discoveries in each country on all NCEs for which the first worldwide introduction occurred between 1958 and 1970. He found that U.S. discoveries for this period on average achieved a somewhat higher rating in terms of a quality index based on worldwide sales but a roughly comparable rating for a quality index based on medical importance (as evaluated by U.K. medical experts).[38] He concluded that a modest adjustment of the raw productivity calculation is warranted in comparing the two countries because of the higher overall quality of NCEs discovered in the United States. His findings in this regard are therefore consistent with somewhat higher (unadjusted) productivity for the United Kingdom in Table 2 for the initial period, 1960-61. Of course, this could also reflect differences in market structures, pre-1962 regulatory environment, and so forth.

Since our primary interest here is in the relative trends in productivity over time, we have included in Table 2 an index of productivities for each country, with productivity in 1966-1970 arbitrarily taken as 100.

The data presented in Table 2 clearly show that there has been a significant decline in the R & D productivities for the two countries over the postamendment period. However, perhaps the most interesting result is the much stronger *relative* decline in R & D productivity that the United States experienced in the decade after 1962. In particular, there is an approximate sixfold productivity decline in the United States and threefold decline in the United Kingdom between 1960-61 and 1966-70. Hence, over this period in which the United States shifted to a much more stringent regulatory environment than the United Kingdom, it also experienced a much more rapid decline in R & D productivity.

We should also note the steeper decline in productivity in the United Kingdom compared to the United States between 1966-70 and 1970-74. A plausible explanation for this phenomenon might be the onset of tighter regulation in the United Kingdom beginning in 1971.

Finally, the decline in the United Kingdom between 1960 and 1971 exhibited a much more steady trendlike character than in the United States. This is reflected in the data in Table 2 by the much more gradual rate of decline in R & D productivities in the United Kingdom over the successive five-year periods 1962-1966 and 1966-1970 than for the United States. When we estimated a time series regression of log N_t/E_t on time for the United King-

[37] G. Teeling-Smith, *supra* note 27.

[38] See *id.* In particular, Teeling-Smith found the weighted average market performance for U.S. compounds to be 2.8 million, while for the U.K. the average was 2.3 million.

dom over this period, we obtained a very good fit with an estimated annual rate of decline of 15 per cent. When alternative starting dates of 1961 and 1962 were used, the estimated rates of decline were 16 per cent and 15 per cent, respectively. Moreover, as noted earlier, the addition of an intercept dummy for 1962 or 1963 yielded statistically insignificant results, in sharp contrast to similarly estimated equations for the United States.[39]

Although these comparisons of simple R & D productivities are hardly definitive, they do suggest some important differences in the observed shifts in R & D productivities for these two countries. In the next section, we report the results of an econometric analysis in which we incorporate a measure of nonregulatory factors based on U.K. data into a production function model of the Baily type.

D. *A Regression Analysis of U.S. R & D Productivity*

In Part I (C), we reestimated Baily's model on U.S. data for the entire 1954-1974 period and found that his measure for depletion (that is, a moving average of past total introductions) became statistically insignificant. In this section, we analyze a similar production function model but make a number of significant changes in the basic functional specification.

i) *Controlling for Nonregulatory Effects Using U.K. Data.* The initial specification that we consider is:

$$\log [N_t/E_t] = a_0 + a_1 D_t + a_2 T_{pre60} + a_{UK} T_{post60}, \qquad (2)$$

where N_t = number of NCEs introduced and discovered by U.S. firms in year t

E_t = average industry-deflated R & D expenditures for ethical drugs in the United States in years t–4, t–5, and t–6 (it is assumed there is a fixed five-year lag from R & D outlays to introduction)

D_t = a zero-one dummy variable representing the effect of regulation (it equals 0 through 1961 and 1 afterward)

T_{pre60} = time trend representing 1954-1960 period (equals t from 1954 to 1960 and 7 thereafter, where $t = 1$ in 1954, 2 in 1955, and so on; see Appendix for details)

T_{post60} = time trend representing 1960-1974 period (equals 0 from 1954 to 1960 and $t - 7$ in 1961 and thereafter, where $t = 1$ in 1954, 2 in 1955, and so forth. See Appendix for details).

[39] See in particular the results presented in note 29 *supra* on this point.

In this specification, we estimate the effects of nonregulatory factors using a time trend calculated from U.K. R & D productivity data. In particular, we assume that in the absence of regulatory differences, R & D productivity in the United States would decline at an identical percentage rate as that for the United Kingdom. Under this assumption, the annual rate of decline of R & D productivity for the United Kingdom provides an external estimate of the impact of the nonregulatory factors for the United States.

In implementing this approach in terms of equation (2), the coefficient on the time trend variable after 1960 is restricted to equal the estimated decline in U.K. productivity after 1960. For the period before 1960, for which no U.K. productivity data are available, we use an unrestricted time trend to control for nonregulatory factors. The effects of the 1962 amendments are represented in this specification by the dummy shift variable D_t that takes on the value 1 after 1962 and 0 before.

Of course, the estimated rate of R & D productivity decline in the United Kingdom probably includes some negative effects from increased regulation in the United Kingdom as well as some "echo" effects for the United Kingdom of increased U.S. regulation. As argued above, we believe these echo effects are minimal since we are analyzing discoveries of U.K. origin rather than total introductions, but some effect is probably unavoidable. However, by attributing *all* of the decline to factors other than regulation, we will, if anything, obtain a conservative estimate of the impact of regulation.

In addition, the functional specification given by equation (2) retains a number of strong assumptions made by Baily as discussed in Section I (C) above. In the subsequent analysis, we will relax many of these assumptions.

The first step in estimating equation (2) is to estimate the annual rate of R & D productivity decline in the United Kingdom for the period 1960 to 1970. As noted earlier, least squares regression of the logarithm of N_t/E_t on time for this period yields an annual rate of decline equal to -0.15.[40] Restricting the coefficient on the *post*-60 trend variable to equal this value, we then estimate the other coefficients in equation (2) on U.S. data over the period 1954 to 1974. This yields the equation.

$$\log [N_t/E_t] = \underset{(1.72)}{-0.49} - \underset{(3.85)}{0.85}\, D_t - \underset{(1.71)}{0.10}\, T_{pre60} - \underset{(\text{restr.})}{0.15}\, T_{post60} \qquad (2')$$

$$R^2 = 0.92 \qquad F = 110.72 \qquad D.W. = 1.89.$$

[40] The least squares regression equation estimated for 1960 to 1970 in the United Kingdom was:

$$\text{Log}\left(\frac{N_t}{E_t}\right) = \underset{(4.00)}{1.39} - \underset{(5.43)}{.15}\, T$$

$$R^2 = .68 \qquad \rho = -.52 \qquad F = 17.22 \qquad DW = 2.44.$$

In effect, the restriction imposes a significantly faster annual rate of R & D productivity decline after 1960 compared to the estimated pre-1960 rate of 0.10. Furthermore, if one estimates equation (2′) without any restrictions on the trend variables, the least squares estimate on the post-1960 time trend variable is −.092, approximately the same as the estimated value on the pre-1960 trend variable. Thus, the restriction on the post-1960 time trend in equation (2′) clearly operates to amplify the implied effects of nonregulatory factors compared with the unrestricted situation.

Turning now to our main point of interest, equation (2′) further indicates that the regulatory shift variable D_t has a negative and statistically significant relation with R & D productivity. The estimated value of the D_t coefficient, −.85, implies that the 1962 amendments increased the average cost of a new NCE by a factor of 2.3. This is similar in magnitude to the rough calculations that we made on the basis of the productivity indices in Table 2.

The functional specification given by equation (2′) of course still retains a number of strong assumptions. In the analysis which follows, we relax a number of these assumptions in order to test the sensitivity of these results.

ii) *Alternative Functional Specifications.* We analyzed a number of alternative functional specifications to the log-linear formulation given by equation (2′). The best-fitting equation turned out to be the specification where the dependent and independent variables are all expressed in logarithmic units.[41] This formulation is presented as equation (3.1) in Table 3. It apparently results in an improvement in explanatory power over the log-linear case because it allows for a diminishing rate of productivity decline over time, rather than the constant rate implied in equation (2). However, aside from this difference, there is little change from the log-linear formulation. Indeed, the estimated coefficient on the regulatory shift variable, −.86, is virtually the same as before.

All the formulations analyzed to this point assume constant returns to scale between NCE introductions and past R & D expenditures. This assumption allows us to formulate our dependent variable as R & D productivity, N/E, and facilitates the econometric estimation of the model. As a check on the reasonableness of this assumption, we reestimated equation (3.1) (and the other variants of this model discussed below) with the inclusion of $\ln E_t$ on the right-hand side as another independent variable. The coefficients of $\ln E_t$ were never significantly different from zero and the estimated

[41] In this case, the restriction was based on the following equation estimated from U.K. data for the period 1960.

$$\operatorname{Log}\left(\frac{N_t}{E_t}\right) = \underset{(4.94)}{3.89} - \underset{(5.53)}{1.76} \log T$$

$$R^2 = .69 \qquad \rho = -.53 \qquad F = 17.65 \qquad DW = 2.52.$$

TABLE 3

REGRESSIONS USING LOG-LOG SPECIFICATION OF PRODUCTIVITY ON REGULATION AND TIME VARIABLES, WHERE COEFFICIENT OF LT_{post60} IS RESTRICTED TO EQUAL ESTIMATED TREND IN UNITED KINGDOM

Eq. No.	Dependent	Int.	D	LS	LT_{pre60}	LT_{post60}	R^2/F	DW	Period
				A. Fixed Lag Case					
(3.1)	Log (N/E)	−.55	−.86		−.28	−1.76	.94/147.31	2.44	1954-1974
		(2.21)	(4.90)		(1.67)	(restr.)			
(3.2)	Log (N/E)	.48		−.46	−.50	−1.76	.90/85.13	1.74	1954-1974
		(1.20)		(2.70)	(2.40)	(restr.)			
				B. Increasing Lag Case					
(3.3)	Log (N/V)	−.65	−.77		−.35	−1.21	.91/102.48	2.77	1951-1974
		(2.89)	(4.99)		(2.73)	(restr.)			
(3.4)	Log (N/V)	.35		−.45	−.49	−1.21	.86/64.45	2.13	1951-1954
		(1.04)		(3.08)	(3.25)	(restr.)			

Notes:

(1) t-statistics are given in parentheses.

(2) N = number of NCEs discovered and introduced by U.S. firms in year t.

(3) E = average deflated R & D expenditures in U.S. in years $(t-4)$, $(t-5)$, and $(t-6)$.

(4) V = "effective" R & D expenditures in year t assuming an increasing mean lag between R & D expenditures and NCE introduction (for details of construction, see Appendix).

(5) D = zero − one variable representing effect of regulation ($D = 0$ in 1954-1961 period and unity thereafter).

(6) LS = log of the continuous regulatory stringency variable S (see Appendix for details).

(7) LT_{pre60} = log of t from 1954 to 1960 and log of 7 in 1960 and thereafter, where $t = 1$ in 1954, 2 in 1955, etc. (see Appendix for further explanation).

(8) LT_{post60} = 0 from 1954 to 1960 and log of $(t/7)$ in 1961 and thereafter, where $t = 1$ in 1954, 2 in 1955, etc. (see Appendix for further explanation).

(9) In the increasing lag case, the definitions for the time variables were adjusted for the longer data period by setting $t = 1$ in 1951, 2 in 1952, and so forth.

coefficients on the other variables remained quite stable.[42] Hence, the constant-returns-to-scale assumption seems warranted.

We also tested the significance of the restriction imposed on the post-1960 trend variable for each specification in Table 3 by computing the appropriate F-statistic. Using the Wallace criterion,[43] the restriction could not be rejected at the 0.05 confidence level (critical values of F are tabulated in Goodnight and Wallace).[44]

[42] The estimated coefficients on ln E were positive in each case, but generally had t-statistics less than one in value.

[43] T. D. Wallace, Weaker Criteria and Tests for Linear Restrictions in Regression, 40 Econometrica 689 (1972).

[44] James Goodnight & T. D. Wallace, Operational Techniques and Tables for Making Weak MSE Tests for Restrictions in Regressions, 40 Econometrica 699 (1972). The computed F-statistics for the equations in Table 3 ranged from 0.10 to 1.45, all of which prevent rejection of the restriction at standard levels of significance.

In a strict sense, the estimated trend of U.K. depletion is not exact, but rather is an unbiased estimate of the trend which possesses substantial variance. If estimates of both mean and variance for coefficients of time trend variables are taken from the United Kingdom, they may be used in the method of J. Durbin, A Note on Regression when There Is Extraneous Informa-

iii) *Regulatory Stringency.* In our earlier discussion, we observed that the use of the zero-one dummy variable D_t to represent the effects of the 1962 amendments embodies a rather strong assumption. That is, it imposes the same shift factor on the entire postamendment period rather than a more plausible differential effect over time. To attempt to overcome this problem, we substitute a continuous proxy variable of regulatory stringency S_t for the shift variable D_t. In particular, our measure of S_t is the mean FDA approval time for a new NCE in each year (that is, the estimated time elapsing between the initial submission of a new drug application (NDA) and its final approval by the FDA). The available data on this question, which is admittedly quite crude, suggests FDA approval time steadily increased from seven months in 1962 until reaching a plateau of twenty-seven months in the period after 1967 (see the Appendix for further details).

Equation (3.2) of Table 3 shows the results of employing S_t to measure regulatory stringency, once again using the logarithmic specification of the model. The S_t variable is statistically significant and has the expected negative sign. Moreover, the estimated value of the coefficient suggests a cumulative impact from regulation that is comparable in magnitude to that previously estimated. In particular, it implies that increased regulation has caused the average cost per NCE to be larger in the post-1967 period by a factor of 1.86 compared to the pre-1962 period.[45]

It should be kept in mind that this measure of regulatory stringency, by its very nature, only considers drugs that successfully gain FDA approval. Another element of regulatory stringency which influences R & D productivity is the attrition rate on drugs that are clinically tested in man but fail to become NCEs. As discussed above, the attrition rate on clinically tested drugs has also significantly increased in the post-1962 period.[46] Hence, the development of a more composite index of regulatory stringency would seem to be a useful direction for further research.

iv) *Increasing Lag.* Another strong assumption embodied in all the model formulations estimated to this point is that the variable E_t assumes a fixed five-year lag between R & D expenditures and NCE introductions. Although

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tion About One of the Coefficients, 48 J. Am. Stat. A. 799 (1953), to restrict coefficients in regressions for the United States. Due to the large variance of U.K. estimates, such inexact restrictions tend to be very much closer to unrestricted equations than those of Table 3. In other words, the statistically best use of information from the United Kingdom results in estimates of regulatory impact which are much higher and estimates of depletion—et al. impact which are much lower than are presented in the text. Again, the most conservative approach is taken.

[45] This was computed by substituting into equation (3.2) values of S of 7 months in the pre-1962 period and 27 months in the post-1967 period.

[46] If this element of regulatory stringency had a more direct and immediate impact on R & D productivity than lengthening approval times, which is not implausible, this may help explain why the D_t shift variable performs slightly better than S in Table 3. This is a question on which further research seems warranted.

good data is not available, there is considerable evidence which suggests that the average lag has increased significantly over the period we are studying.[47] Using the best estimates we could obtain on the average lag in different time periods, as well as some linear extrapolations, we constructed a variable lag variant of the equations estimated above. While the details of this construction are given in the Appendix, the basic assumption is that the average lag between expenditures and NCE introduction increased from 2.5 to 8 years over this period in the United States and increased by a somewhat lesser amount in the United Kingdom.

Equations (3.3) and (3.4) in Table 3 present the estimates for this variable lag variant of the model.[48] Essentially, the results are qualitatively similar to those given in the top half of Table 3. The estimates for this increasing lag formulation do indicate moderately lower impacts for the regulatory variables.[49] This is what one would expect, since an increasing lag over time (compared with the fixed lag used previously) operates to reduce the size of the decline in our R & D productivity dependent variable. However, it also should be kept in mind that an increasing lag *by itself* has a negative effect on innovative output and social welfare. Since it is commonly held that regulation is a major cause of this lag, it is appropriate to regard the estimated coefficients on D_t and S_t in equations (3.3) and (3.4) as only partial measures of the negative effects of regulation on innovative output and productivity.

To review briefly, all of the variants of the model analyzed imply a statistically significant and quantitatively important impact of the 1962 amendments. In particular, making conservative assumptions throughout, the estimated coefficients imply that increased regulation caused average costs per NCE to rise by a factor of between 1.8 and 2.3 over the first decade following the amendments. This amounts to more than one-third of the total increase in average costs experienced during this period.

E. *Qualifications and Possible Extensions*

It should be borne in mind that our analysis focuses only on the direct effects of regulation on R & D productivity or the average cost of discovering and introducing a new NCE. To the extent that increased regulation in fact has significantly increased the cost of introducing a new NCE, as our analy-

[47] L. H. Sarett, *supra* note 5.

[48] Ideally, the lag lengths and weights should have been estimated along with other coefficients, but multicollinearity and the paucity of data prevent this approach. The shift to a 2.5-year lag for early years made it possible to start regression analysis in 1951.

[49] Compared to the top part of Table 3 (that is, the fixed lag case), the implied effect of regulation on average cost per NCE changes from 2.36 to 2.16 in the case of the regulatory shift variable D_t and from 1.86 to 1.83 for the regulatory stringency variable S_t.

sis indicates, it should also affect the equilibrium level of industry R & D expenditures. In an expanded analysis, the total effect of regulation on NCE introductions, N, could be estimated by combining its effect on R & D productivity (N/E) with its effect on industry R & D expenditures E. The estimation of such expanded models would seem to a fruitful direction for further research.[50]

It may be noted that in a related analysis, David Schwartzman[51] has estimated the rate of return to pharmaceutical industry R & D for NCEs introduced over the period 1966-1972. He found a 6.6 pre-tax rate of return on R & D for this period, significantly below the average return on manufacturing investment and down from a 22.8 per cent return on pharmaceutical R & D in the early 1960s. If his estimates are correct, it would suggest that a significant part of the adjustment in equilibrium R & D has yet to occur. This is clearly a question on which more research would seem warranted.

Another important direction for further research would be to perform a more disaggregate analysis of R & D productivity in the two countries. William Wardell, a clinical pharmacologist, has compared the availability and therapeutic quality of NCE introductions in the United States and the United Kingdom after 1962 for a select number of therapeutic classes. He found a "drug lag" in the introduction of therapeutically beneficial NCEs into the United States compared with the United Kingdom, a lag which varied significantly in intensity across particular therapeutic classes.[52] It also would seem useful to compare R & D productivity in the two countries disaggregated by therapeutic class. This would allow one to see whether significant differences do exist and, if so, whether these differences might be plausibly associated with regulatory differences.[53] In order to undertake such an analysis, however, the necessary R & D data would have to be obtained from individual firm questionnaires, since these data are not presently available from public sources.

[50] We experimented with some simple reduced-form models on R & D expenditures that included regulation as well as various other supply-and-demand side factors as explanatory variables. Formulation of these equations on the basis of an optimality model incorporating our production function equation and a demand function results in a quite complex lag structure between R & D and the different explanatory variables. Using some very simple lag structures as a first approximation, we generally obtained the expected sign on the explanatory variables; but they were frequently not statistically significant. If one had a greater data base than the annual time series observations available here, one could presumably estimate these equations in a more precise fashion.

[51] David Schwartzman, *supra* note 35, at 36.

[52] For a summary of this work see Louis Lasagna & William M. Wardell, *supra* note 7, Part II, at 51-123.

[53] For example, it is presumably much easier to prove efficacy for an antibiotic than for several other classes such as cardiovascular drug therapies. Wardell found a much greater drug lag in the latter case compared to the former one. It would be useful to see if such patterns also emerge in a comparison of R & D producturies.

IV. Summary and Conclusions

Innovation in the pharmaceutical industry has been subject to a number of adverse structural developments in recent years. There has been a sharp decline in the annual number of introductions of new chemical entities and rapid increases in costs and risks. We have reviewed these developments and listed five hypotheses that have been used to explain them: (1) increased regulation of the industry associated with the 1962 amendments to the Federal Food, Drug, and Cosmetic Act is the cause; (2) the decline is illusory since only ineffective NCEs have declined; (3) a depletion of research opportunities has taken place; (4) the thalidomide incident has made firms and physicians more cautious; and (5) costs have risen as a result of advances in the technology of safety testing.

In order to separate the effects of regulation from these other confounding factors, we developed an international comparative analysis of R & D productivity changes in the United States and the United Kingdom.

A principal finding that emerges from this international comparative analysis is that U.S. "productivity"—defined as the number of new chemical entities discovered and introduced in the United States per dollar of R & D expenditure—declined by about sixfold between 1960-61 and 1966-70. The corresponding decrease in the United Kingdom was about threefold. Clearly, some worldwide phenomenon, which might be labelled a "depletion of research opportunities"—but which probably also includes the effects of other factors such as the thalidomide incident and higher costs due to new developments in safety testing—seems to hold for pharmaceutical R & D. However, there is also strong support for the hypothesis that an additional factor has been at work in the U.S. industry.

We conclude that this additional factor, which has lowered U.S. productivity at a significantly more rapid rate, is the increased regulation resulting from the 1962 amendments. On the basis of the regression analysis presented in Section III, we estimate that the 1962 amendments have probably, at a minimum, doubled the cost of a new entity.

Our analysis also suggests that nonregulatory factors have an important aggregative effect on innovation, but does not allow us to say which factors in particular have been most important in this respect. Further research on this question would seem warranted.

APPENDIX

This appendix presents in summary form the sources and methods of computation for statistics used in the paper.

NCE Introductions and Discoveries

Data on new chemical entities and their years of introduction for both the United States and the United Kingdom were obtained from the publications of Paul de Haen.[54] In a very few cases, information on British introductory dates was supplemented by the work of William Wardell.[55] Biologicals and diagnostics were here deleted from data lists and analysis due to problems of data availability and reliability prior to 1966.

Information as to which of these NCEs were also discoveries by industry research laboratories was obtained for the United States from Paul de Haen,[56] for the United Kingdom in 1960-1970 from the National Economic Development Office,[57] and for the United Kingdom in 1970-1974 from, again, Paul de Haen.[58] An NCE was regarded as discovered in a particular country if the research laboratory producing the entity was located in that country, irrespective of the nationality of laboratory ownership. Thus the discoveries of Pfizer in the United Kingdom are credited to Britain while those of Hoffmann-La Roche in the United States are considered as American. It should be recognized that the discoveries of NCEs are denoted by year of introduction in either the United States or the United Kingdom (depending on origin) rather than first year of introduction on a worldwide basis (should these dates differ).

R & D Expenditures

Expenditures for research and development are here considered as those domestic outlays by the pharmaceutical industry for discovery of humanly usable ethical drugs. In the United States, data were obtained from publications of the Pharmaceutical Manufacturers Association (PMA)[59] for worldwide human R & D expenditures, 1948-1974, of member firms. However, the breakdown of domestic versus foreign

[54] Paul de Haen, Compilation of New Drugs, 33 Am. Professional Pharmacist 25-62 (Nov. 1967); *id.*, 7 New Drug Analysis USA, 1966-1970 (1971); *id.*, 10 New Drug Analysis USA 1969-1973 (1974); *id.*, New Products Parade (20th ed., mimeographed, Feb. 1975); *id.*, New Single Drugs Marketed in England, France, Germany, and Italy 1960 to 1965 (mimeographed, Feb. 1973); *id.*, New Single Drugs Marketed in England, France, Germany, and Italy 1966, (mimeographed, Oct. 1973); *id.*, 1 New Drug Analysis Europe, 1967-1971 (1972); *id.*, 4 New Drug Analysis Europe, 1970-1974 (1975).

[55] W. M. Wardell, Introduction of New Therapeutic Drugs in the United States and Great Britain: An International Comparison, 14 Clinical Pharmacology & Therapeutics. 773-90 (1973).

[56] Paul de Haen, Compilation of New Drugs, 33 Am. Professional Pharmacist 25-62 (Nov. 1967); *id.*, 7 New Drug Analysis USA, 1966-1970 (1971); *id.*, 10 New Drug Analysis USA, 1969-1973, (1974); *id.*, New Products Parade (20th ed., mimeographed, Feb. 1975).

[57] National Economic Development Office, A List of 466 Pharmaceutical Compounds and Country of Discover (mimeographed, 1971) (prepared for NEDO by the Centre for the Study of Industrial Organization as part of the study, Innovative Activity in the Pharmaceutical Industry).

[58] Paul de Haen, 1 New Drug Analysis Europe, 1967-1971 (1972); *id.*, 4 New Drug Analysis Europe, 1970-1974 (1975).

[59] Pharmaceutical Manufacturers Association, Annual Survey Report (various years); *id.*, Office of Econ. Research, Prescription Drug Industry Factbook (1967).

expenditures in this total was available only for 1960-1974, from the same sources. By fitting an exponential trend for foreign R & D expenditures of PMA member firms against time, 1960-1974, estimates of this parameter were obtained for earlier years. Subtraction of these estimates from the worldwide total gave the data used in the text.

R & D data for the United Kingdom for 1954-1966 and 1973 were taken from releases of the Association of the British Pharmaceutical Industry.[60] For 1954 to 1965, the data aggregated human and veterinary research expenditures. These statistics were multiplied by 86.1 per cent (the 1966 value) to obtain estimates of expenditures for purely human research. For the years 1966 to 1974 an exponential trend on time was fitted to obtain R & D estimates for intervening years.

R & D estimates for both industries were deflated by the gross national product deflator to constant (1958) dollars for the United States[61] and to constant (1958) pounds for the United Kingdom.[62] Statistics for deflated expenditures on R & D as well as introductions and discoveries of NCEs are plotted in Figures I and II of the text.

Pharmaceutical Sales

Data on U.S. sales of ethical drugs were obtained from the publications of a marketing research firm, Intercontinental Medical Statistics.[63] These data were based on a projection from a 1,000 drug store sample to the population of all U.S. drug stores, and on a sample of about 10 per cent of total hospital beds. Sales directly to other institutions, such as to the U.S. government are here excluded, but they account for less than 20 per cent of U.S. ethical drug sales.

FDA Stringency

Estimates of the mean time in months to FDA approval of NCEs introduced in the United States were taken from an unpublished dissertation of Joseph M. Jadlow.[64] Jadlow obtained his estimates through private communication with the FDA. The figures used in the text extrapolate from Jadlow's and are as follows:

1954-1961	7.0 months
1962	9.3 months
1963	11.3 months
1964	14.0 months
1965	19.0 months
1966	24.0 months
1967-1974	27.0 months

[60] Association of the British Pharmaceutical Industry, Annual Report 1973-1974, (1974); *id.*, Pharmaceutical Research and Development Survey (mimeographed, Jan. 17, 1975).

[61] Economic Report of the President, Together with the Annual Report of the Council of Economic Advisors (1975).

[62] Central Statistics Office, Annual Abstract of Statistics (London, various years).

[63] Intercontinental Medical Statistics, Pharmaceutical Market—Hospitals (various years); *id.*, Pharmaceutical Market—Drugstores (various years).

[64] J. M. Jadlow, Jr., The Economic Effects of the 1962 Drug Amendments 174 (1970) (unpublished Ph.D. dissertation, University of Virginia).

These values are defined as the variable S, the logarithm of which is used in equations (3.2) and (3.4) of Table 3.

Lags for Effective R & D Expenditures

Estimates of development times for NCEs were interpolated from figures offered by Dr. Lewis Sarett.[65] Addition to these development times of the regulatory approval times given above yields the following estimates of total lag times, from first expenditure to introduction:

1954-1958	2.5 years
1959	3.0 years
1960	3.25 years
1961	3.5 years
1962	4.0 years
1963	4.65 years
1964	5.25 years
1965	5.8 years
1966	6.4 years
1967	7 years
1968	7.3 years
1969	7.65 years
1970-1974	8 years

R & D expenditures in a given year become effective over a three-year period centered around the (mean) total development period. For example, expenditures in 1967 are seen as effective in 1973, 1974, and 1975 at the rate of one-third of original 1967 expenditures. Total effective expenditures are obtained by summing over all expenditure portions which become effective in the given year and are defined as the variable V_1 in Table 3. While admittedly stylized, this lag system appears to capture the essence of the process at issue. Further, alternative lag structures based on the above mean lag estimates, as well as minor alterations of the mean lag estimates themselves, yielded qualitatively similar results in all cases.

It should also be noted that in estimating the U.K. trend for the restriction in the increasing lag case, an increasing development period ranging from two to five years was assumed.

Mechanics of Estimation

The specification assumed for equation (2) in the text can be written as:

$$\log(N/E) = a_0 + a_1 D + a_2[(1 - X)\, t + 7X] + a_3 X\,(t - 7),$$

where (1) a_3 is restricted to equal U.K. trend
(2) t is 1 in 1954, 2 in 1955, . . .
(3) $X = 0$ from 1954 to 1959 and unity thereafter.

Hence, the variable T_{pre60} in equation (2) is the multiplier of a_2 above and T_{post60} is the multiplier of a_3. The reason for the rather complex definitions of these two time trend variables is to ensure that the two time trend segments join properly in 1960. Thus, a_2 is the rate of decline of N/E from 1954 to 1960 and a_3 is the rate of decline thereafter.

Similarly, the specification of the log-log version of the above equation, equation (3.1) in Table 3, can be written in terms of t and X as follows:

$$\log(N/E) = b_0 + b_1 D + b_2[(1 - X)\log t + X \log 7] + b_3(X \log t - X \log 7),$$

where b_3 is restricted to equal U.K. trend.

Thus, as above, the variable LT_{pre60} in Table 3 is the multiplier of b_2 above and LT_{post60} is the multiplier of b_3.

[65] L. H. Sarett, *supra* note 5.

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LESSONS FROM THE DRUG LAG: A RETROSPECTIVE ANALYSIS OF THE 1962 DRUG REGULATIONS

by

LEONARD G. SCHIFRIN*

INTRODUCTION

This paper examines the medical and economic literature concerning the effects of the 1962 Drug Amendments[1] on drug innovation in the United States. The effects represent different facets of what has come to be called the "drug lag," and have been discussed and debated in a wide variety of studies over many years. Among these studies have been periodic overviews of the literature that have weighed the sum total of the existing evidence on the magnitude, causes, and impacts of the drug lag.

This study follows the overview approach, but extends its perspective both within and beyond the drug industry. While continuing to survey the literature as a whole in order to test hypotheses about the characteristics of the drug lag, it also examines the methods by which the impacts of a lag may accurately be assessed and the processes by which regulation generates or contributes to such a lag. By understanding the strengths and weaknesses of available assessments and the dynamic causation linkages between regulation and innovation, we can move closer to accomplishing what quantitative estimates alone of the lag cannot provide. First, we may be able to render more accurate evaluations of the effects of existing drug regulations and of proposed changes in those regulations. Second, knowledge of the successes and failures in assessing the full societal impacts of drug regulation and of the

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1 U.S. Code 1976, Title 21, § 321 *et seq.*, P.L. 87-781, 76 Stat. 780 (October 10, 1962).

regulation-innovation dynamics for drugs can provide very valuable lessons for the on going shaping and re shaping of public policy across a wide range of other sectors in the economy.

The conclusions on the regulatory experience in the drug industry are relevant for other industries. The first conclusion is that none of the assessments of the over-all effects of the drug lag made thus far have identified fully and quantified accurately the total societal benefits and costs resulting from the lag, but they have laid the beginnings of a good foundation for doing so. Parenthetically, in the absence of a definitive impact assessment, it is not surprising that the 1962 Amendments have not been amended, despite strong criticism of their effects on innovation.

The second conclusion is that there is a causal relationship between drug regulation and innovation: drug regulation of the sort imposed by the 1962 Amendments has increased the cost of new drug development; cost increases, in turn, have altered the relative abilities of firms to pursue drug research and development ("R&D"), and thus have affected R&D concentration in the drug industry. Increases in development times additionally have shortened effective commercial patent lives of new drugs. Higher monetary and time costs, by affecting structural conditions in drug markets, ultimately have directly and indirectly impacted on both the magnitude and pattern of new drugs developed by firms.

This study is structured along lines suggested by the above description of its orientation and conclusions. This statement of introduction serves as section I. Section II reviews the well traveled ground of the economic and medical literature on the drug lag, touching lightly on findings in regard to the existence of the lag and its relation to the 1962 Amendments, and somewhat more heavily on assessments of the full societal impacts of the Amendments and/or the lag.

Sections III, IV, and V relate respectively to the ways described above in which the 1962 Amendments have affected R&D activity in the drug industry. Section III sets out the effects of the Amendments on the development costs and periods for new drugs. Section IV assesses the impact of higher R&D costs on the essential structural elements of drug markets — economies of scale, concentration of R&D efforts, and product patent life — that affect the capabilities and incentives for innovation. Section V examines firm R&D strategies that reflect the cost and structural influences described in sections III and IV. Finally, section VI reviews the findings of the study, suggesting methods for improving the assess-

ment of the full impacts of the 1962 Amendments and articulating the "lessons from the drug lag" that may be most useful for other areas of regulation.

II. The Evidence on the Drug Lag

This section assesses the economic and medical evidence on the three major hypotheses in the drug lag debate: (1) that the U.S. is experiencing a gap between the present record of drug innovation and that of the past, or between our record and that of other countries; (2) that this gap, or lag, results largely from the stricter testing and approval standards imposed by the 1962 Amendments; and (3) that this lag, on balance, imposes costs on society that significantly outweigh its benefits.

The studies on the drug lag issue range from simple data presentation that offer only limited implications regarding the existence of a drug lag to sophisticated medical and economic analyses that offer more substantial conclusions about all three hypotheses. This section briefly reviews the more important of these studies and their conclusions on the magnitude, causes, and impact of a drug lag in the United States.[2]

The Drug Lag and Its Causes

The simplest type of evidence on the existence and magnitude of a drug lag compares the rate of introduction of all or some subset of new drugs before and after some point in time, usually 1962. These studies generally agree that both the overall rate of new drug introduction and the rate of introduction of new chemical entities ("NCEs") have declined substantially during the 1960s and at a slower — albeit still substantial — rate during the 1970s.

Yet this approach has shed little light on the three hypotheses. These conclusions are challenged by other comparisons of the rates of introduction of "significant" or "important" therapeutic discoveries before and after 1962. Moreover, the subjective nature of selecting which discoveries to include in the comparative studies limits their use as a precise measure of innovative achievement in drugs. The degree to which comparisons based on such selective categories conflict with those based on more inclusive measures of drug R&D output qualifies any firm conclusions about the significance of the observed changes in the rate of innovation. A

2 An earlier, more comprehensive analysis of these studies appears in Schifrin & Tayan, *The Drug Lag: An Interpretive Review of the Literature*, Int'l J. Health Services, (Winter 1977).

much greater limitation of these comparative studies is that as the relevant data are more closely observed, the downturns in drug innovation clearly began before the Amendments were passed and long before they were implemented. Thus such studies tell us, at most, that recent rates of drug innovation, by some measures, are lower than previous rates; they do not tell us whether the observed rates are below the normal or expected rates and if so, what factors, including the 1962 Amendments, are the cause.

A major improvement on this comparative approach was made by Peltzman[3] in an imaginative, if not fully successful, effort to measure the drug lag and to assess its impacts. Peltzman first defines the lag in an intertemporal fashion, as the difference between the actual flow of NCEs each year after 1962 (through 1969) and the flow predicted for each year from regression analysis of the determinants of the pre-1962 annual rate of introduction of NCEs. Peltzman finds the actual post-1962 rates were approximately half of the predicted post-1962 benchmark rates.

Peltzman's work has been criticized on several counts. The most important is that he has overstated the lag by failing to give proper weight to the downward trends in drug development that began to appear in the late 1950s. If other factors were contributing to this decline before 1962, then identifying it as a post-1962 phenomenon wholly attributable to the 1962 Amendments clearly is in error. Yet Peltzman's study should not be dismissed solely on this basis, for it measurably raised the level of discourse on the drug lag. Furthermore, its qualitative conclusions about the drug lag and the role of the 1962 Amendments generally have been substantiated.

Subsequent analyses of the drug lag in the United States have not used intertemporal comparisons of drug innovation rates. They have avoided the errors of failing to account for diminishing research opportunities, exogenous increases in R&D costs, and other influences on drug innovation not related to the new regulations by using international comparisons of drug innovation. Since major changes in drug research opportunities, methodology, and productivity would affect innovation rates in many countries, the effects of a significant regulatory change made only in the United States would be measured more accurately by the differences in the

3 Peltzman's work has been published in several forms. His most complete presentation is S. PELTZMAN, THE BENEFITS AND COSTS OF NEW DRUG REGULATION, R. Landau, ed. 1973); *see also* S. PELTZMAN, REGULATION OF PHARMACEUTICAL INNOVATION, THE 1962 AMENDMENTS (1974); *An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments*, 81 J. POL. ECON. 1049-91 (1973).

innovation rates in the United States and other countries. Most of these studies have used Great Britain as the basis of comparison for the United States, but some also have included other European countries, Canada, and Japan.

Wardell has provided the most thorough and persuasive medical assessments of the drug lag using international comparisons.[4] Comparing the United States and British records for three time periods since 1962 (1962-1971, 1971-1974, and 1972-1976), he found that drug availability is more constrained in the United States in three respects: there are more drugs available in Britain that are not available in the United States than vice versa; drugs that are available in both countries are more often introduced in Britain before being introduced in the United States; and drugs that are available in both countries are more likely to be approved for a wider range of indications in Britain than in the United States.

These phenomena were first observed in the original study of the drug lag during the decade 1962-1971. In his second study, covering 1972-1974, Wardell found some aspects of the earlier lag to have narrowed, but for drugs introduced in the three years after the first study the same sorts of lag in the U.S. appeared as had in 1962-1971. Finally, in a recent study of drugs introduced during the 1972-1976 period in Britain and the United States, Wardell again found a narrowing of the original lag, but nevertheless a continued lag for the newly-introduced drugs in the United States. Wardell found that the overall lag in the United States relative to Great Britain has diminished in recent years. Yet there still is a lag, more significant in some therapeutic areas than others, in the availability, time of introduction, and range of application of drugs in the United States.

Grabowski has contributed greatly to identifying and estimating the drug lag in the United States by combining the best features of Wardell's and Peltzman's methodologies.[5] Like Wardell,

4 For a listing of Wardell's significant drug lag publications through 1975, *see* Schifrin and Tayan, *supra* note 1. Among his many later studies, most of which are available from the Center for the Study of Drug Development, University of Rochester Medical Center, Rochester, New York, are Wardell, 24 CLINICAL PHARMACOLOGY AND THERAPEUTICS 499-524 (1978); Wardell, Development of New Drugs Originated and Acquired by U.S. Owned Pharmaceutical Firms 1963-76 (unpublished manuscript).

5 H. Grabowski, DRUG REGULATION AND INNOVATION (1976); *see also* H. Grabowski, Regulation and the International Diffusion of Pharmaceuticals, Conference on the International Supply of Medicines, American Enterprise Institute, Washington, D.C. (September 15, 1978); Grabowski, Vernon & Thomas, THE EFFECTS OF REGULATORY POLICY ON THE INCENTIVES TO INNOVATE: AN INTERNATIONAL COMPARATIVE ANALYSIS, *reprinted in* IMPACT

Grabowski uses international comparisons of NCE introduction rates; and like Peltzman, he employs econometric methods to estimate the extent of the lag. His key findings are that both the U.S. and Great Britain (and by extension, probably all countries) have experienced a declining productivity in drug R&D, meaning fewer R&D outputs (NCEs) per R&D dollar input. However, Grabowski also finds the productivity decline in the United States during the 1960s was approximately twice that of Britain. He attributes half of the U.S. decline and all of the British decline in drug R&D productivity to various factors, most notably a worldwide "depletion of research opportunities," that affect all nations. The remaining half of the productivity decline in the United States (the United States "drug lag") is attributed to regulatory policy.

Grabowski thus avoids the pitfalls encountered by Peltzman by using international rather than intertemporal comparisons. His definition of the regulatory-induced lag is much different than Peltzman's, and his estimation of it is decidedly smaller. Yet his qualitative findings that drug innovation in the U.S. has been influenced negatively by the 1962 Amendments are in agreement with Peltzman.

Peltzman, Wardell, and Grabowski, particularly the latter two, offer persuasive evidence that since the early 1960s there have existed differences in the availability of drugs in the United States relative to Great Britain that may properly be labelled a drug lag. Data provided by others, particularly de Haen[6] and Lasagna,[7] reinforce and extend this conclusion. Their calculations of new drug introductions in the United States, Great Britain, Germany, and France show that, to some extent, each country experiences a drug lag relative to at least a few others, and that the magnitude of the lag varies from one class of drugs to another. Their major point is that by most measures of new drug innovation the United States clearly lags behind most other Western countries in both the rate and timing of such introductions. Thus the first of the drug lag questions — whether such a lag in fact exists — must be

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OF PUBLIC POLICY ON DRUG INNOVATION AND PRICING, (Mitchell and Links, eds. 1976); Grabowski, Vernon & Thomas, *Estimating the Effects of Regulation on Innovation: An International Comparative Analysis of the Pharmaceutical Industry*, 21 J. LAW & ECON. 133-63 (1978).

6 de Haen, *The Drug Lag — Does It Exist in Europe*, 9 DRUG INTELLIGENCE AND CLINICAL PHARMACY 144-50 (1975).

7 Lasagna, *Research, Regulation, and Development of New Pharmaceuticals Past, Present, and Future, Part II*, 263 AMERICAN JOURNAL OF MEDICAL SCIENCE 66-78 (1972).

answered affirmatively. The second hypothesis — that the lag to a significant extent is the result of the 1962 Amendments — is also justified by the evidence at hand.

The Impact of a Drug Lag

The presence of a drug lag in itself suggests no normative judgments. The unavailability of some drugs in this country that are marketed elsewhere may be a gain or loss, depending on their therapeutic value. The delayed introduction of useful drugs may be a benefit or cost, depending on the extent to which the delay leads to wiser use of the drugs. Finally, the more limited approved usage ranges of some drugs may be a gain or loss, depending on the efficacy and risk involved in the additional uses to which they are put in other countries. Thus determining the impact of a lag requires careful assessment, not only because of the complexity of the area, but also because it provides the ultimate test of the wisdom of the philosophy of drug regulation in the United States.

The evaluation of the impact of the drug lag, like the questions of its identification and measurement, has been done from both economic and medical perspectives. The most prominent economic studies, which employ the benefit/cost approach, are the works of James Jondrow, Joseph Jadlow, and Sam Peltzman.

Jondrow[8] states that the main benefit of the 1962 Amendments is the reduction in market sales of ineffective drugs, as determined in the efficacy review conducted by the National Research Council of the National Academy of Sciences. The societal cost of the Amendments is the increased price level paid by consumers because of the higher R&D costs resulting from the stricter approval requirements. Jondrow estimated the values of this one benefit and this one cost, and calculated the benefit/cost ratio to be 2.24, which demonstrated to him that the Amendments were clearly beneficial to consumers.

Jondrow's work has two major flaws. First, he has drawn too narrow a list of the benefits and costs resulting from the Amendments. By not including other benefits gained from eliminating inefficacious new drugs, such as the averted health care costs of drug-induced problems, he has understated the benefits to consumers; and by not including any legislation-induced lag effects, he has omitted the costs to patients from the unavailability of even

8 J. Jondrow, *A Measure of the Monetary Benefits and Costs to Consumers of the Regulation of Prescription Drug Effectiveness*, Ph.D. Dissertation, University of Wisconsin, 1972.

slightly useful new drugs. Thus, he has understated, probably very unevenly, both the total benefits and total costs of the Amendments. Second, Jondrow's quantification of the one benefit and one cost he has considered also is flawed. As Grabowski has pointed out,[9] the "ineffective" drugs which experienced losses in sales were not entirely ineffective, but only ineffective for certain promoted uses, so that reduced purchases by consumers were not wholly gains to them. Moreover, the costs to consumers from higher prices due to higher R&D costs are probably also overstated, since it is unlikely that the entire R&D cost increase could be shifted to consumers. Thus, Jondrow's estimated benefits and costs both understate and overstate the true benefits and costs of the legislation, and therefore offer little basis for any judgment as to the full impact of the Amendments.

A second benefit/cost analysis of the 1962 Amendments was undertaken by Jadlow.[10] He weighed consumer benefits from improved drug quality against the costs of slower new drug development and the increases in drug prices, both of which are attributable directly and indirectly to the increased R&D costs resulting from the Amendments. Unlike Jondrow, Jadlow estimates the total costs to outweigh the benefits, and predicts that these negative net benefits will worsen over time in the absence of offsetting changes in regulatory policy.

Jadlow, by being more inclusive in his list of benefits and costs, is closer to the mark than Jondrow. However, his conclusions that costs of the Amendments outweigh the benefits and are likely to do so by an increasingly wide margin are based largely on the structural changes in drug markets that reduce competitiveness among firms. He has not provided any quantification of the gains and losses to consumers from the drug lag per se. Again, like Jondrow, he has introduced meaningful variables into the calculation, and extended the range of consideration; but he has not provided a full specification of the relevant benefits and costs or a useful quantification of their magnitudes.

Peltzman, whose measurement of the lag was discussed earlier, also presented a benefit/cost analysis of the effects of that lag.

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9 Grabowski, DRUG REGULATION AND INNOVATION *supra* note 5, at 65-66.

10 J. Jadlow, *The Economic Effects of the 1962 Drug Amendments*, Ph.D. Dissertation, University of Virginia 1970; *see also* Jadlow, *Competition and "Quality" in the Drug Industry: The 1962 Kefauver-Harris Drug Amendments as Barriers to Entry*, 5 ANTITRUST LAW & ECON. REV. (1971-72); Jadlow, *Price Competition and the Efficacy of Prescription Drugs: Conflicting Objectives?*, 11 NEB. J. ECON. & BUS. (1972).

Like Jondrow and Jadlow, Peltzman states that the only benefit from the Amendments or the lag is the savings to consumers from fewer inefficacious new drugs.

Peltzman cites two types of costs: the losses in consumer utility from fewer NCEs and from later introduction of NCEs, and the monetary losses from higher prices. Through a complex quantification process, Peltzman determines that these costs exceed the benefit by $300 to $400 million per year. Peltzman's work has been strongly criticized on a variety of grounds,[11] including its exclusion of other potentially large benefits and its use of some questionable theoretical assumptions in estimating the utility losses. The most serious flaw results from his measurement of the lag, and the effects of the Amendments, in intertemporal terms. As indicated earlier, Peltzman probably has overstated the lag by at least 100%. While Peltzman's analysis of the benefits and costs of the lag is an imaginative piece, his attempt to quantify precisely the societal benefits and costs of the Amendments and the drug lag fails.

The difficulties in applying economic analysis to an evaluation of the drug lag have helped to shift the emphasis to the use of medical assessments of the actual drugs that comprise the United States lag. These drugs have not been made available here, have been introduced later than in other countries, or have been approved for a narrower range of indications. This method eliminates much of the hypothetical nature of Peltzman's approach, but at the expense of bringing a good deal of subjectivity into the evaluation process. One simple approach of this sort is merely to look for "major" therapeutic advances available elsewhere but not here. Other approaches involve measuring the approval periods within the FDA for "significant" new drugs as compared to all new drugs or NCEs or determining whether there are medical problems for which "effective" drug therapies are available in other countries but not the United States. These approaches contribute some limited evidence about the more observable manifestations of the drug lag, but do not delineate precisely its total effects.

Wardell again has cut through many of these problems, developing a large body of evidence that approximates the scope, if not the exact cost, of the lag. Wardell's major conclusions, built

11 *See* Smith & Visconti, *On the 'Costs' of the 1962 Drug Amendments*, 11 INQUIRY 61-64 (1974); T. McGuire, R. Nelson, and T. Spavins, *An Evaluation of Consumer Protection Legislation: The 1962 Amendments: A Comment*, 83 J. POL. ECON. 655-61 (1975); Grabowski, *supra* note 5.

in his earlier measurement of the U.S. drug lag relative to Great Britain, are these:

(1) Among the lagging drugs are some of important therapeutic value, including cardiovascular drugs, sedatives, diuretics, bronchodilators, gastrointestinal drugs, and others.

(2) The impact of the lag is not restricted to "important" new drugs; even those that are not generally more efficacious than available drugs may, for certain patients, be superior. Slightly more efficacious drugs, or differentiated versions, are likely to offer incremental benefit to some patients. These benefits in some instances may be dramatic and, in the aggregate, probably are large.

(3) One of the large burdens of the lag stems from the restrictions on the indications of approved drugs. Many drugs approved for some uses in the U.S. are proving effective for other uses, but physicians are reluctant, if not constrained, in using them for unapproved indications, again to the large aggregate detriment of patients.

(4) American physicians generally tend to underestimate the therapeutic implications of the drug lag, since their educational and informational systems focus on the available inventory of drugs. In brief, American physicians are unaware what drugs are denied to them and their patients; upon being educated to these facts, they want to have these lagging drugs available to them.

Wardell's thorough studies argue strongly, as did Peltzman's, that the drug regulatory process in the United States, especially since 1962, is an unwise inhibition on drug innovation and development. While conclusive proof is unattainable, Wardell has at least provided substantial specific evidence that the therapeutic costs of the drug lag (without reference to either therapeutic benefits or economic costs and benefits) have been very large.

Peltzman's conclusion that the lag's costs exceed its benefits has been widely used as an argument against the wisdom of perpetuating the 1962 Amendments. Wardell's emphasis on therapeutic costs suggests that modification of the Amendments, or at least of their administration by the FDA, may *at the margin* bring large benefits in the form of reductions in therapeutic costs. Wardell, unlike Peltzman, argues less against the Amendments per se than for a piecemeal relaxation of their stringent application, as long as the marginal gains of this relaxation continue to be positive.

There is strong evidence that the United States has had a drug lag for two decades, and fairly strong evidence that the 1962 Amendments have been a major factor in producing this lag, but the evidence that the lag has imposed on balance a negative impact

on society is much less compelling. Yet Wardell has argued persuasively that the *absolute* (v. *net*) costs of the lag are very large. Thus, a more plausible policy than eliminating the 1962 Amendments would be reshaping and reinterpreting them to provide gains to society *at the margin*.

However, the costs of the lag largely result from the unanticipated effects of the 1962 Amendments. These effects, particularly the reduction and delay in NCEs being introduced in the United States market, have occurred because of the the impact of the regulations (1) on the cost of drug R&D; (2) on the market structure that affects the incentives and capabilities for R&D; and (3) on the internal firm strategies that determine the amount and pattern of R&D. Any proposed marginal changes in drug regulatory policy must be evaluated in the light of their possible effect on the factors that contribute to a drug lag; more challenging, such changes must also be evaluated in the light of other possible pathways that may connect public policy with market performance, or may emerge because of specific new facets of public policy or because of changes in the institutional setting in which public policy operates.

Because identification and explanation of these pathway effects is of major importance to subsequent regulatory policy decisions within the drug industry, this study now turns to their careful consideration.

In section VI of the study we will again consider the benefit/cost approach to an assessment of the lag or the 1962 Amendments, in order to develop guidelines for future studies that may provide more reliable estimates of the positive and negative impacts.

III. The Cost and Duration of Drug Development

The Drug Amendments of 1962 substantially altered the approval process for new drugs. The major changes in the law were a response to the Thalidomide tragedy, and thus focused on the new drug testing process and the standards for approval to market a new drug. Since 1962 the law has required that all new drugs be certified as Investigational New Drugs ("INDs") before their clinical testing can begin, that such testing be governed by protocols established by the FDA, and that these tests provide proof of efficacy as well as safety before the drugs are approved for general marketing.

While some critics of the 1962 Amendments have argued that

the "efficacy" requirement adds a heavy burden to the cost and gestation period for new drug development, most students of the industry, officials of drug firms, and FDA spokesmen disagree. They assert that the efficacy requirement in practice already was part of the "safety" standard applied to new drug approval, since a drug not efficacious for its intended use was an unsafe therapy, delaying or interfering with the use of a more appropriate therapy. However, the "efficacy review" of new drugs approved between 1938 and 1962 and already on the market, called for in the 1962 Amendments and conducted by the National Research Council/ National Academy of Sciences, demonstrated that many of these drugs were being used for purposes for which proof of efficacy was lacking in whole or in part. The NCR/NAS review and the 1962 efficacy requirement together served to eliminate these differences between the advertised and approved uses of new drugs for both pre-1962 and post-1962 introductions; whether they did so by eliciting additional proof or by narrowing the scope of therapeutic claims is not clear, but there is some evidence that the latter effect was the one that predominated.

The IND protocol, on the other hand, imposes structured, detailed, and often elaborate testing procedures for the data submission in support of the New Drug Application ("NDA"), which is the formal request for approval to market a new drug. It is argued these additional testing requirements have increased the development cost and time to drug firms. Drug development, the argument continues, thus involves larger direct costs and longer delays before the returns on these costs can be earned.

On the other hand, some portion of the observed increases in developmental costs and time may not be the result of changes in the standards for approval. One often-heard thesis holds that advances in scientific knowledge and capability permit more sophisticated tests of drug safety and efficacy, and that scientific and corporate consciences — and the laws on product liability — would compel the use of such improved procedures, even in the absence of regulatory requirements. Another line of argument contends that drug discovery follows a "life cycle," moving with quick success as those research opportunities most easily fulfilled are exploited first, leaving successively more difficult problems to challenge the academic and industrial scientific community. Thus, it has been contended, we may have moved from a "golden age of discovery" to an era of "depleted research opportunities" beginning shortly before the 1962 Amendments were passed.

Therefore, there are two major, somewhat conflicting positions on the effects of the 1962 Amendments on new drug development costs and times. Both positions agree that there has been a large escalation in the costs and gestation periods for new drugs since the early 1960s. But there the agreement ends. In one view, this cost and time escalation is primarily the result of the 1962 Amendments. In the other view, this escalation since 1962 is a continuation of trends begun earlier, and reflects other influences on the drug development process; the 1962 Amendments, it is argued, are not the only influence generating these trends and may well be a relatively unimportant one.

This section reviews the most important studies that present and discuss the evidence on trends in new drug development costs and times, in order to assess both the quality of the data and the arguments used to support the hypothesis that the 1962 Amendments have been a key factor contributing to significant increases in the monetary and time costs of new drug development.

Harold Clymer has described the long process culminating in FDA approval of a new drug in two studies.[12] Clymer has partitioned this process into six phases, from "preparation for clinical" through Phases I-III of the clinical testing, to submission of the NDA and obtaining its approval. In his first study (1965), Clymer estimated the total time expended on an NDA before marketing to have increased by a factor of three to four since the late 1950s, reaching an average of five to seven years; in his second study (1971) the range had widened to 4.5 to 8.5 years. In terms of the dollar costs behind ultimately successful NDA's, by 1968 they also had increased three to four fold over their late 1950s levels, reaching $2.5 to $4.5 million, and, by 1971, $2.7 to $4.7 million. Other phenomena noted by Clymer in the decade between the late 1950s and the late 1960s include (1) a fairly constant number of new INDs filed each year, (2) an increasing ratio of IND terminations to filings, and (3) a resulting large and steady decline in the annual number of approved NDAs. Yet Clymer did not place any blame on the 1962 Amendments or on the FDA. On the contrary, he stated:

> More pertinent to my point . . . are the factors that have entered the pharmaceutical equation in recent years. Perhaps

12 H. Clymer, THE CHANGING COSTS OF PHARMACEUTICAL INNOVATION 109-24, *reprinted in* THE ECONOMICS OF DRUG INNOVATION, (Cooper, ed. 1970). *See also* DRUG DISCOVERY — SCIENCE AND DEVELOPMENT IN A CHANGING SOCIETY, (Bloom & Ullyat, ed. 1971).

> most important is the fact that our methodology is superior to what it was only a few years ago. Our science is more rigorous, more likely to find potential hazards in an experimental compound."

Almost simultaneously with Clymer's work, Vernon A. Mund[14] studied several aspects of the relationship of R&D "investment" to the development of "new single chemical entities" (NCEs) introduced into the market. Using the widely accepted data provided by Paul de Haen, Mund pointed out a peak of sixty-three NCEs in 1959, followed by a sharp downward decline to 1963's sixteen NCEs, and then wide variations but no downward trend to 1968. Mund next related annual ethical drug R&D outlays for Pharmaceutical Manufacturers Association ("PMA") member firms to the annual market introduction of NCEs, assuming a five-year time lag between the R&D and the resulting newly-marketed NCE. Comparing a steadily rising annual aggregate R&D outlay relative to the annual number of approved NCEs five years later, Mund found that, in the 1950s, there was about one NCE for each $1.5 million in R&D: in the later 1960s, there was one NCE for each $10–20 million spent five years earlier on R&D. If no time lag were considered, by 1968 the cost of each NCE was $43 million in concurrent R&D outlay.

Mund's ratio of R&D expenditures of all PMA members to all lagged NCEs gives a development cost per NCE four times larger than Clymer's cost per approved new drug. However, this difference is easily explained. First, Clymer considered only the costs directly associated with each approved NDA; Mund related aggregate R&D outlays to the total number of NCEs approved, thereby assigning to the successful drugs the additional R&D outlays of the unsuccessful ones. Second, Mund uses a smaller denominator — NCEs — rather than all approved drugs.

More important than these differences in the dollar cost of new drugs is the implicit support offered by Mund for Clymer's "methodology" thesis or for a "depletion of opportunity" thesis. The rise in Mund's R&D input cost per unit of output clearly begins in the 1955 input-1960 output "year," substantially before the 1962 Amendments were passed or introduced. Thus, factors other than the Amendments seem to have set the rising cost per development into motion, and perhaps were major factors in maintaining this trend after 1962.

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13 *Id.* at 121.

14 V. Mund, *The Return on Investment of the Innovative Pharmaceutical Firm, reprinted in* Cooper, *supra* note 12, 125-48.

Jadlow[15] also examined the R&D input-output relationship for the 1956-1970 period, using two input measures (NSF and PMA R&D data). The R&D outlay (NSF measure) per NCE shows a ten fold rise, from $2.3 million per NCE in 1956 to $23 million in 1966, with the upward movement beginning in 1960, then increasing sharply in 1962, 1963, and again in 1966; the PMA input data show essentially the same phenomenón, with occasionally very high R&D-to-NCE ratios in the late 1960s. Jadlow, unlike Mund, specifically pinpoints the 1962 Amendments as the cause of the increase, on a "post hoc, propter hoc" argument. He supports that conclusion with his comparison of Clymer's estimate of the R&D cost per NCE in the late 1960's ($3.5 million) to Jerome Schnee's estimate (using firm specific data) of $587,000 per NCE for 1950-1963. Since Clymer's figure for the late 1960s is about six times larger than Schnee's figure for the 1950s and early 1960s, Jadlow takes this as support for his results, in which the post-1962 costs per NCE run about six times higher than the pre-1962 costs.

Lewis Sarett,[16] President of Merck Sharpe & Dohme Laboratories, Merck & Co., distinguished between "research" and "development" costs, and between "development" and "regulatory" approval times for "new pharmaceutical products" rather than NCEs. Sarett's data show differences in development costs through time and between the U.S. and foreign nations (U.K., Holland, Sweden, France, and Germany). These data are presented in Table 1.

TABLE 1
DRUG DEVELOPMENT COSTS, U.S. AND OVERSEAS

	1962	1967	1972
U.S.	$1.2 m.	$3.0 m.	$11.5 m
OVERSEAS	$ .9 m.	$2.1 m.	$ 7.5 m.

These cost figures relate only to development costs, and are for all projects, including both ultimate failures and successes. Therefore, comparing the data of Clymer, Mund, and Jadlow, with Sarett's data on development costs requires adding the research costs of generating "successful candidates for development." This combined numerator should be related to the commonly employed denominator of significant innovation approved NCEs. However,

15 Jadlow, *Competition and "Quality," supra* note 10.

16 Sarett, *FDA Regulations and Their Influence on Future R&D*, RESEARCH MANAGEMENT, March, 1974, at 18-20.

Sarett's objective was not to offer the same data, but to delineate important dynamic factors influencing R&D in the industry. By employing international comparisons of changes in drug development costs, Sarett added to the previous studies in much the same way as Wardell and Grabowski added to Peltzman's. Thus, the widening absolute and relative development cost margin in the United States compared with other nations implies that certain unique factors are present in the United States; by implication, these factors are the effects of the 1962 Amendments.

This line of argument is reinforced by reviewing Sarett's data on development and approval times. While the data on increasing "average product development times" in the United States, presented below in Table 2, are interesting, they are limited because they concern drug development only in the U.S.

TABLE 2
AVERAGE PRODUCT DEVELOPMENT TIMES, U.S.

1958-62	2 years
1963-67	4 years
1968-72	5½-8 years

But additional data on "average regulatory approval times," provided in Table 3, again give some indication that the American experience is different than that of other countries, and that both the absolute and relative regulatory time lag in the U.S. had grown greatly from 1962 to 1969.

TABLE 3
AVERAGE REGULATORY APPROVAL TIMES,
U.S. AND OVERSEAS COUNTRIES
(Ranges for Latter in Parentheses)

	1962	1969	1972
U.S.	6 months	40 months	variable
Overseas (U.K., Holland, Sweden, France, Germany)	6 months (0-24)	9 months (2-24)	16 months (6-24)

While Sarett's study was concerned more with the implications of rising drug development costs in the United States than with the causes of these increases or the possibilities for containing them, it indicates the possible effects of the 1962 Amendments on the costs and times of drug pre-marketing phases.

Additional attribution of rising research and development costs to the 1962 regulations comes from a study by Martin Baily.[17] He offered additional data on research and development cost changes afer 1962, which he partly attributed to the Amendments. Using three year moving averages of deflated R&D expenditures (PMA estimates), and using "new drugs" as the R&D output (lagged an average of five years), Baily derived a theoretical estimate of the "annual expenditure required to develop a constant number of new drugs." As indicated in Table 4, he estimated this expenditure to be about 2½ times greater "after the 1962 regulations change" than before; the dummy variable representing the 1962 Amendments was shown to have a statistically significant effect on the R&D expenditure function.

TABLE 4
ANNUAL EXPENDITURE REQUIRED TO DEVELOP
A CONSTANT NUMBER OF NEW DRUGS (N)
(Millions of 1957-59 Dollars)

N	Before the 1962 Regulations Change	After the 1962 Regulations Change
5	12.35	29.09
10	29.94	70.55
15	54.45	128.3
20	88.03	207.4
25	133.4	314.4
30	194.1	457.4

Jerome Schnee,[18] in a detailed econometric study of the drug development activities of one (unidentified) major drug firm, found the development costs and times for NCEs, not surprisingly, to be much greater than for imitative drugs, and all development costs to have risen in the time period 1950–early 1960s. Schnee identified "comparable" NCEs at different points in time, and estimated the increase in their development cost to have been on the order of 1100% between 1950 and 1960. In his regression equation, each year of time is found to add $100,000 to the NCE development cost. However, this dramatic rise occurs before 1962, and since he had no sufficient data to compare cost increases after 1962, there was no basis on which to attribute the observed cost in-

17 Baily, *Research and Development Costs and Returns: The U.S. Pharmaceutical Industry*, J. POL. ECON., Jan.-Feb. 1972, at 70-85.

18 J. Schnee, THE DETERMINANTS OF DEVELOPMENT COSTS, *reprinted in* Mansfield, RESEARCH AND INNOVATION IN THE MODERN CORPORATION 64-85 (1971).

creases to the 1962 Amendments. In fact, Schnee attributes these increases to "cost increases for the same technical effort" and "changes in the nature of drug development tasks." The first of these is not clearly, though possibly, related to regulation; the second may result from changes in regulation, but is at least partly explained in other ways, as Clymer has done. Indeed, while suggesting that the 1962 Amendments "significantly affected" the drug development process, Schnee reiterates Clymer's point that "advances in knowledge of drug action and increased technical sophistication have resulted in clinical investigations that are more intensive and broader in scope."[19]

While accepting the 1962 Amendments as a factor contributing to higher development costs, Schnee attributes the dramatic rise in these costs partly to input inflation (which he suggests is greater for research and development activity than for consumer or wholesale prices) and to improvements in the methodology of drug testing; further, he implies that other studies may inaccurately measure the effects of regulation on development costs because they fail to take account of a changing R&D composition within the firm.

Another impressive study on drug development costs and times is by Ronald W. Hansen[20] who improved on past studies by relating total current or lagged annual new product introductions to expenditures on "specific development projects," rather than total annual R&D budgets and by using multi-company rather than single firm specific data. Further, Hansen included the opportunity cost of capital, the earnings on capital foregone by its "investment" in the drug development process, in development costs. Hansens' results indicated that for the fourteen firms (some large, some relatively small) supplying data, "where expenditures are capitalized at the date of marketing approval at an 8% interest rate, the estimated cost per marketed NCE in the period 1950–1967 (measured in 1976 dollars) is $54 million."[21] While the cost specifically attached to an approved NCE averaged a little more than one-tenth that amount ($5.69 million), the high rate of failure (approximately 7 failed NCEs per approval) greatly raised the development cost assigned to each success. Capitalizing these specific and assigned costs provided the $54 million figure.

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19 *Id.* at 75.

20 R. Hansen, *The Pharmaceutical Development Process: Estimates of Development Costs and Times and the Effects of Proposed Regulatory Changes, reprinted in* ISSUES IN PHARMACEUTICAL ECONOMICS (Chien, ed. 1979) 151-81.

21 *Id.* at 151.

While Hansen's cost per NCE figures are the largest of any of the studies, partly because he standardizes all his figures in 1976 dollars, these estimates would be even larger if he had inflated pre-1976 outlays at a rate higher than provided by the Consumer & Wholesale Price Indexes, which probably seriously understate R&D input inflation. Despite these very high costs, Hansen is reluctant to place responsibility squarely on the 1962 Amendments. He states that "the fact that many of the provisions of the 1962 Amendments were not fully implemented until late in the 1960's and their gradual implementation coincided with other important changes makes it difficult to estimate the independent effects of regulatory changes."[22] Yet he believes the Amendments are an important, if not measured, contributor to the observed NCE cost escalation.

Summary and Conclusions

In this section, seven important studies of changes in drug development costs and/or times have been reviewed. Briefly, their salient findings are these:

(1) Clymer observes that both development costs and periods for approved NDAs in the late 1960s were at levels three to four times larger than ten years before; he attributes the increases largely to improved testing methodology.

(2) Mund finds that the R&D cost per NCE rose from $1.5 million in the early 1950s to $10-20 million in the later 1960s, using a five year input-output lag; with no lag, the later 1960s cost per NCE was $43 million. Mund does not identify causal factors for this increase.

(3) Jadlow measures changes from the mid 1950s to the mid-1960s in R&D cost per NCE. The increase is about tenfold, from $2.3-2.6 million to $23-29.6 million. Jadlow identifies the 1962 Amendments as the cause of this increase.

(4) Sarett analyzes research and development costs and development and regulatory costs from the later 1950s to the early 1970s with international comparisons. He finds development costs per NCE to have increased about tenfold between 1962 and 1972; development times to have increased from two years in 1958-1962 to five and one-half to eight years in 1968-1972; and approval times to have grown from six months in 1962 to forty months in 1969. All of these costs and time periods are larger and have increased more quickly in the United States than overseas. Sarett,

22 *Id.* at 152.

though, does not specifically attribute these changes to any particular causes.

(5) Baily compares development costs per NDA for pre 1962 and post-1962 time periods. He finds these costs to be approximately 2½ times greater after 1962 than before, and labels the 1962 Amendments as a significant causal factor.

(6) Schnee compares NCE development costs through the 1950s and early 1960s. In his statistical results, development costs per NCE increased by $100,000 each year. The identified contributing causes are improved testing methodology, R&D input inflation, and changes in the mix of drug R&D.

(7) Hansen estimates the cost per approved NCE more precisely than anyone else. For the 1950-1967 period, using 1976 dollars, he finds this cost to have risen to $54 million. He does not argue that the 1962 Amendments are a major factor in this increase.

The main feature of the data is the wide range of estimates of the R&D input-new drug output cost relationship. This wide range exists because of differences in the way the monetary values of input factors are calculated (aggregate v. firm-specific data; current v. constant dollars; different indexes of input cost changes when constant dollars are used; inclusion or exclusion of opportunity costs of capital), differences in the output denominator (approved NDAs, or only approved NCEs), differences in the output lag period, and the changes in the setting of the drug development process over the almost three decades covered by the studies. In the early 1950s the estimated cost of an NCE was $1.5 million (Mund); by the mid 1960's it was $23-30 million (Jadlow); and by the mid 1970's $54 million (Hansen). Total development and approval times were estimated to have increased by three or four fold between the mid 1950's and the later 1960's (Clymer), and perhaps to have doubled again since then (Sarett).

Of these studies, only Jadlow's and Baily's conclude that the 1962 Amendments have been a major contributing cause of these increases. Advances in drug testing methodology are widely accepted as a major factor behind the increases, and R&D inflation and a changing R&D output mix as lesser factors. When all evidence is considered as a whole, the 1962 Amendments do not emerge as the major cause of the observed trends; yet Baily and Sarett, in particular, have provided a strong case for their significance, and others have added to that point. The 1962 Amendments may also have had an indirect effect on costs and times by contributing to development and utilization of improved testing methodology, R&D input inflation through demand

generation, and higher R&D outlay opportunity costs by increasing the development and approval times.

There is no conclusive evidence on the effects of the 1962 Amendments. Yet the evidence that does exist, and the plausible hypotheses connecting regulation to increasing costs of development, create some foundation for not rejecting the view that the 1962 Amendments have had a significant effect on the costs and timing of new drug development.

IV. Impacts on the Structure of Drug Markets

Increased Concentration of New Drug Development.

Whether or not the 1962 Amendments have been the major contributing factor, the rising costs of drug development have had important effects on competition in drug markets. The increases in R&D efforts behind successful drug discovery and introduction described in the preceding section influence the rate and pattern of such success; it may also move the line of demarcation between those research intensive firms that in large part characterize the ethical drug industry and those whose R&D efforts are sufficiently modest to represent a sizeable difference in kind. To the extent that R&D efforts have become concentrated among fewer firms, then R&D outcomes, particularly NCEs with their large therapeutic and economic impacts, can be expected to show increasing concentration. In turn, sales concentration in these markets and rates of turnover among dominant firms may also be affected. In economic terms, the hypothesis is that the rising cost barriers to effective R&D competition have resulted in increasing concentration of new drug discovery, introduction, and of market shares among fewer, larger firms.

Jadlow[23] has argued that cost increases in R&D fall disproportionately on smaller drug firms, and as these costs have escalated these firms have moved from being the most efficient researchers (as measured by "annual R&D performance cost per R&D scientist or engineer") in 1957 and 1958 to the least efficient in 1965 and 1966.

A response to Jadlow is that raw measures of resource support per R&D scientist or engineer are poor indicators of R&D efficiency; moreover, the great expansion of the industry during the period examined by Jadlow may have generated highly uneven

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23 Jadlow, *Competition and "Quality,"* *supra* note 10.

growth patterns among firms, with the more successful R&D performers becoming the larger firms, rather than vice versa. Nonetheless, Jadlow contends that we have seen a substantial "reduction in the proportion of new drugs originated by the relatively smaller firms." First, he cites the decline in the number of drug firms "originating" NCEs, from 108 in 1962 to 48 in 1969 and 70 in 1970. This decline, he states, has been in firms at the "lower end of the size spectrum." Second, he makes the same point regarding the "marketing" (i.e., introduction) of NCEs: the share of the smaller firms has declined substantially between the mid-1950s and 1970. Jadlow's specific findings on these trends are presented in Tables 5 and 6.

TABLE 5
Dispersion of the *Origination* of New Single Chemical Entities Among Drug Firms of Different Sizes for Drugs First Marketed in the United States During the Periods 1955-58, 1959-62, and 1962-66[24]

	Percentage of New Entities Originated by the:			
Period	Smallest[a] 98 percent of U.S. Drug Firms (1)	Smallest 99 percent of U.S. Drug Firms (2)	2nd Percentile (2)-(1)	1st Percentile 100-(2)
1955-1958	12	31	19	69
1959-1962	12	39	27	61
1963-1966	0	30	30	70

[a]Firm size-rankings are according to assets in 1958 for the 1955-1958 and 1959-1962 periods and assets in 1964 for the 1963-1966 period.

TABLE 6
Dispersion of the *Development* (Marketing) of New Single Chemical Entities Among Drug Firms of Different Sizes for Drugs First Marketed in the United States During the Periods 1955-58, 1959-62, 1963-66, and 1967-70[25]

	Percentage of New Entities Developed by the:			
Period	Smallest[a] 98 percent of U.S. Drug Firms (1)	Smallest 99 percent of U.S. Drug Firms (2)	2nd Percentile (2)-(1)	1st Percentile 100-(2)
1955-1958	18	27	9	73
1959-1962	17	37	20	63
1963-1966	4	44	40	56
1967-1970	5	15	10	85

[a]Firm size rankings are according to assets in 1958 for the 1955-1958 and 1959-1962 periods and assets in 1964 for the 1963-66 and 1967-1970 periods.

24 *Id.* (Table 5 (corrected). Columns (3) and (4) added).
25 *Id.* (Table 6 (corrected). Columns (3) and (4) added).

The data in Tables 5 and 6 show the following phenomena: (1) for both NCE origination and marketing, the shares of the smallest 98% of firms were at a much lower level after 1962 than before; (2) the 99th percentile of small firms (2nd percentile of large firms) experienced a sizeable increase in its share of both NCEs originated and marketed between 1955-58 and 1963-66; for NCEs marketed, however, this share dropped greatly between 1967-70. (Data for NCEs originated in 1967-70 are not included.) (3) Correspondingly, the share of NCEs originated by the largest 1% of firms (their dominance is clearly shown by the absolute value) declined through 1962, after which it rose. For NCEs marketed their share declined through 1966, after which it rose very substantially.

In sum, Jadlow's data shows a shift in the smallest 98% of firms' shares of NCE discovery and development first to the remaining 2% of firms and eventually to the largest 1% during the mid 1960s. While the data obviously are too limited to establish post-1962 trends clearly or strongly, they offer considerable support that increasing concentration in drug discovery and development has occurred. Jadlow argues that these trends in R&D cause declining competition in drug markets, resulting in higher prices to consumers and higher profit rates to dominant firms.

In his work in conjunction with Edwin Mansfield, Schnee[26] studied various aspects of drug innovation and discovery, including changes in the relationship between innovation and firm size. He has analyzed this relationship at two levels. At the simpler level, he has measured the proportions of total sales and total innovations for the periods 1935-1949 and 1950-1962. Schnee's findings are reproduced in the Table 7 below:

TABLE 7
Percent of Innovations and Industry Sales Accounted for by Four Largest Ethical Pharmaceutical Firms[27]

ITEM	UNWEIGHTED	MEDICALLY WEIGHTED	ECONOMICALLY WEIGHTED
		(percent of industry total)	
1935-1949			
Innovations	37	45	50
Total Sales	50	—	—
1950-1962			
Innovations	27	48	33
Total Sales	33	—	—

26 J. Schnee, *supra* note 18.
27 *Id.* at 168.

The essential conclusions from these data are that, for the four largest firms as a unit, (1) their share of unweighted (i.e., absolute) innovations was less than their share of market sales in both time periods, (2) but when using a "medically weighted" measure of innovation, their share was almost equal to that of sales in 1935-1949 and considerably above it in 1950-1962; (3) using "economic weights," the shares of innovations and sales of the four firms were equal in both time periods; and (4), perhaps most important, there was an increase in the innovative performance of the four firms (unweighted, or weighted by medical significance) relative to total market sales share from the earlier period to the latter (an increase in the innovation-sales ratios from .74 and .90 in 1935-1949 to .81 and 1.4 in 1940-1962).

At a more detailed level, Schnee has analyzed the full range of firm sizes. He found that the largest firms improved their innovation records, weighted by therapeutic and economic significance, relative to other firms, from 1935-1949 to 1950-1962.[28] Accordingly, the trends observed by Jadlow, showing an increased R&D output share for the top 1-2% of all firms are supported by Schnee's data. However, while Jadlow attributes this increase to the burdensome effects of the 1962 Amendments on smaller firms, Schnee has shown these trends existed before the Amendments were passed. Dramatic broadening and growth of drug markets, beginning in the late 1940s and accelerating throughout the 1950s, were generating changes in the relationship of the rate of innovation to size in the drug industry. Schnee's disaggregation of the pre-1962 period shows these incipient trends, while studies that lump together the entire pre-1962 data fail to reveal them.

Trends in such R&D concentration have been strong into the 1970s, when the "broadening and growth" of drug markets slowed. Grabowski[29] presents evidence similar to Schnee's, but covering also the periods 1962-1966 and 1967-1971. Part of that evidence, reproduced in Table 8 below, shows the four-firm concentration of innovational output (NCEs) and total ethical drug sales for three periods between 1957 and 1971. These data indicate that concentration remained essentially stable into the 1960s, and then accelerated very sharply, while for sales the aggregate four-firm concentration levels remained essentially unchanged throughout the entire period. Grabowski's data thus show a sharp

28 The only exception to the improved innovation record of the largest firms between the two periods occurs for "small size" firms, in terms of unweighted innovations. Schnee explains this in terms of the development of small, specialty markets (e.g., ophthalmics, dermatologicals) which the small firms had to themselves.

29 Grabowski, Vernon & Thomas, *supra* note 5.

increase in the later 1960s in the short-term trends noted by Jadlow and the long-term trends described by Schnee.

TABLE 8
Percentage of Innovational Output and Total Ethical Sales Accounted for by the Largest Four U.S. Drug Firms, 1957-61, 1962-66, and 1967-71[30]

Period	Four Largest Firms' Share of Innovational Output	Four Largest Firms' Share of Total Ethical Drug Sales
1957-1961	24.0	26.5
1962-1966	25.0	24.0
1967-1971	48.7	26.1

Grabowski offers more specific data on innovation in the drug industry, contained in Table 9:

TABLE 9
Concentration of Innovational Output in the United States Ethical Drug Industry[31]

Period	Total Number of New Chemical Entities (NCEs)	Number of Firms Having an NCE	Concentration Ratios of Innovational Output 4-Firm	8-Firm	20-Firm
1957-1961	233	51	.462	.712	.931
1962-1966	93	34	.546	.789	.976
1967-1971	76	23	.610	.815	.978

These data indicate: (1) a reinforcement of Jadlow's findings of a declining NCE output after 1962; (2) a reduction in the number of firms accounting for an NCE in each time period; and (3) increasing concentration ratios at the four-firm and eight-firm levels, and, very slightly the twenty-firm level. Perhaps this last statistic warrants emphasis: although innovational concentration has increased at the four-firm and eight-firm level, it has not increased very much at the twenty-firm level. Thus, the top twenty research-intensive firms in the industry have not increased their share of total drug innovation during this time period. The gains of the top four and eight firms apparently have come at the expense of smaller firms within the top twenty. These results are consistent with Jadlow's, for in an industry of perhaps 600 firms, those ranking 9th through 20th in terms of innovational output are among the "smallest 99 and 98 percent" of all firms.

Grabowski concludes that the drug industry has displayed what most other industries have not: "a strong shift toward greater concentration of innovational output in the U.S. in the very largest . . . firms." While he states that this shift, given the "large upward shifts in development costs," is not surprising, he also noted

30 *Id.* at 73 (Table 5).
31 *Id.* at 72 (Table 4).

that it may be a characteristic of the chemical industry in general. The 1962 Amendments seem to be an implicit factor, perhaps an important one, in this shift. The validity of Schnee's earlier observation that this trend was clearly underway before 1962 is supplemented by Grabowski's observation that institutional features within the chemical industry as a whole, and perhaps special ones within the drug industry, may have been important contributing factors.

Decreased Effective Patent Life

At least one factor has been a countervailing force against increasing concentration in the drug industry. Longer development and approval times between discovery and marketing have reduced the effective (commercial) life of drug patents, resulting in earlier market penetration by generic rivals. Since there have been relatively fewer drug innovations than in earlier years, it would seem plausible to expect that the average commercial life of drugs has increased. On the other hand, the increase in the length of development periods for drugs has reduced the remaining patent period after market introduction ("average effective patent life"). While the impacts on profitability from these opposing factors have not been studied, some estimates of the changes in average effective patent life over recent years have been made by Schwartzman, Statman, and Evanoff.

Schwartzman[32] has estimated the effective patent life of eighty NCEs introduced into the United States market between 1966 and 1973. While these estimates do not compare effective drug patent life before and after 1962, they suggest trends in patent life that may have been influenced by the Amendments. The key findings, which compare NCEs introduced in 1966-1969 with those introduced in 1970-1973, are presented in Table 10.

TABLE 10
Changes in Average Effective Patent Life from 1966-69 to 1970-73, by Therapeutic Field[33]

	Average effective life (years)			
	1966-69	1970-73	Difference (years)	Change percent
Anti-infectives	13.8	13.6	-.2	-1.2
Anti-inflammatories	17.3	7.4	-9.9	-57.0

32 D. Schwartzman, INNOVATION IN THE PHARMACEUTICAL INDUSTRY (1976) (Ch. 8: "The Life of Drug Patents").

33 *Id.* at 173.

Psychotropics	17.4	12.5	4.9	28.2
Analgesics and anesthetics	12.5	9.1	3.7	29.6
Cancer chemotherapy	11.4	11.6	.2	1.7
Diuretics and cardiovascular	15.4	5.3	10.1	65.4
Antispasmodics and muscle relaxants	11.9	11.7	.2	1.7
Other hormones	13.4	13.3	.1	.6
Miscellaneous	11.6	11.9	2.3	19.4
All fields	11.9	12.4	1.5	10.8

While the data do not directly show the effects of the 1962 Amendments, they show that average effective patent life is substantially shorter than the full statutory patent life. Moreover, it has decreased for drugs in each therapeutic field, if unevenly so, between the late 1960s and early 1970s. This decrease in average effective patent life may have serious implications for the profitability of such drugs and for prices that consumers ultimately pay in the marketplace.

Statman[34] also has examined the effective patent life of NCEs for 126 drugs introduced between 1949 and 1975, thus covering a wider period than Schwartzman and including years before 1962. Using simple regression analysis, Statman finds a continuous decline in the effective life of drug patents of .375 years for each year of introduction after 1960. Thus, expected effective patent life for NCEs introduced was 16.5 years in 1960, 14.6 years in 1965, 12.7 years in 1970, 10.9 years in 1975, and 9.7 years in 1978. However, Statman's findings are tenuous for many reasons, including his assumption of a total development and regulatory period of only .5 years for 1961 and before. This figure seriously conflicts with Sarett's estimate of over two years for the post patent-premarketing period at the time. Nonetheless, Statman's data generally agrees with Schwartzman's.

Evanoff[35] has derived estimates of "average expected patent life ("AEPL")" for the years 1949-1975 from data in other studies pertaining to estimated development and regulatory periods. Subtracting these development and regulatory periods from the 17-year statutory patent life, Evanoff finds AEPL to have been stable at fifteen years between 1949 and 1962, and then to decline steadily to nine years in 1973, remaining at the level through 1975. Evanoff's results thus fit well with Statman's; together, they imply

34 Meir Statman, "The Effect of Patent Expiration on the Market Position of Drugs." Paper presented at Conference on Drugs and Health: Economic Issues and Policy Objectives, American Enterprise Institute, Nov. 15-16, 1979.

35 Douglas D. Evanoff, "An Econometric Model of the Ethical Pharmaceutical Industry: The Effect of Legislative Alternatives," paper presented at the annual meeting of the Southern Economic Association, Nov. 6-9, 1979.

that these shorter patent life periods may have some serious effects on market profitability.

Yet the shorter average effective patent life is largely the mirror image of longer development and regulatory periods, and so is not conclusively attributable to the 1962 Amendments. While effective patent life appears to have been stable for NCEs introduced in the years before 1962 and to have grown shorter in the years after 1962, a variety of factors have contributed to that phenomenon, including a reduction in the "patent pending" period because of greater efficiency in patent issuance. A reduced effective *patent* life may well lead to a reduced effective *commercial* life, with resulting negative effects on profitability and R&D. A solution may be revising the patent laws to remedy a feature of those laws that singularly discriminates against drugs; unlike the many products for which marketing approval is not required, large parts of the patent period for drugs are used up before the product is thoroughly tested, studied, and approved for marketing.

Summary

In conclusion, the data on increasing concentration of R&D success, whether measured by source of discovery or by source of market introduction, show trends toward higher concentration among the largest firms from the 1950s through the 1970s. The largest firms experienced a decline in their share of total drug sales in the 1950s, as industry growth diluted their prominence; yet their dominant R&D positions declined relatively less than their sales shares during this period. During the 1960s and 1970s their market shares have become stable and their relative R&D endeavors have grown substantially, when measured at the four-firm, eight-firm and twenty-firm levels in the early 1960s, and continuing at the four-firm and eight-firm levels in the late 1960s.

As R&D has become more costly and time consuming, there have been fewer NCEs and fewer firms introducing NCEs. Correspondingly, the average effective patent life for new drugs has declined to as low as nine or ten years.

Yet, as before, the role of the 1962 Amendments as a factor in these developments is not yet fully clear, for some of these trends began before 1962. Strong currents of increasing drug R&D concentration have been at work, but these currents also seem to have begun as early as the latter 1950s. The tentative conclusion at this point in the analysis is still unchanged: the 1962 Amendments are not clearly demonstrated to have been the only, or the major,

cause of the observed changes in the drug industry's R&D performance and structure. Many of the effects attributed to the Amendments on closer analysis can be seen to have been under way before 1962. Yet the 1962 Amendments appear to have magnified these effects, as shown by post-1962 changes in the industry's R&D characteristics. Accordingly, one should judge them to have been significant contributing factors to the continuance and acceleration of the structural trends described by the foregoing data.

V. Impacts on Firm Innovation Strategies

The preceding two sections have described significant trends in the monetary and time costs of drug R&D and approval processes, and in certain structural features of the industry, namely R&D concentration and effective patent life. Both sets of factors directly and indirectly affect the abilities and incentives to innovate new drugs in the drug industry.

One major effect attributable at least in part to these factors has been extensively described in the literature and already considered in this study: the decline in the rate of new drug innovation, measured either by all new drugs or NCEs only. But the therapeutic impacts of the drug lag depend perhaps more on its effect on quality than on its effect on the number of new drugs. This effect has received considerable attention, which focuses on changes in the pattern of both R&D activity and in the resulting R&D outcomes.

Clymer pointed out one effect of more costly and time consuming development efforts on the pattern of new drug R&D in these terms:

> Research programs today must be aimed at markedly superior, and indeed breakthrough, therapy, for it takes as long and costs as much to develop a compound representing only a slight improvement over existing therapy as it does one representing totally new therapy. All the major steps to demonstrate safety and efficacy will have to be carried out, even if only a single atom has been altered in the molecule of a standard agent. It is no longer economically sound to carry such projects through the long, costly, and sometimes just risky process if one can predict only marginal differences — perhaps a slight increase of efficacy or a slight reduction in side effects.[36]

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36 Clymer, *"The Changing Costs of Pharmaceutical Innovation,"* *supra* note 12, at 121.

While a shift in emphasis from molecule modification to innovative R&D seems desirable, Clymer also pointed out some of the potential losses from this shift:

> Even as I say this, however, I am concerned. What might appear to be minor modifications to an existing standard agent may well have great meaning therapeutically; but without good ways to predict this, prudent management will consider minor modifications to be, economically, awfully borderline undertakings. As the investment in time and money has increased in the last few years, many of these compounds and combinations have had to be dropped, and this too has added to the attrition rate.[37]

Sarett also has provided insight into the impacts of increases in R&D costs on drug development, identifying a much wider range of impacts than did Clymer. These impacts as seen by Sarett include:

> (1) a relative shift of dollars from research to development . . .; (2) a shift away from "me-too" drug research . . .; (3) an increase in minimum critical mass for a viable research project . . .; (4) a decrease in the number of research projects . . .; (5) increased emphasis on epidemiologically important diseases . . .; (6) transition to a more target oriented (research) structure . . .; (7) emphasis on total safety of drugs . . .; (8) overseas shift in clinical pharmacology and related support . . .; (9) increasing emphasis on research for drugs with short-term usage . . .[38]

Sarett did not discuss the causes or effects of these relationships. However, the linkages are fairly easy to discern. The first impact, the shift from research to development, affects the distribution of the pool of available funds, for these two components of R&D are complementary endeavors. As development costs increase for research findings perceived to represent the most likely commercial success, a diversion of funds from marginal research activities to sustain these development efforts will occur. Closely related effects are (3) an increase in the minimum critical (resource) mass for a viable research project, (4) a decrease in the number of such projects, and (5) increased attention to epidemiologically (and commercially) more important diseases. An increase in development costs has also reduced marginal or "blue sky" research, producing (6) a shift to more goal-specific research. Conforming to

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37 *Id.*
38 Sarett, *FDA Regulations and Their Influence on Future R&D,*" *supra* note 16.

stricter approval standards leads to (7) emphasis on total safety; greater cost consciousness is also likely to result in (8) a shift to other countries for clinical testing and trials; and the particular toxicity problems associated with drugs for long-term usage, which makes their development especially risky, is likely to (9) increase the emphasis on drugs for short term use.

Clymer's and Sarett's general observations about shifts in R&D input patterns are supported by evidence on R&D outcome patterns. Grabowski, for example, presents data in graphic form on the annual number of new drug approvals "by degree of therapeutic importance."[39] These data, reproduced below in Figure 1, indicate that during the 1954-1970 period (eight years on either side of 1962) the erosion of the rate of innovative output was negatively associated with the rate of therapeutic gain of new drugs. In other words, the decline in R&D outcome was relatively greatest for those drugs representing little or no therapeutic gain, less for "important and modest improvements" considered together, and least for "important" new drugs considered alone. Thus, there has been little long-term change for the "important" new drug category.

These data, and other measures of changes in the rate of innovation of "significant" new therapies or "major" therapeutic advances, do not prove that there are no therapeutic consequences of a lag; they tell nothing about delayed introduction of new drugs or the decrease in modest and even unimportant drugs. Their purpose here is to lend support to the thesis that compositional changes in R&D activity patterns have occurred since 1962.

A somewhat different effect of the changes in R&D output patterns and input strategies is the so-called "orphan" or "public service" drugs. Such drugs generally are those which are not directly profitable to produce, because the relationship between the company's costs and its expected revenues is not favorable. Two magnifications of the orphan drug problem result from R&D cost escalation: first, the number of orphan drugs increases as new drugs on the margin of profitability become unprofitable; second, the loss to the firm from developing such a drug becomes larger as its costs increase, thereby weighing increasingly against the public service motives of the firm for doing so.

While it is hard to quantify the number of potentially successful development projects thus foregone, a general estimate is provided

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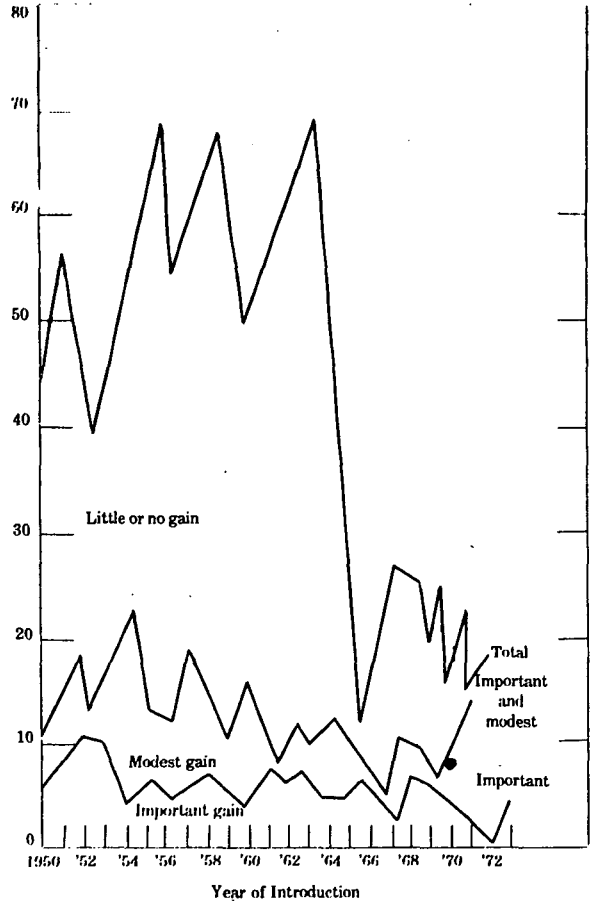
39 Grabowski, *Drug Regulation and Innovation*, *supra* note 5, p. 22.

FIGURE 1

FDA CLASSIFICATION OF ANNUAL NEW DRUG APPROVALS BY DEGREE OF THERAPEUTIC IMPORTANCE, 1950-1973[40]



40 Reproduced from Grabowski, *id.*

by the shift from the existence of an impressive list of available, but not profitable, new drugs, to growing pressure for the federal government to act in one way or another to resolve a growing absence of "public service" drugs. Former Representative Holtzman of New York, for one, recently advocated a new office in the National Institute of Health to "assist in the development of drugs for diseases and conditions of low incidence."[41] She, like many others, cited numerous factors other than small markets that contribute to the problem, including "issues of legal liability, complex and costly drug approval requirements, shortage of research funds, concerns over the patentability of certain compounds, lack of coordination of research and information on rare diseases, and the small size of the possible test population."[42]

Lasagna also has addressed the problem of orphan drugs. Among the factors he cites for "orphanization" include the 1962 Amendments, which he believes have greatly raised development costs. As a result, it is too costly to divert resources away from "large-market" drugs to an orphan drug, with the result that new public service drugs are becoming increasingly rare.[43]

In sum, the available studies suggest that the patterns of new drug development have changed significantly. While there are not a large number of such analyses, nor do they cover all facets of the patterns of R&D inputs and outputs, there seems to be strong agreement. Further, at the time the 1962 Amendments were adopted the trends in R&D costs already underway were not clearly recognized. The prospective effects of the Amendments on these changes, and ultimately on the pattern as well as the magnitude of new drug development, were not accurately identified. As a result, the most important long-run impacts of the 1962 Amendments, the effect on firms' R&D strategies, were not recognized until long after the Amendments were passed.

VI. Conclusions, Implications, and Suggestions

This final section serves three purposes. First, it sums up the findings on the drug lag in the United States by comparing the characteristics of this lag to what microeconomic theory would predict to be the results of legislation such as the 1962 Amend-

41 *Cf. PMA Newsletter*, Vol. 22, No. 18, May 5, 1980.
42 *Id.*
43 Lewis Lasagna, "Who Will Adopt the Orphan Drugs?" *Regulation*, Nov./Dec. 1979, pp. 27-32.

ments. Second, it offers lessons from the drug lag that are applicable to other industries. Finally, it suggests how the difficult problem of assessing the societal impacts of the lag may be resolved more adequately in the future.

The Predicted and Actual Effects of Drug Regulation on Innovation

Regulations such as the 1962 Amendments raise a firm's costs of drug development, reduce its chances of R&D success, and delay the time of payoff for successful innovation. Economic theory has identified the effects of such cost increases. The first type of effect concerns R&D activity. Cost increases will alter the amount of R&D activity; firms finding it commercially infeasible to attempt to innovate will find that to be even more the case; those finding it marginally profitable to do so may well find it now to be unprofitable; and firms that are active innovators will find that fewer of the available projects will remain advantageous to pursue.

Qualitative changes also can be expected. To the extent the R&D strategies and targets of smaller firms differ from larger ones, the mix of total R&D results will increasingly reflect the strategies and successes of the larger firms. Additionally, as all firms become more selective in allocating their R&D funds, the pattern of activity within the firm will shift in favor of the more profitable projects.

These expanded results, as we have seen, have materialized in the drug industry. The evidence is quite clear that the 1962 Amendments accelerated the increase in R&D costs. These cost increases have influenced firm strategies, reducing the over-all rate of innovation. There also has been a shift in the pattern of R&D activity. That pattern, measured by inputs or outputs, has shifted toward the top four and eight firms in the industry. The rate of introduction of new drugs has declined most heavily in categories of drugs with little therapeutic advance and only slightly for important new drugs. There seem to be fewer simple modifications, new congener, (i.e., related within a chemical family) drugs, and public service drugs (because of their limited market potential and/or lack of therapeutic importance); additionally, there has been a shift in emphasis away from long-term therapies due to the higher R&D costs and to progress in epidemiology and biostatistics.

A second type of effect of the Amendments predicted by economic theory that has materialized is a lengthened development and approval process. The lengthened pre-introduction period

contributes to higher R&D costs and delays new drug introduction dates. In the sequential development process used for drugs, additional or expanded tests and longer approval periods will occur even under conditions of maximum operational efficiency. The data show that, on average, drugs are introduced later in the United States than in most other industrial nations.

Lessons From the Drug Lag

The first three lessons from the regulation of drug innovation for other industries follow directly from the above observations about drugs:

(1) Regulation that requires more economic resource inputs into the R&D process will raise R&D costs, thus inhibiting R&D activity.

(2) The increased costs of R&D activity are likely to be felt by all firms, but unevenly. The effects will be an absolute reduction in the rate of innovation and a change in its composition, in favor of the more commercially viable opportunities. Further, the slowing of the pace of innovation also causes time lags in the final success of those projects that continue to be pursued.

(3) The prospective effects of the drug regulations were not carefully assessed, and thus provide no specific lessons for prospective impact studies in other situations. Retrospective benefit/cost studies have been attempted, but without noteworthy success, again providing little guidance for policy decisions in other areas. Yet a compelling implication does emerge: that prospective benefit/cost analyses of proposed policy alternatives can provide very helpful guidance in the choice of policies, and retrospective benefit/cost monitoring can be equally helpful in the continuous shaping of policy.

A second set of implications relates at a somewhat more detailed level to what this Article has called the pathways of interaction between regulation and firm innovation strategies. Above, we have dealt with the "regulation-cost of R&D-effect on R&D" pathway. Additionally, one should consider:

(4) The effects of regulation on the structural variables in markets will affect the forms and degrees of market rivalry. Specifically, the effects of regulation on market concentration, size, product availability, and buyer power will have a strong influence on the incentives to compete in terms of innovation, price, and marketing. Thus, the firm's response to regulation will involve

not only its "ceteris paribus" response to higher R&D costs, but its additional response to regulation-induced changes in its industrial environment. These latter responses may be difficult to ascertain without careful study, since they are likely to be subtle, to be offsetting, and to be unique to the circumstances of each industry.

(5) Regulation may not only affect many different static variables in an industry, but may also affect the dynamics of an industry's operations. The effects of regulation may set into motion a sequence of changes that ultimately impact on innovation, but may also run in opposition to, or in the same direction as, other forces of change already at work. It also is inaccurate to consider the effects of regulation merely as additive to these other effects. They may well be multiplicative or synergistic in their impacts on firm strategies. Thus, special attention must be given to the trends already underway or just emerging in an industry to accurately predict the likely effects of new regulatory policy.

(6) Most importantly, regulation is more than rule making. It is an expression of philosophies and attitudes about the economy and about specific industries and groups. These philosophies and attitudes strongly influence the interpretation and administration of regulations, expanding or mitigating their impacts on the activities being regulated. In the case of drugs, the strict regulation in the United States is a paradigm for our attitudes toward medical care, science, and medical innovation. These are attitudes that pervade the administration and interpretation of the law as well as its language. These attitudes are not easily changed, and thus the strong commitment society has toward the regulation of drugs has not been shaken by the voluminous body of criticism of the ultimate effects of the 1962 Amendments. However, an evaluation of a specific regulation does not have to become a conflict between larger attitudes if shaped by clearly formulated performance objectives. The performance of the regulation can only be evaluated in relation to specific goals. The performance objectives for the drug industry are poorly drawn, for they are at best unsystematic static criteria such as "efficacy," "safety," "purity," and "good manufacturing practices." The philosophy and goals of regulation need to be articulated as clearly as the form of regulation, especially for industries that have a widespread impact on society, such as the drug industry.

We still do not know if the 1962 Amendments have generated more good than harm: Jondrow says they have, Ludlow and Peltzman contend they have not, but all three analyses suffer from serious limitations or errors. Wardell argues that the therapeutic costs of the Amendments are very large, yet he does not consider the therapeutic gains or any of the economic effects.

While benefit/cost analyses of the 1962 Amendments are useful, Wardell has suggested that much of the therapeutic cost of regulation can be mitigated through administrative practices and interpretation. The implication is that much of the benefit of the Amendments, and regulations in general, can be maintained and much of the cost reduced by relatively small changes in the existing regulations rather than by wholesale repeal or major reconstruction. Accordingly, benefit/cost analysis with a large scope (drug regulation as a whole or of major portions of it), or a small scope (pertaining to revisions, perhaps minor, of existing regulatory policy), may well provide useful guides as to both the direction and form of change that will serve society best. None of the studies to date, as we have seen, has provided a satisfactory frame of reference for such analyses. However, they collectively offer most of the necessary components. This study now turns toward an integration of these components to provide guidelines for benefit/cost analyses of existing and proposed drug regulatory policies.

The appropriate benefits and costs to include in such an analysis are presented in Table 11. The table shows those benefits and costs applicable to the drug lag, and those additional benefits and costs necessary for an assessment of the regulations as a whole.

The quantification of these benefits and costs is more readily accomplished by following Wardell's approach rather than Peltzman's, thus using actual experience of the drugs in question rather than hypothetical or generalized historical results. Such an approach relies heavily on subjective medical judgment, but it must suffice in the absence of other ways of measuring health care outcomes.

Carefully selected foreign experience, perhaps that of Canada, or Great Britain, or several countries who lead the United States in the rate and timing of innovation, provides the basis for quantifying most of the benefits and costs in Table 11. Benefit I and Cost I, which probably are the largest of the components comprising total

TABLE II

IDENTIFICATION OF BENEFITS AND COSTS FROM THE DRUG LAG AND FROM DRUG REGULATION

BENEFITS AND COSTS OF THE DRUG LAG

BENEFITS	COSTS
I. BENEFITS FROM AVERTED ADVERSE THERAPEUTIC CONSEQUENCES FROM LAGGING DRUGS A) HEALTH TREATMENT COSTS B) PRODUCTIVITY LOSSES	I. LOSSES FROM REDUCED AVAILABILITY OF LAGGING DRUGS A) HEALTH TREATMENT COSTS B) PRODUCTIVITY LOSSES
II. REDUCED EXPENDITURES ON INEFFICACIOUS DRUGS	II. INCREASED R&D EXPENDITURES FOR LAGGING DRUGS

ADDITIONAL BENEFITS AND COSTS FOR MEASURING THE EFFECTS OF 1962 REGULATIONS

III. BENEFITS FROM AVERTED ADVERSE THERAPEUTIC CONSEQUENCES FROM NON-LAGGING DRUGS A) HEALTH TREATMENT COSTS B) PRODUCTIVITY LOSSES	III. VALUE OF ADDITIONAL RESOURCES USED TO MEET REGULATORY REQUIREMENTS FOR NON-LAGGING DRUGS IV. ADDITIONAL ADMINISTRATIVE COSTS BY REGULATORY AGENCY

benefits and costs, can be estimated by following the general steps:

(1) Identify the specific new drugs "lagged" in their introduction into the United States.

(2) Estimate the incidence ratios both of adverse consequences (whose aversion is a benefit) and of outcomes more favorable than offerred by the best alternative therapy available in the United States at the time (these foregone superior outcomes are costs of the lag to U.S. patients).

(3) Apply these ratios of adverse and superior outcomes to the respective American populations-at-risk to determine the absolute frequencies of both in the United States that would have occurred but for the lag.

(4) Estimate increased or reduced disability and work, subtracting periods that result from these adverse or superior outcomes.

(5) Calculate the dollar values associated with the averted or incurred medical treatments and productivity gains and losses. The product of (3) and (5), with appropriate discounting, represents the value of the benefit or cost in question.

Benefit II can be calculated by looking at foreign drugs that are removed from the market after appearing only in countries outside of the United States. Their usage rates and prices, adjusted for differences between the United States and foreign nations, estimates the savings that patients in the United States would have obtained from drugs never entering the American market.

Benefit III is the gain to customers from the increased knowledge about all drugs resulting from increased testing. We can calculate this benefit by employing inter-temporal U.S. comparisons, international comparisons, or some combination of both that show shifts or differences in the ratio of unfavorable to favorable outcomes associated with drug use attributable to the additional information generated by the heightened requirements. Complex factors are involved, including the effects of learning by experience, international transfers of knowledge, improved testing methodology, and legal liability. However, multivariate analysis may enable us to sort out the relative influences of each such factor.

Costs II and III, the increase in real costs both for lagged and other drugs, can draw on the many studies cited in this report that deal with changing R&D outlays. Special attention here needs to be given to the use of appropriate definitions of R&D activity and accurate indexes of changing R&D input prices. Cost IV, administrative costs of the regulations, can be quite easily derived from FDA budgetary and activity reports.

The above guidelines admittedly are very general and unqualified. All the nuances of benefit/cost analysis must eventually be utilized; but as a general overview, they offer initial directions that can produce useful retrospective studies of the effects of the lag and of the regulations creating the lag. Once this approach is worked out, it can tell us much about the marginal benefits and costs resulting from changes in the requirements that apply to the quantity or timing of drug development in general, or certain drugs or groups of drugs in particular. While the prospective benefit/cost analysis of major regulatory changes may be the most problematical task of all, this framework at least provides some useful methodology for both identifying and quantifying those anticipated effects.

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Commentary

New drug development during and after a period of regulatory change: Clinical research activity of major United States pharmaceutical firms, 1958 to 1979

The 1962 drug amendments fundamentally changed the way in which U.S. pharmaceutical firms could test new drugs in man and receive New Drug Application (NDA) approval. Although it is well known that the amendments and associated events caused a profound decline in the annual number of new drugs receiving NDA approval, the amendments' effects on clinical research into new chemical entities (NCEs) have not been investigated because data were unavailable. To study this we requested drug development information dating back to 1958 from most major United States–owned pharmaceutical firms and obtained complete responses from nine. The results showed that the introduction rate of NCEs into human testing dropped sharply in the early 1960s and declined substantially thereafter. The number of NCEs entering human testing fell from a mean of 89 a year in 1958-1962, to 35 a year in 1963-1972 (a reduction of 61%), and to 17 a year in the last 5 years of the survey, 1975-1979—an overall reduction of 81%. The number of NDA approvals received by these firms fell sharply by 49% in the early 1960s and more slowly for 10 years thereafter, from the mid-1960s to the mid-1970s. In the case of self-originated NCEs, the size of this later fall was 71%. Causes of these changes in NCE flow include the amendments and the events that prompted them: changes in scientific philosophy, standards, and state of the art; and economic factors.

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In 1962 and 1963 fundamental changes occurred in the way in which the Food and Drug Administration (FDA) regulated the development of new drugs in the United States. The enactment of the 1962 drug amendments to the federal Food, Drug, and Cosmetic Act of 1938 greatly increased FDA control over clinical research into Investigational New Drugs (INDs). The new amendments required that the FDA be notified about preclinical studies and given detailed descriptions of the planned clinical investigations before clinical trials could commence. For the first time, subjects' informed consent was required, along with full progress reports about the distribution and use of drugs in clinical investigations, and the FDA was given more power to halt trials.[6-8] At the same time the system for approving a New Drug Application (NDA) was transformed from one that emphasized safety data into one that also required rigorous proof of efficacy[16] and active approval by the FDA before a drug could be marketed.

It is well known that the entry rate of new drugs into the market decreased sharply at that time,[4,12,13,15,19] but the effect of the amendments on the entry of New Chemical Entities (NCEs) into clinical testing has not been analyzed because no data were available. In previous studies of United States drug development, we have analyzed both the annual rate of entry of NCEs into clinical testing from 1963 onward and the subsequent fate of these drugs.[20,21,23] In this paper we have extended the previous studies back in time to 1958 in order to study the effect of the amendments on the clinical testing of NCEs.

The reason no data were available for the pre-1962 period is the absence of an external reporting requirement at that time. This means any data that still exist from this period are available only in the archives of the pharmaceutical firms. Because such old data are of little or no current use to the firms, they are rapidly becoming inaccessible and in many cases have already been discarded. Our objective was to obtain and analyze as much of the data as possible that still exist at this time from the events of 1962.

We surveyed most major United States firms to assemble information about the NCEs first tested in man in the 5-year period 1958 to 1962. By combining the data obtained from this survey with other data previously collected from the same firms in 1963 to 1979, we were able to analyze all the NCEs tested by the set of responding U.S. firms for the years 1958 to 1979.

Methods

Companies surveyed and NCEs included in analysis. As in our earlier studies,[20,21,23] an NCE is defined as a compound of molecular structure not previously tested in man. Vaccines, antigens, antisera, immunoglobulins, surgical products, diagnostics, and new salts or esters of existing agents are excluded from the analysis.

Fifteen major firms (which accounted for approximately two thirds of all NCE research by U.S.-owned firms in the period 1963 to 1979) were asked to provide data (1) on all self-originated NCEs first tested in man anywhere in the world in the 5-year period 1958 to 1962 and (2) on all acquired NCEs that they were the first to test in man in the United States in this period. (Self-originated NCEs are those discovered, owned, and developed by the parent company, whereas acquired NCEs are obtained by licensing or other means.) These 15 firms were the largest U.S.-owned firms that we considered likely to have the required information, judging from the post-1962 data we obtained from them.

Nine firms were able to give us a full response. The remaining six firms were unable to supply reliable data (for reasons such as loss of records in a fire and destruction of very old records on NCEs for which research had been terminated many years ago). The nine responding firms accounted for 49% (514) of the 1041 NCEs tested in man between 1963 and 1979 by the 39 firms included in our most recent study of NCE drug development undertaken by U.S.-owned firms.[23] Although the nine firms are large ones, their drug development trends were similar to those of all U.S. pharmaceutical firms for 1963 to 1979.

Information requested. The questions asked in the survey were a subset of those asked in the full questionnaire used in our earlier studies.[20,21,23] We obtained data on the numbers, the

Table I. *Number of NCEs investigated in man by nine major U.S.-owned pharmaceutical firms and numbers of NDAs submitted and approved on these NCEs between 1958 and 1979*

	1958 to 1979				1958 to 1962	1963 to 1979
Source of NCEs	NCEs investigated	IND/eqs	NDA submissions	NDA approvals	NCEs investigated	NCEs investigated
Total*	981 (36)	922	111	99	467 (22)	514 (14)
Self-originated	804 (3)	749	76	66	374 (1)	430 (2)
Acquired	174 (33)	170	35	33	92 (21)	82 (12)

Numbers in parentheses denote NCEs for which year values were missing or (in case of acquired NCEs) not applicable.

*Total includes self-originated and acquired NCEs and three for which the source was missing (one in the 1958 to 1962 cohort and two in the 1963 to 1979 cohort).

pharmacologic types, and the subsequent fate of the NCEs, to the point at which they either obtained NDA approval or were withdrawn from active research. Corresponding data on NCEs tested from 1963 to 1979 were taken from responses to previous surveys.

The data on marketed NCEs were obtained from our earlier studies and from publicly available sources.[5,7]

Quality of data obtained. Although this survey was more limited in scope than our earlier ones, the data we obtained on drugs investigated in the pre-1963 years was more variable and less complete. Approximately 5% of the values were either missing or ambiguous for the pre-1963 drugs because of the age of the data and the fact that, since there was no official requirement for external reporting prior to 1963, company internal records were the only source of information. We were able, however, to clarify a number of points in discussions with company personnel who compiled the information, and we believe that the data are now the best available on pre-1963 research. Although some NCEs entering clinical trials in 1958 to 1962 have probably been omitted, such omissions would only cause us to underestimate the size of the large decline in NCEs entering clinical testing that we found to have occurred over the 1958 to 1962 period.

Terminology: IND-equivalent NCEs. To avoid cumbersome terminology, the abbreviation "IND" is used to denote the first IND filing on an NCE from 1963 (when IND requirements were implemented) onward. The abbreviation "IND/eq" (IND equivalent) is used to denote the first administration of an NCE to man *in the United States* before 1963. The abbreviation "IND/eqs" is used to refer collectively to both groups of NCEs: those for which INDs were filed and those that were first tested in man in the United States before 1963.

Results

Number of NCEs under clinical investigation, 1958 to 1979. Table I summarizes data supplied by the nine major firms on their NCE research. Over the whole period from 1958 to 1979, 981 NCEs were investigated clinically, of which 804 (82%) were self-originated NCEs and 174 (18%) were acquired. Nine hundred twenty-two IND/eq filings were made on the total NCE cohort, of which 749 were self-originated NCEs and 170 were acquired. Most of the remaining NCEs were not brought to the United States. By the end of 1979, 99 of the 111 NDAs submitted had reached approval; these consisted of 66 approvals from 76 submissions on self-originated NCEs and 33 approvals from 35 submissions on acquired NCEs.

Table I also shows the number of NCEs investigated in the 5 years (1958 to 1962) that preceded enactment of the IND requirements and the number investigated in the 17 years that followed (1963 to 1979). This comparison reveals that the annual number of NCEs entering clinical testing was far higher in the pre-1963 years than it was thereafter. Nearly half (48%) of the NCEs were first investigated in 1958 to 1962; whereas the remaining 52% were spread over the subsequent 17 years.

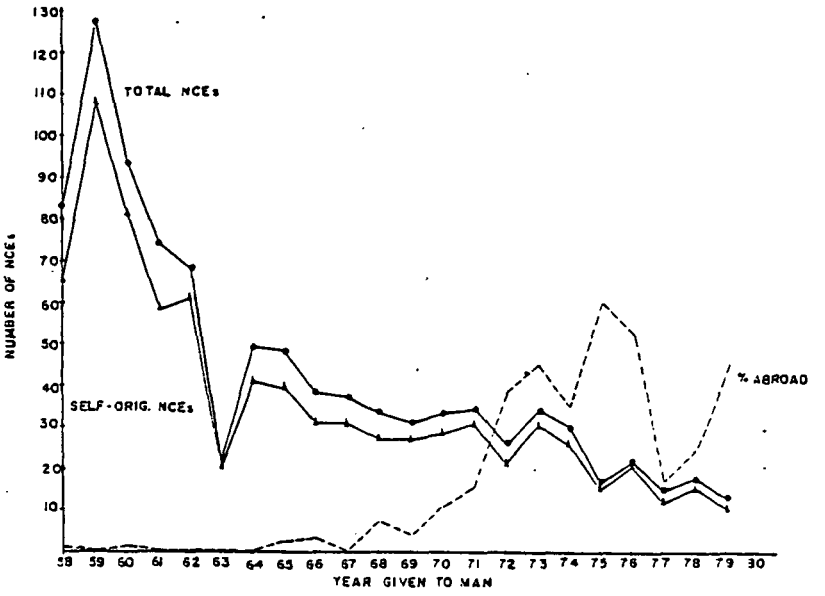

Fig. 1. Total number of NCEs and number of self-originated NCEs given to man by nine major firms *(solid lines)* and percentage of self-originated NCEs first tested in man abroad *(dashed line)*: indicated by year given to man, 1958 to 1979.

A detailed picture of the annual rate of entry of NCEs into clinical investigation between 1958 and 1979 is shown in Fig. 1. After the first observation in 1958, there was a steep rise in 1959. Then beginning in 1960, there was a sharp decline for 4 consecutive years with the largest drop (67%) from 1962 to 1963. Comparing the 5-year period 1958 to 1962 to the following decade, 1963 to 1972, there was a 60% overall decline from a mean of 89 a year to 35 a year. In the last 5 years of the survey (1975 to 1979) the mean rate declined further, to 17 a year—an 81% drop from the pre-1963 average level.

Fig. 1 also shows the number of self-originated NCEs studied in man each year. Since self-originated NCEs account for approximately 80% of the total sample, they follow trends that are similar to those for all NCEs. Entry of self-originated NCEs into clinical testing dropped sharply in the early 1960s and continued to decline thereafter.

From 1958 until the late 1960s, only 3% or less of self-originated NCEs were first tested abroad (Fig. 1). In the first half of the 1970s, however, a strong trend developed toward initial testing abroad. This trend peaked at 60% in 1975. The proportion has since fluctuated but in general has declined: in 1977 to 1978 only 21% of self-originated NCEs entered clinical trials abroad, although the percentage rose to 45% in 1979. The trends shown here for the nine firms are similar to those we observed for all U.S. firms over the period 1963 to 1979.[23]

Fig. 2 shows the number of IND/eqs filed on self-originated and acquired NCEs and the percentage of those that were self-originated. Although IND/eq filings by the nine firms have decreased over time, the self-originated percentage has remained at approximately 80%.

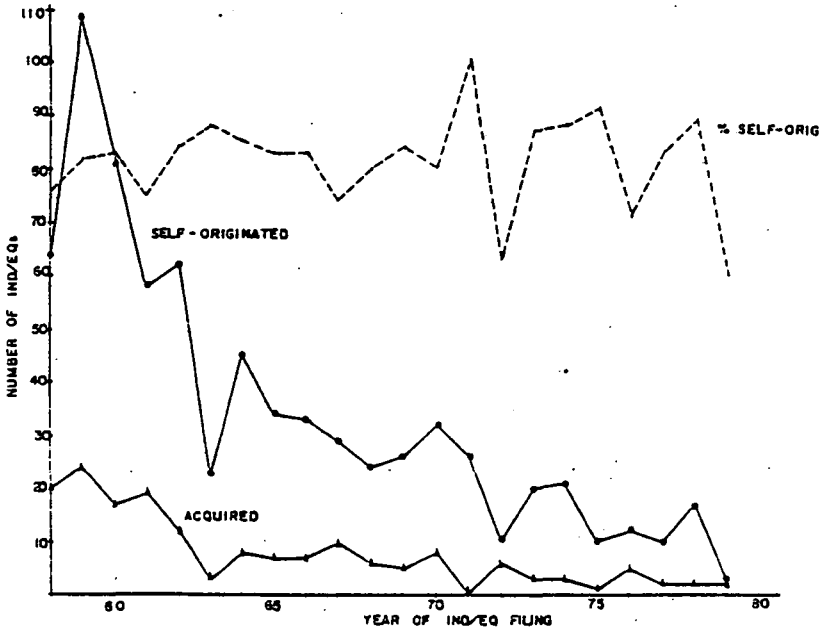

Fig. 2. Number of IND/eqs (see Methods) filed on self-originated NCEs, number filed on acquired NCEs (*solid lines*), and percentage of total that were self-originated (*dashed line*); indicated by year of IND/eq filing, 1958 to 1979.

Time required to reach NDA approval. We compared the average time required for NCEs to progress from IND/eq filing to NDA approval at the beginning and at the end of the observation period. Self-originated NCEs that entered clinical trials between 1958 and 1963 averaged 54 months from IND/eq filing to NDA approval, whereas those approved between 1972 and 1979 averaged 112 months.*

Comparison of pharmacologic types of NCEs under investigation in 1958 to 1963 and in 1975 to 1979. We compared pharmacologic types of the NCEs investigated in the first and last 5 years of the survey period (Table II).

The emphasis on certain pharmacologic areas has changed. In particular, psychotropic and neurotropic drugs, analgesic and anti-inflammatory drugs, and drugs acting on the motor system and on body fluids and electrolytes accounted for larger percentages of the pre-1963 NCEs than the 1975 to 1979 NCEs. On the other hand, cardiovascular, endocrine, and digestive system drugs accounted for smaller percentages in the pre-1963 period than they did in 1975 to 1979.

This comparison also highlights the decline in the number of NCEs entering clinical investigation. Although the 11 major pharmacologic areas in Table II accounted for approximately 90% of the NCEs under investigation both in the pre-1963 period and in the last 5 years, they

*With a data base of this type that has fixed start and finish dates, in order to avoid biases because of start-up artifact and right censoring of the data, one must calculate values for the early years by the date of IND/eq filing and values for the later years by NDA approval. This removes one type of bias but makes the values not exactly comparable, so that the precise size of the increase cannot be obtained from these values.

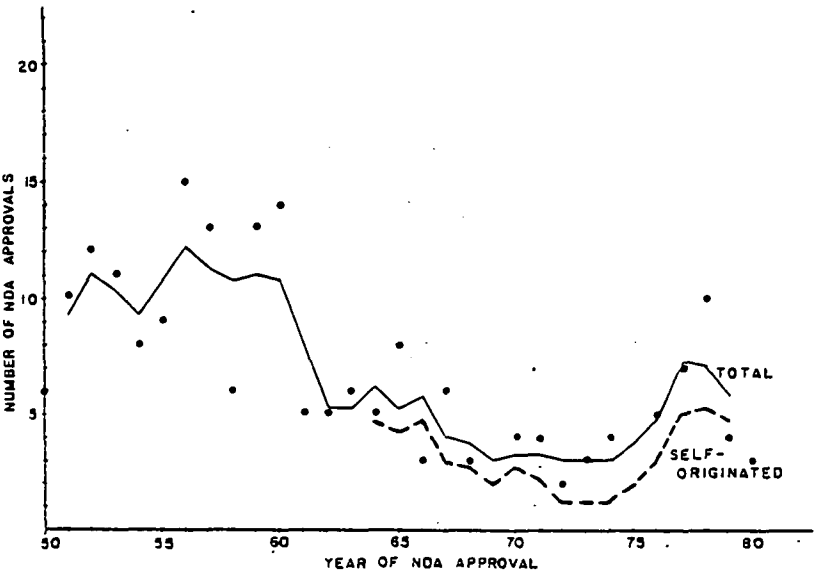

Fig. 3. Number of NCEs for which the nine firms received NDA approval a year, 1950 to 1980. Yearly totals are represented by *points; continuous line* represents a 3-year moving average. *Dashed line* shows number of total that were self-originated in 1963 to 1980.

previously encompassed many more NCEs (420 and 77).

New drug approvals, 1950-1980. In addition to studying the entry rate of drugs into clinical research, we also examined the approval rate of drugs for the market. The total number of NCE-NDA approvals granted to the nine firms each year from 1950 to 1980 and the number granted for self-originated NCEs from 1963 to 1980 are shown in Fig. 3. This graph shows that the number of NCE-NDA approvals fell sharply in 1961 from a mean of 10.6 a year in 1950 to 1960 to a mean of 5.4 a year in 1961 to 1967 (a decline of 49%). The decline continued from the mid-1960s to the early 1970s, to a mean of three a year in 1968-1975, with an overall decline of 72% from the 1950-1960 level.

The number of self-originated NCEs approved (shown in the dashed line of Fig. 3), declined even more (71% from the mid-1960s to the early 1970s alone) to only one a year. Subsequently the numbers recovered, so that by 1980 they had returned to the levels of the early 1960s. These trends are similar to those shown for NCE drug approvals granted in the same period to all U.S.-owned pharmaceutical firms.[22]

Discussion

The manner in which pharmaceutical firms in the United States could test their drugs in man and obtain NDA approval for marketing changed importantly with the passage of the Kefauver-Harris Drug Amendments on Oct. 10, 1962, and issuance by the FDA of procedural and interpretative regulations that came into effect on Feb. 7, 1963.[3,6,8,9] Before 1963 the regulations governing clinical trials on INDs did not require either an initial notice to the FDA or

Table II. *Comparison of main pharmacologic areas under investigation in 1958 to 1962 and in 1975 to 1979*

Pharmacologic area	Number of NCEs investigated		Percentage of total for period	
	1958 to 1962	1975 to 1979	1958 to 1962	1975 to 1979
Anti-infective	91	17	19.6	19.1
Psychotropic/neurotropic	74	6	15.9	6.7
Analgesic/anti-inflammatory	65	9	14.0	10.1
Endocrine	48	15	10.3	16.9
Cardiovascular	39	15	8.4	16.9
Body fluids and electrolytes	30	0	6.5	0.0
Digestive system	13	8	2.8	9.0
Motor system	18	0	3.9	0.0
Antineoplastic	16	2	3.4	2.2
Central depressant	15	2	3.2	2.2
Respiratory system	11	3	2.4	3.4

subsequent reports on ongoing trials. Under the new regulations a sponsor who wished to test a new drug or antibiotic in man had to file with the FDA a "notice of claimed investigational exemption" (IND) before clinical trials could commence. For the first time the FDA required substantial information before clinical work could begin. This information included data on the nature of the new drug, the preclinical toxicity tests that had been performed, the proposed plans for clinical trials, and the identity and qualifications of the investigators who had to supervise and be responsible for the trials. Informed consent of clinical subjects was also required for the first time. The subsequent clinical research was to be closely monitored, and detailed reports on its progress were to be filed regularly with the FDA. If the FDA deemed the plans inadequate or the trials unsafe, it could require corrective action or termination of the studies.

The criteria for approving an NDA also changed in 1962.[3,6,8,9,13,16] The provision in the 1938 act that had required the FDA to approve an NDA automatically 60 days after its submission* was dropped; the requirement for premarket notification was changed to a requirement for premarket approval. A requirement was added that the manufacturer should provide "substantial evidence" through "well-controlled investigations" to show that a drug was effective, as well as safe, for its proposed indications.* The impact of the efficacy provisions on drug development in 1962 and the years immediately following is not clear-cut, however, because it took almost 8 years for the FDA to establish detailed criteria for "well-controlled investigations:" these regulations were not made final until May 8, 1970.[10]

Although the effects of the 1962 drug amendments on the number of drugs being marketed in the United States since 1962 have been analyzed extensively,[1,2,11,12,18,19] there have been no previous studies of the other primary intent of the amendments, namely to control clinical drug research. Our study shows how large the impact was: the amendments were associated with a steep reduction (by 60% or more) in the number of NCEs entering clinical testing. In subsequent years there was a corresponding decline in the number of NCEs reaching NDA approval, an increase in the time required to do so, and a further reduction of NCEs entering clinical testing.

The temporal changes described in this paper are complex, and the reasons for them are complicated as well. The peak in the number of

*Automatic approval was granted unless the FDA deemed within that time that the information supplied was incomplete or that more time was required (up to 180 days) to review the application.

*The 1938 law required that the drug be safe for its intended uses. Although proof of efficacy had not formally been required, the safety judgment had presumably been made in light of the drug's intended uses and information about its efficacy.

NCEs tested in man in 1959 may be a statistical fluke that represents a chance variation: for instance, in this sample the number of NCEs tested in man per company in the period 1958 to 1962 ranged from as few as one to as many as 32 a year. Alternatively, a specific scientific development may have come to a peak in that year, such as the culmination of activity in many firms searching for better semisynthetic penicillins. Another possibility is that 1959 was a high-water mark of industrial enthusiasm and financial commitment after the dramatic scientific and commercial successes of the 1940 to 1950 decade. Whatever the explanation for the peak in 1959, the 4 following years unquestionably represent a marked and permanent decline in the number of NCEs entering human investigation.

Commentaries about both investigational NCEs and NDA approvals during this period tend to assume that anything occurring before or during 1962 cannot be blamed on the Kefauver-Harris amendments passed in October of that year or on the implementing regulations that followed. The 1962 legislation, however, was the culmination of 4 years of congressional hearings that attacked the pharmaceutical industry, its products, and its advertising and pricing policies. Congressman Blatnik and, later, Senator Kefauver chaired extensive hearings over those years, and the actions of the FDA and industry during the period were subject to extensive media coverage. Added to this was the growing realization of the thalidomide tragedy in Europe. Indeed, the FDA itself had published proposed new IND regulations on Aug. 10, 1962—under the existing law—2 months before the Kefauver-Harris amendments were enacted. Thus it is obvious that a change in conditions and attitude existed well before the amendments passed and that this was one likely inhibitor of both the industry's clinical NCE studies and the FDA's NDA approvals.

The permanent decline in investigational NCEs in the early 1960s would be expected (if no compensatory factors operated) to have led to a decline in NDA approvals after a latency period corresponding to the average IND-plus-NDA time. Analysis of the yearly NCE-NDA approvals obtained by the nine firms showed that after the sharp decline in the early 1960s, there was indeed a further decline in approvals (Fig. 3), which was slower but of a considerable magnitude (49%), from the mid-1960s until the mid-1970s. The later decline was even more marked (71%) in the case of self-originated NCEs. In a separate paper dealing with the whole U.S. pharmaceutical industry,[25] we discuss (1) wider aspects of this link between the flow of investigational NCEs and subsequent NDA approvals and (2) the possible future significance of the further NCE decline of the mid-1970s.

Other influences, perhaps more subtle but as fundamental, were also contributing to the reduction in NCE flow. Running through this whole period, but difficult to quantify, were changes in both philosophy and state of the art. Scientific attitudes are changed by many forces, including technologic progress. In the 1940s and 1950s many in industry believed that preclinical testing was not highly predictive of a drug's clinical utility and that after a modest amount of toxicity testing, a new drug should (and safely could) be tested promptly in man. However, the public's concern about adverse drug effects prompted the FDA and industry to add many preclinical tests that had not been routinely conducted previously (e.g., tests for teratogenicity, carcinogenicity, and recently mutagenicity). Whether or not these tests vindicated the time and money spent on them is beside the point: it became almost unthinkable not to do them, and the result—for both scientific and economic reasons—would be fewer drugs left to enter clinical testing. At the same time, laboratory scientists were becoming more accurate in predicting therapeutic activity. Today, for example, it is rare for an NCE not to show the proposed therapeutic effect postulated by chemical theory and animal experimentation. Such methodologic progress justifies more nonhuman pharmacodynamic evaluation, and again the trend would be for fewer compounds to reach clinical testing.

Finally, the scientific rules for convincing scientists about efficacy were changing. The modern controlled trial became firmly established as the premiere method for demonstrating clinical activity in an unbiased and convincing

way. Such trials, however, are more time consuming than uncontrolled ones and more likely to end ambiguously. The economic consequence is that fewer drugs can be studied clinically for a given research effort.

The flight of early clinical research abroad that began in the late 1960s seems most readily explained as industry's reaction to regulatory and economic constraints in the United States and the eventual shutdown of drug testing in prisoners. The possibility of testing drugs abroad in a less cumbersome and less expensive environment was attractive. The reversal of this trend in the late 1970s was probably related to the economic and regulatory climate abroad, where changes were occurring to reduce the benefits of foreign testing that had seemed attractive a few years before.

In the early 1960s, product candidates were dropped and time was lost as drug companies struggled to satisfy the new statute and the developing FDA regulations. With time, however, the companies increased their regulatory affairs personnel and learned how to satisfy the new requirements and the FDA. These developments may help to explain not only the return of some early human testing to the United States in recent years but the recovery in the numbers of NDA approvals in the late 1970s. Other possible explanations for the recovery of approvals include an increase in the number of NCEs that U.S. firms license from abroad, a moderation of official policy and informal regulatory attitudes in the FDA, clearing of an accumulated backlog of aging compounds, and the pass-through effect of the large increase in development time that occurred in the 1960s.

In conclusion, our studies have shown that before and coincident with the enactment of the 1962 amendments, the number of new drug candidates entering clinical testing declined sharply and permanently, and subsequently the time required for them to reach the market increased. This caused a long-lasting reduction in the number of U.S. firms' new drugs reaching the market, in addition to the immediate, direct effect of the amendments on new drug approvals. The consequences of this are far-reaching. For example, the serendipitous discovery of valuable, although unpredicted, clinical uses of NCEs can occur only when there has been some clinical experience with the drug.[17] Consequently, if fewer new drugs are being tested in man, the probability of finding new therapies by this method is reduced.

Although many drugs continued to reach the market, certain pharmacologic areas have been neglected, and some believe there has been a definite shortfall in the introduction of important new drugs in both the United States and Europe.[14] We consider that the decline in the number of new drugs introduced in the United States is attributable in part to the 1962 amendments and the regulations implementing them and in part to the other factors discussed. In the light of these profound and long-lasting changes in the levels of clinical drug investigation and approval that resulted, it will be important to monitor the course and outcome of the new decline we have observed in the number of investigational drugs in the 1970s.[23] Such monitoring needs to identify the causes of this recent change in drug development and the ultimate effects.

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PATENT TERM EXTENSION: AN OVERREACHING SOLUTION TO A NONEXISTENT PROBLEM

by Alfred B. Engelberg

The proponents of extended life for drug patents argue that the "effective patent life" of pharmaceutical composition and use patents has been cut in half due to the additional time now required to comply with government safety and efficacy regulations prior to commercial marketing. They define "effective patent life" as the period of actual commercial exploitation of a patent monopoly and claim that it has been reduced from seventeen to 7.5 years. Since the proposed legislation (S. 255; H.R. 1937) would extend patent life only for a maximum of seven years, they contend that it would provide less than the full return of time to which pharmaceutical innovators are entitled as a matter of equity.

To those who lack a basic understanding of our complex patent system, this argument seems simple and logical, and for that reason it has attracted broad support. In reality, the arguments which have been made in support of patent extension have no reasonable foundation in fact or law; and the extension legislation undermines fundamental principles on which the entire patent system is based for, at least, the following reasons:

1) Effective patent life.

The term "effective patent life" is the creation of those who are promoting patent extension legislation and has no counterpart in patent law or the fundamental philosophy on which the patent system is based. The notion that the seventeen-year patent grant carries with it any guarantee that the patent owner will enjoy seventeen years of commercial exploitation of the patented invention is contrary to that philosophy, as well as to the requirements which must be met to obtain a patent, particularly in the pharmaceutical field.

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2) Government regulation.

Government regulation is only one of many factors which have an effect on the length of a commercial monopoly, and it is less significant than many others, all of which are largely under the discretion and control of the patent owner. These factors include when the patent application is filed in relation to the state of development of the invention; how long the patent application remains pending in the United States Patent and Trademark Office before a patent is granted; the scope of the patent in relation to the commercial product which it seeks to dominate; the number and type of patents which may be available to cover different aspects of the commercial development; the time at which clinical investigations are commenced in relation to the patent application and issue date; and the pace of commercial development in terms of the time, effort, and money invested to reach the commercial stage. The statistics which have been put forth in support of the proposition that "effective patent life" is now 7.5 years do not tell us which of the foregoing factors actually played a significant role in the net result and make the inaccurate assumption that regulatory delay is the exclusive cause.

3) Equity concept.

The extension legislation in its present form goes far beyond the "equity" concept on which it is being promoted. The application of equitable principles would dictate that any patent extension would be no greater, in either duration or scope, than the delay actually caused by the government. In fact, the legislation would extend the life of a product patent claim for all therapeutic end uses and not merely the end use which is the subject of regulatory review. It would also make it possible to obtain extended patent protection for compositions which were not specifically known or disclosed in the patent, but were covered by broad hypothetical composition claims. This approach will serve to discourage improvements and innovations by third parties which the patent system was designed and intended to encourage. Further, the true length of government-caused delay is, in fact, no greater than the difference between the date on which a reasonably prudent businessman, subject to product liability claims, would commercially release a product and the date on which the government commercially releases the product by approval of a new drug application (NDA). The Senate-passed bill would grant an extension from a time commencing long prior to the first clinical tests in human subjects, thereby rewarding rather than discouraging delay.

Effective Patent Life Is a Nonexistent Concept

The patent system was established to promote the progress of science and the useful arts by encouraging inventors to make early disclosure of their inventions to the public in the belief that such disclosures would prevent wasteful duplication of research. This would stimulate further inventions and improvements which would make the earlier disclosures on which they were based obsolete. The system was primarily designed to benefit society and not to create private fortunes for the owners of patents, although it has always been recognized that some reward is essential as an inducement for the invention disclosure.[1]

The inducement provided by the patent law is not a positive grant of the right to commercial exploitation of the invention for the life of a patent, but rather a negative grant, namely, the right to exclude others from making, using, or selling the invention for a period of seventeen years. Whether or not the patentee derives a commercial benefit from that exclusion is a matter which is totally divorced from the patent system and depends upon a multitude of other factors including the commercial practicality of the invention disclosed in the patent, the state of its development, the existence of a market and, of course, the existence of other laws which determine whether a particular device can be used or sold and, if so, under what conditions.

Until the present controversy concerning patent extension, no one connected with the patent system believed or argued that the grant of a patent created a positive right to exploitation for a fixed period of time. Indeed, the fundamental rules pertaining to what must be disclosed in a patent make it clear that patents are designed to disclose ideas and not necessarily to support the ultimate commercial manifestation of those ideas.

If the basic purpose of the patent system was to convey to the inventor a positive grant of a fixed period of commercial exploitation, a logical requirement of the patent system would be a full disclosure of the commercial embodiment of the invention, and the patent claims would precisely define that commercial monopoly. In contrast, one of the fundamental rules of our patent system prohibits the grant of a patent if the invention was publicly disclosed or commercially used for more than one year prior to the date on which a patent application is filed.[2] This rule exists because the patent grant is a reward solely for the early disclosure of the invention to the public and not a reward for either its discovery or for an investment in its commercial development and exploitation. If society would eventually obtain the benefit of the invention through its public disclosure or commercial use, no reward to the inventor is necessary and none is given by the patent system.

Under the United States patent system, with certain difficult-to-prove

exceptions, the patent is granted to the first inventor who actually discloses the invention in a patent application and not to the first person who may have actually made the discovery.[3] It is self-evident that this system encourages the filing of patent applications at the idea stage, rather than at a stage when they are ready for commercial exploitation.

A patent may only be obtained if the invention described in the patent is useful, but the standard for determining utility is not a commercial standard. Indeed, after the passage of the 1962 amendments to the Food and Drug Law which required pharmaceutical manufacturers to establish safety and efficacy prior to marketing therapeutic compositions, the United States Patent and Trademark Office took the position that patents covering therapeutic compositions could not be granted without proof that the claimed compositions met the Food and Drug Administration (FDA) standards with respect to safety. This position was overruled by the highest patent court, the Court of Customs and Patent Appeals, on the ground that an invention could be "useful" in the sense of the patent law, even though it might not be commercially saleable under other laws.[4] In so ruling, the court adopted the argument that one fundamental purpose of the patent grant, recognized by the *Report of the President's Commission on the Patent System*, was to stimulate the investment of additional capital needed for the further development and marketing of the invention. Having successfully taken the position that patents should be granted on therapeutic compositions which are clearly not in commercial form at the time the patent is granted as a stimulus to investment, it is completely disingenuous for the pharmaceutical companies to now urge that the grant of a patent entitles them to seventeen years of commercial exploitation.

Clearly all of the foregoing fundamental principles on which the patent system is based completely undermine the argument that the concept of "effective patent life" exists, or that, in any event, it is intended to be equal to the seventeen-year life of a patent. Pharmaceutical companies are not, as they allege, the victims of any inequity caused by the granting of a monopoly by one government agency (the Patent Office) and an alleged interference with the exploitation of that monopoly by a different agency (the FDA). Rather, they seek to redefine the concepts on which the patent system is based by urging that the patent grant is a guaranteed seventeen-year monopoly.

Factors Affecting Commercial Patent Life

Given the basic principles of the patent system, what are the factors which actually affect so-called "effective patent life", or more accurately, the length of the commercial monopoly on a therapeutic composition?

How can it be that it is demonstrably far longer than seventeen years in some instances and significantly shorter in others? Regulatory review is not the exclusive answer to these questions. There are a multitude of patent and economic factors, *largely under the discretion and control of the patent owner*, which can dramatically affect the answer.

The patent application filing date, patent issue date, and scope of a patent application are factors which may have an important effect on the length and scope of a commercial monopoly. This can be readily demonstrated by considering the following patent rules and practices:

- The patent law contains no requirement that a patentable idea be at any particular stage of development before a patent application may be filed. Obviously, if no patent application is filed until the invention is reasonably well along in the development process, it is likely that the inventor will enjoy a longer period of commercial exploitation. By waiting, the inventor runs a risk that others will file earlier patent applications on the same invention with the possible result that all patent protection will be denied and, worse yet, that someone else will possess a monopoly which will prevent the commercial practice of the invention. Not surprisingly, many patent applications are filed long before it is known if the inventions are commerically practical, solely as a defensive measure and without regard to any possible impact on the life of any subsequent commercial monopoly.
- It is perfectly permissible to file a patent application on a concept which has never been tested or which is far broader that the limited concept which has actually been tested. In pharmaceutical composition cases, for example, it is quite common to define the invention by a broad hypothetical chemical formula which encompasses hundreds or thousands of possible compounds having certain structural similarities, even though, at the time the original patent application is filed, only a small handful of compounds have actually been made and tested.
- The seventeen-year patent monopoly runs from the date on which the patent is actually granted, after it is examined by the United States Patent and Trademark Office, and does not run from the filing date of the patent application. How long a patent application remains pending in the Patent Office is highly variable and, to a significant extent, can be controlled by the inventor. It is entirely permissible to keep a patent application pending for a long time by abandoning the original patent application in favor of so-called continuation or continuation-in-part applications which supplement or expand upon the original invention disclosure, and which are based on work carried out by the inventor subsequent to the original application filing date. The use of this practice is widespread and has been common in pharmaceutical industry patents.
- By law, each patent must be limited to a single invention and, in many

instances, the method of making a product or the method of using a product. Although initially disclosed in a single patent application which also discloses the product, these methods are required to be set forth in separate, so-called divisional applications. This practice leads to a multiplicity of patent applications, all of which travel through separate tracks in the Patent Office and may issue at separate times. Indeed, it is common practice to refrain from filing divisional patent applications covering processes or methods of use until just prior to the issuance of the product patent. Thus, the expiration of a single patent cannot be automatically equated with the loss of commercial monopoly because the methods of making and using that product, which are disclosed in the expired patent, are also the subject of separately issued patents having later expiration dates. In addition, commercially crucial composition variations or methods may also be set forth in later filed continuation-in-part applications, or independent patent applications as research proceeds towards a more precise definition of the nature of the commercial products, methods, and uses.

The permissible and discretionary manipulation of the foregoing patent rules can sometimes lengthen and sometimes shorten the actual commercial monopoly. For example, the early filing of a patent application covering an extremely broad class of chemical compounds based on preliminary research with only a handful of compounds, makes it more likely that the date of initial commercial exploitation of a product may not occur until long after the patent issues. Indeed, the specific structure of the actual compound to be marketed may not even be known either at the time the patent application is filed or the time when the patent issues, despite the fact that the patent contains broad claims which cover it! One leading advocate of the patent extension concept has described this as "a situation of common occurrence" in pharmaceutical patents.[5] Obviously, any reduction in "effective patent life" which flows from the fact that the true invention was not made until after the patent was granted cannot be blamed on regulatory delay.[6]

There is, of course, a definite benefit to the patent owner which flows from the filing of early speculative patent applications, even though there is a potential loss in the length of the actual commercial monopoly. The industry rapidly becomes aware that broad patent protection is being sought by a company in a particular area of chemistry, both as a result of publication in scientific journals and the publication of corresponding foreign patent applications within eighteen months of the U.S. filing date. These publications serve to discourage competitive research, thereby preserving that area for one company on a long-term basis. Any marginal loss suffered as a result of shortened commercial life for the first broad patent application can, and often is, offset by a long

and complicated series of additional patent applications covering the methods of use, methods of production, further composition variations, varying dosage forms, and the like. It becomes a relatively simple matter in the absence of direct competition to obsolete the original commercial compounds as they near their patent expiration dates and promote the use of a variant covered by a new generation of patents.

An alternative and commonly used strategy involves the early filing of a broad speculative patent application which is eventually abandoned in favor of one or more continuation or continuation-in part applications as additional research begins to focus on the preferred compositions. The use of this procedure not only strengthens and broadens the scope of protection, but also postpones the issue date of the patent, thereby extending the period of commercial monopoly.

The possible variations are limitless, and some examples may serve to illustrate at least some of the foregoing principles. In the case of Valium, the original patent application was filed in December 1959 and disclosed the specific chemical entity Diazepam which is sold under the Valium trademark. But the patent application also contained broad claims to a large class of compounds having a structure similar to Valium, although many of those compounds had never actually been produced or tested. In May 1960, the Patent Examiner indicated that he was willing to grant a patent which specifically covered Valium, but was unwilling to grant the claims to the broader class of compounds because of the lack of specific disclosure to support them. Rather than accept a patent which covered the specific commercial compound, Roche abandoned the original patent application in favor of a series of continuation-in-part applications which were intended to supplement the original disclosure and support the broader claims. The procedures relating to these matters consumed approximately eight years, and no patent covering Valium issued in the United States until 1968. Since Valium had actually been discovered before the initial patent application was filed, the clinical research occurred wholly within the period when the patent application was pending and NDA approval to market Valium was granted in 1963. Accordingly, Roche will have enjoyed twenty-two years of commercial monopoly by the time its patent expires in 1985. The laws of the United States are far more generous in this regard than the laws of other countries. In most industrial nations, the patent monopoly expires twenty years after the patent application is filed, so that any procedural delays in obtaining issuance of the patent cannot benefit the patentee. It is for that reason that the Valium patent expired in much of the rest of the world in 1980.

The history of Keflex, generically known as cephalexin monohydrate,

demonstrates a different set of circumstances affecting the length of a commercial monopoly, and undermines the assertion that the expiration of a single patent eliminates the commercial monoply. The initial patent application describing a large new class of cephalosporin antibiotic compositions was filed by Lilly in 1962, but only the method of making those products was actually claimed in the initial patent application. The first patent application actually claiming those products was not filed until 1966, shortly before the method patent was granted. That product patent application contained a hypothetical chemical formula, which was broad enough to cover the compound known as cephalexin, although that compound had not yet been discovered. Cephalexin monohydrate, the commercial form of Keflex, was not actually discovered until a later date, while the patent application which broadly covered (but did not disclose) cephalexin was still pending in the Patent Office. Lilly then filed a new patent application claiming cephalexin monohydrate as a separate invention. The broad patent covering cephalexin was granted in 1970, and the specific patent covering cephalexin monohydrate issued in 1972.[7] When the cephalexin patent expires in 1987, no one will be free to market Keflex because the second patent which specifically covers that compound does not expire until 1989. In short, Lilly will enjoy eighteen years of commercial monopoly on a product which was not even discovered until after the initial patent application covering that product was filed.

These are clearly not isolated examples. The Generic Pharmaceutical Industry Association (GPIA) has documented the fact that the twelve top-selling patented drugs, with U.S. sales of $1.37 billion in 1980, had an average effective patent life of 18.5 years, and the twenty-five top-selling patented drugs had an average effective patent life of 16.7 years. Obviously, the rules of the patent game were effectively manipulated in those instances to ensure maximum commercial exclusivity.

Apart from patent rules, there are also important investment and marketing decisions which affect the timing and speed of research and development work and, therefore, the length of the commercial monopoly. While much has been said about the adverse impact of regulatory review on the length of effective patent life, until recently little, if any, attention was directed to the fact that the totally discretionary decision as to when a clinical investigation is started and how fast it proceeds has an impact on "effective patent life." An Office of Technology Assessment (OTA) analysis of a Pharmaceutical Manufacturers Association (PMA) chart designed to show that effective patent life for new chemical entities approved in 1980 had shrunk to 7.5 years, establishes that there is a direct correlation between the patent application filing date and the date on which clinical investigations are commenced.[8]

The low average effective patent life figure derived from the PMA

study was significantly influenced by several situations where clinical investigations were not commenced for many years after the composition and its end use were known, and jumps to 11.6 years when these situations are eliminated. PMA claims that this observation is irrelevant since the patent extension legislation would restore only such time as is lost after the patent issues. Significantly, in disputing the relevance of this finding, PMA is in the embarrassing position of disputing one of the key findings in the Eisman and Wardell study on which it has so heavily relied until this point.[9] That study concluded that the starting date of clinical testing is an important factor which influences effective patent life. Wardell also found that for the twelve-year period from 1968 to 1979, for unknown reasons, declining effective patent life can be explained, in part, by a later starting date for clinical testing in relation to the patent application filing date. Rep. Albert Gore, Jr. (D-Tenn.) has correctly observed that these facts demolish PMA's argument that the decline in effective patent life is due solely to delay caused by regulatory review.

Clearly, the search for the definition of "effective patent life," or the belief that meaningful statistics may be developed to establish that it is shrinking as a result of government regulation, is an exercise in futility. Each product has its own unique development, commercialization, and patent history, which makes any generalization in this area highly suspect. An average effective patent life figure which is derived solely by subtracting the NDA approval date from the patent expiration date without considering that history has no validity.

The Proposed Legislation Is Seriously Defective

Senate Bill S. 255 provides that "... the term of a patent which encompasses within its scope a product, or a method for using a product, subject to a regulatory review, shall be extended by the amount of time equal to the regulatory review...." The term "regulatory review" is defined as the date of initiation of a "major health or environmental effects test," a term defined as an experiment which requires at least six months to conduct. Accordingly, with respect to therapeutic compositions, the extension period would usually commence with the long-term animal toxicity test which precedes the human clinical investigation phase of drug development.

The legislation also provides that the regulatory review period will not be deemed to have started until the patent is actually granted, even though tests which would qualify as regulatory review tests were started prior to that date. Finally, the legislation would go into effect immediately for all therapeutic compositions currently under "regulatory reveiw," although the starting date for measuring the length of the extension

would be the effective date of the legislation.

The interaction between the proposed legislation and some of the basic patent and commercial practices discussed in earlier sections of this paper will clearly result in benefits which go far beyond curing any real or imagined inequity caused by current regulatory practice. The legislation will actually create broad, new, and unwarranted monopoly power. The following are some of the most obvious flaws in the legislation:

- The starting point for measuring the length of an extension precedes, by a wide margin, the date on which any reasonable and prudent businessman would place a product on the market in the total absence of any regulatory review. Surely, the entire period of long-term animal toxicity testing and clinical investigation cannot be characterized as a "delay" caused by government regulation.
- The legislation actually rewards delay. As previously noted, effective patent life is shortened when there is a long lapse between the patent application filing date and the commencement of clinical investigations. The legislation provides an incentive for lengthening rather than shortening the gap between these two dates since the regulatory review period is not considered to have started until a patent is actually granted. Accordingly, an innovator who is diligent in commencing a clinical investigation while a patent application is still pending would receive a shorter extension, whereas a party who delays "regulatory review" activities until a patent is granted would actually receive a longer patent extension.
- The regulatory review process normally relates to a single specific compound and is designed to seek approval to market that compound for a specifically defined end use or indication. As previously noted, patent claims are normally far broader in scope. Thus, a patent which claims a broad hypothetical formula encompassing thousands of compounds would be entitled to an extension, even though the specific compound or end use which is the subject of subsequent regulatory review was not disclosed in the patent.[10] Obviously, the availability of extensions under these circumstances will encourage the filing of even broader and more speculative patent applications and will eventually serve to convert patents from disclosure documents into research proposals. The research "preserve" carved out by such broad and speculative patents, coupled with a patent having a twenty-four year life, will surely serve to discourage third party investigation into the area defined by the patent.
- The extension legislation may induce the owner of a patent covering a commercially significant product to invest the time and money needed to obtain regulatory approval of some commercially insignificant new therapeutic use because the patent extension would apply to the

product, and not merely the specific new use which is subject to regulatory review. S. 255 contains the following limitation with respect to the scope of any patent extension:

> The rights derived from any claim or claims of any patent so extended shall be limited in scope during the period of any extension to the product or method subject to the regulatory review period and to the statutory use for which regulatory review was required.

Since the extended rights are limited to "the product *or* method" and not "the product *and* method" which is subject to regulatory review, a product patent claim would be enforceable against all methods of using that product for therapeutic purposes, both old and new, during the period of any extension. The prospect of seven additional years of monopoly prices on an important drug such as Valium can certainly justify a large expenditure of research dollars on an unimportant new use for that composition as a means of extending patent life for the commercially significant old uses.

Moreover, as a result of experience gained by the medical community in using an approved drug for an approved indication, it is not uncommon for significant new therapeutic uses to be discovered, and these discoveries need not necessarily result from the efforts of the original patent owner. The discovery that Inderal (propranolol) is useful in limiting the size of a heart attack among high risk patients is a recent example of such a discovery which was funded by the government. Is the owner of the Inderal patent now properly entitled to up to seven years of additional patent protection on the product simply because it now files an NDA for the independently discovered new end use? Is there any justification for granting an extension of a scope that would provide monopoly power and monopoly prices over the original end uses of Inderal as to which the innovator has already obtained the full benefits of a patent monopoly? Will companies other than the original patentees invest time and money in developing new uses for previously patented drugs, if the discovery of those new uses will lead to extensions of the original patents, thereby blocking them from commercially exploiting the new uses? The legislation does not even recognize that these problems exist, let alone deal with them in any effective manner.

To the extent that government regulation causes delay in bringing products to market, that problem should be addressed and solved. The solution to the problem does not, however, reside in tampering with the patent system in a manner which will create broad new monopoly rights that extend well beyond any real or imagined problem caused by premarketing regulation of drug products.

NOTES

1. Motion Picture Patents Company v. Universal Film Manufacturing Co., 243 U.S. 871, 876 (1917).
2. In most other industrialized countries, the one year grace period does not exist, and any disclosure or use prior to filing a patent application bars the patent grant. Since most pharmaceutical patent applications are filed internationally, it is normally the international rules which control the decision as to when applications are filed.
3. The "first to file" rule is essentially absolute in most other patent systems.
4. Application of Anthony, 414 F2d 1383 (C.C.P.A. 1969).
5. Anderson, "Patent Term Restoration," APLA *Journal* 8, no. 4, p. 198.
6. The patent extension legislation would clearly encourage the early filing of broad, speculative patent applications on products of unknown commercial value, since it would permit the patent owner to recapture up to seven years of the time lost as a result of the fact that the commercial embodiment of the alleged invention was unknown when the initial patent application was filed.
7. See U.S. Patent No. 3,507,861 issued April 21, 1970, and U.S. Patent No. 3,655,656 issued April 11, 1972.
8. U.S., Congress, House, Hearings before the Committee on Science and Technology, Subcommittee on Investigations and Oversight, February 4, 1982.
9. Martin M. Eisman and William Wardell, "The Decline in Effective Patent Life of New Drugs," *Research Management*, January 1981, p. 18.
10. The extension would be limited in scope to the specific product which was subject to regulatory review, but this limitation in the legislation would, nevertheless, permit an extension for an undisclosed product which happens to fall within the scope of a broad patent claim.

THE IMPORTANCE OF PATENT TERM RESTORATION TO SMALL, HIGH TECHNOLOGY COMPANIES

Thomas D. Kiley

The importance of patents and of a strengthened patent incentive to the small, high technology company is difficult to overstate. When under the umbrella of patent protection, a small company can compete on the strength of its innovative capability with larger, older, and more entrenched concerns, the patent system operates to best purpose as an essentially procompetitive mechanism.

Nothing in my experience has been more instructive with regard to the vital role patents play in our free enterprise system than the opportunity I have had to look at the world from the vantage point of the small start-up company. Although surrounded by trees that cast great shade, we at Genentech are seeking our own place in the sun, and we expect that the availability of meaningful patent protection will help us do it. Thus, we strongly support patent term restoration legislation as should every small company whose competitive edge lies in its innovative capabilities and whose activities must undergo regulatory review before the onset of commercialization.

My thesis is straightforward. Innovation is important. It arises most frequently in the small, entrepreneurial company context.[1] Patent term restoration will make patent protection more meaningful. More meaningful patent protection will permit small companies to flourish and grow, where otherwise they might not. Conditions that encourage the growth of start-up companies also encourage investment in them, and therefore investment in innovation. The formation of small, innovative companies that can grow up under the shelter of patent protection only enhances competition, by increasing the number of market entrants and by the downward pressure the new products of innovation exert on the prices of older products. The genius of the patent term restoration legislation

Mr. Kiley is vice-president and general counsel of Genentech, Inc. in South San Francisco, California. *On 30 April 1981, Mr. Kiley testified before the Senate Judiciary Committee in support of patent term restoration legislation.*

APPENDIX 3

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

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ROCHE PRODUCTS, INC., MEMORANDUM AND ORDER

Plaintiff, CV 83-4312

-against- (Wexler, J.)

BOLAR PHARMACEUTICALS CO., INC.,

Defendant.

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APPEARANCES:

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WEXLER, J.

This matter comes before the court as an action to permanently enjoin certain acts as threatened infringement of a patent. Suit was originally filed in U.S. District Court in New Jersey pursuant to 35 U.S.C. §§271 and 283, and under the grant of jurisdiction provided in 28 U.S. C. §1338. After District Judge H. Lee Sarokin issued a temporary restraining order on September 2, 1983, defendant was granted a change of venue pursuant to 28 U.S.C. §1406(a). District Judge Debevoise transferred venue to the Eastern District of New York for a

hearing on the preliminary injunction, which was scheduled for October 5, 1983. At that time plaintiff moved to consolidate the hearing with a trial on the merits pursuant to Rule 65 (a)(2) Fed.R.Civ. P. Defendant did not oppose and the court ordered the hearing consolidated with a trial on the merits.

Plaintiff Roche Products, Inc. (Roche) holds patent number 3,299,053 for flurazepam hydrochloride (flurazepam hcl). That compound is the active ingredient in a prescription sleeping pill manufactured by plaintiff under the brand name DALMANE. Plaintiff's seventeen year patent expires on January 17, 1984. Bolar Pharmaceutical Company (Bolar) is a generic drug company that duplicates drugs no longer under patent and sells the compounds to wholesale distributors. Bolar is in possession of five kilograms of flurazepam hcl, which it imported from a foreign manufacturer not subject to United States patent law. Plaintiff seeks to permanently enjoin defendant from performing required FDA experiments with the drug during the term of the patent.

There are no disputed facts in this case. There is no argument that the patent is for a pioneer invention and is valid and in force. Plaintiff's sales of DALMANE are in excess of $40,000,000 annually. There is no contention that Bolar will manufacture or sell flurazepam hcl before the patent expires, nor is it contended that Roche has authorized Bolar to make, use or sell the drug. Defendant acknowledges that it is in possession of five kilograms of imported flurazepam hcl and freely admits

that it intends to form the compound into capsules and commence the testing and experiments necessary for a New Drug Application to the Food and Drug Administration (FDA) before the January 17, 1984 expiration date of the patent.

Title 35 U.S.C. §271(a) provides in pertinent part:

> [W]hoever without authority makes, uses or sells any patented invention, within the United States during the term of the patent therefor, infringes the patent.

Plaintiff argues that putting the drug through the FDA required testing and experimentation before the patent expires constitutes infringement under section 271(a), even if there is no intent to make, sell or otherwise realize a monetary gain until after January 17, 1984. Roche asserts that such action constitutes a use prohibited by the law. Bolar concedes that its tests do not fall under the infringement exception known as experimentation for philosophical, amusement, or curiosity purposes. It maintains that its testing does not constitute infringement use because it is de minimis, it does not by its nature infringe and no commercial value or profit will be realized before the patent on the drug expires. The defendant characertizes its activity as limited pre-expiration preparation for post-expiration entry into the market.

The question before the court is a very narrow one: does the limited use of a patented drug for experiments strictly related to FDA drug approval requirements during the last six months of the term of the patent constitute use prohibited by 35 U.S.C. §271(a)? The court holds that it does not.

An underlying issue in this case is the procedure for getting FDA approval, without which a drug cannot be marketed. Bolar asserts that it will take two years to amass required data and obtain approval, in effect delaying entry into the market and exending the patent de facto for the same period. Rocbe claims that it is entitled to that delay in competition, but can point to no legal support. It can only be observed that patent protection is contained in a single, general body of law meant to apply to inventions of every sort, not only drug compounds. The protection is for a seventeen year fixed term and the marketing delaying regulations of the FDA could hardly he considered a part of the monopoly benefits Congress sought to bestow. See 35 U.S.C. §154. Viewed from this vantage, what is at stake is a post-expiration competitive benefit for Bolar at Roche's expense.

The plaintiff urges the adoption of the reasoning and holding of the recent case of Pfizer, Inc. v. International Rectifier Corp., 217 U.S.P.Q. 157 (C.D. Calif. 1982). There the district court in California had issued a 1980 injunction against defendant's activities as infringement of plaintiff's drug patent. Before that court were two years of post-injunction product testing and development involving at least 400 kilograms of the drug and apparently profitable overseas manufacture and sale. The defendant in Pfizer was clearly doing more, for a longer period of time than Bolar intends to do here. More significantly, in Pfizer the defendant was reaping commercial value in defiance of a court injunction. The substantial and long term acts in violation of an injunction present in Pfizer are not present in the case at bar. Consequently, this court

declines to make a wholesale adoption of the California court's reasoning and holding.

The Pfizer court, although it draws on the analysis and reasoning of cases from all the circuits, is bound by the Ninth Circuit Court of Appeals' reading of the law, which strictly limits the experimental use exception to purposes of amusement and philosophical gratification. Spray Refrigeration Co. v. Sea Spray Fishing, Inc., 322 F.2d 34 (9th Cir. 1963). This court, of course, is not bound by the Ninth Circuit, and although plaintiff advocates their analysis, the court instead turns to the line of reasoning followed by the Court of Appeals for the Second Circuit.

Bolar's experimentation cannot be classified as merely for amusement or philosophical gratification. At the same time, it cannot be connected with any act of competition or profit during the term of the patent in either domestic or foreign markets. Its experimentation is commerical preparation of a nonproduction nature for post-expiration competition. In analagous cases this has been held a non-infringing use. In Arko Agate v. Master Marble Co., 18 F. Supp. 305 (N.D.W.Va. 1937), the experimentation with a marble manufacturing device covered by plaintiff's patent prior to going into production was held not an infringing use. The use of the apparatus was clearly a commercial test, yet in the absence of any profit from the activity, the court found no infringement. Similarly, in Dugan v. Lear Avia, Inc., 55 F. Supp. 223 (S.D.N.Y. 1944), aff'd 156 F.2d 29 (2d Cir. 1946), building and commercial testing of a device without commercial

manufacture or sale was deemed not to be an infringing use. Again, in Chesterfield v. United States, 159 F. Supp. 371 (Ct. Cl. 1958), no infringement was found where the federal government conducted tests and experiments. Citing Bosnack Mack Co. v. Underwood, 73 F. 206 (C.C. 1896), the Court of Claims stated flatly, "Experimental use does not infringe." 159 F. Supp. at 375. Bolar's FDA-mandated testing clearly falls in line with the sort of commercial experiments without profit, manufacture, or sale during the patent term that the Court of Appeals holds is non-infringing.

To find infringing use there must be a benefit at the expense of the patent. In Kaz Manufacturing Co., Inc. v. Chesebrough-Pond's, Inc., 211 F. Supp. 815 (S.D.N.Y. 1962), aff'd 317 F.2d 679 (2d Cir. 1963), the court declared use to be "the commercially valuable use of which patentee could or would avail himself." The court held that as long as defendant was not helping himself to a benefit ~~of a type~~ secured by the patent, there was no infringement. Similarly, post-expiration advantage would not be a value secured by the patent. Furthermore, Bolar's activity cannot be connected with any benefit during the term of the patent.

In a like vein, the de minimis doctrine would seem to apply. Stated more fully, the law does not concern itself with small matters. In Maxon Premix Burner Co. v. Eclipse Fuel Engineering Co., 471 F.2d 308 (7th Cir. 1972), the Seventh Circuit Court of Appeals held the experimental construction of a prototype even paired with a sale was de minimis and insufficient to support an action for threatened infringement. In the case at bar, Roche

can point to no substantial loss that would stem from Bolar's studies. The only harm Roche can point to is a violation of the principle of its monopoly.

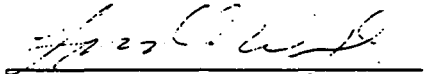
A court should be cautious in applying the equitable remedy of a permanent injunction in patent cases, American Safety Device Co. v. Kurland Chemical Co., 68 F.2d 734 (2d Cir. 1934), particularly where, as here, there remains little more than three months to the term of the patent. This is doubly true where the case involves only a threatened infringement.

More importantly, the court cannot find a basis for holding that Bolar's limited experimental use of flurazepam hcl would constitute infringement. First, Bolar realizes no benefit during the term of the patent; its activities are in no way connected with current manufacture or sale here or abroad. Nor do its activities lessen Roche's profits during the patent's term. Second, post-expiration delay in competition unintentionally imposed by FDA regulation is not a right or benefit granted by the patent law. This court will not act to protect a right or benefit that is without legal basis. Third, Roche can point to no substantial harm it will suffer from Bolar's FDA studies before the patent expires. Bolar's threatened activity is at best de minimis and will not support an action for infringement.

If, however, it develops that Roche suffers substantial harm or loss during the patent's term, it still has available to it action at law for damages against Bolar.

Accordingly, no permanent injunction will issue and the temporary restraining order is dissolved. Parties will bear their own costs.

SO ORDERED.



LEONARD D. WEXLER, U.S.D.J.

Dated: Brooklyn, New York
October 11, 1983

United States Court of Appeals for the Federal Circuit

ROCHE PRODUCTS, INC.,
Appellant,
v.
BOLAR PHARMACEUTICAL CO., INC.,
Appellee.

Appeal No. 84-560

6,15-16

DECIDED: April 23, 1984

Before MARKEY, Chief Judge, NICHOLS, Senior Circuit Judge, and KASHIWA, Circuit Judge.

NICHOLS, Senior Circuit Judge.

This is an appeal from a judgment entered on October 14, 1983, in which the United States District Court for the Eastern District of New York held United States Patent No. 3,299,053 not infringed and denied relief. We reverse and remand.

I

At stake in this case is the length of time a pharmaceutical company which has a patent on the active ingredient in a drug can have exclusive access to the American market for that drug. Plaintiff-appellant Roche Products,

Inc. (Roche), a large research-oriented pharmaceutical company, wanted the United States district court to enjoin Bolar Pharmaceutical Co., Inc. (Bolar), a manufacturer of generic drugs, from taking, during the life of a patent, the statutory and regulatory steps necessary to market, after the patent expired, a drug equivalent to a patented brand name drug. Roche argued that the use of a patented drug for federally mandated premarketing tests is a use in violation of the patent laws.

Roche was the assignee of the rights in U.S. Patent No. 3,299,053 (the '053 patent), which expired on January 17, 1984. The '053 patent, which issued on January 17, 1967, is entitled "Novel 1 and/or 4-substituted alkyl 5-aromatic-3H-1,4-benzodiazepines and benzodiazepine-2-ones." One of the chemical compounds claimed in the '053 patent is flurazepam hydrochloride (flurazepam hcl), the active ingredient in Roche's successful brand name prescription sleeping pill "Dalmane."

In early 1983, Bolar became interested in marketing, after the '053 patent expired, a generic drug equivalent to Dalmane. Because a generic drug's commercial success is related to how quickly it is brought on the market after a patent expires, and because approval for an equivalent of an established drug can take more than 2 years, Bolar, not waiting for the '053 patent to expire, immedi-

ately began its effort to obtain federal approval to market its generic version of Dalmane. In mid-1983, Bolar obtained from a foreign manufacturer 5 kilograms of flurazepam hcl to form into "dosage form capsules, to obtain stability data, dissolution rates, bioequivalency studies, and blood serum studies" necessary for a New Drug Application to the United States Food and Drug Administration (FDA).

On July 28, 1983, Roche filed a complaint in the United States District Court for the District of New Jersey against three parties: Bolar, Bolar's principal officer, and the importer of the infringing flurazepam hcl. Only Bolar remains a party defendant. Roche sought to enjoin Bolar from using flurazepam hcl for any purpose whatsoever during the life of the '053 patent. When Bolar stated during discovery, on August 30, 1983, that it intended immediately to begin testing its generic drug for FDA approval, Roche moved for and was granted a Temporary Restraining Order, on September 2, 1983.

On September 26, 1983, Bolar was granted a change of venue and the case was transferred to the United States District Court for the Eastern District of New York. That court consolidated Roche's motion for a preliminary injunction with the trial on the merits pursuant to Fed. R. Civ. P. 65(a)(2) (both parties had stipulated to all the

pertinent facts so no testimony was necessary) and on October 11, 1983, issued a Memorandum and Order denying Roche's application for a permanent injunction. The court held that Bolar's use of the patented compound for federally mandated testing was not infringement of the patent in suit because Bolar's use was de minimis and experimental. The court entered judgment for Bolar on October 14, 1983, and Roche filed its notice of appeal that same day.

II

The district court correctly recognized that the issue in this case is narrow: does the limited use of a patented drug for testing and investigation strictly related to FDA drug approval requirements during the last 6 months of the term of the patent constitute a use which, unless licensed, the patent statute makes actionable? The district court held that it does not. This was an error of law.

III

A

When Congress enacted the current revision of the Patent Laws of the United States, the Patent Act of 1952, ch. 950, 66 Stat. 792 (codified at 35 U.S.C.), a statutory definition of patent infringement existed for the first

time since section 5 of the Patent Act of 1793 was repealed in 1836. Title 35 U.S.C. § 271(a) incorporates the disjunctive language of the statutory patent grant which gives a patentee the "right to exclude others from making, using, or selling" a patented invention, 35 U.S.C. § 154. Congress states in section 271(a):

> [W]hoever without authority makes, uses or sells any patented invention, within the United States during the term of the patent therefore, infringes the patent.

It is beyond argument that performance of only one of the three enumerated activities is patent infringement. It is well-established, in particular, that the use of a patented invention, without either manufacture or sale, is actionable. See Aro Manufacturing Co. v. Convertible Top Replacement Co., 377 U.S. 476, 484, 141 USPQ 681, 685 (1964); Coakwell v. United States, 372 F.2d 508, 510, 153 USPQ 307, 308 (Ct. Cl. 1967). Thus, the patentee does not need to have any evidence of damage or lost sales to bring an infringement action.

Section 271(a) prohibits, on its face, any and all uses of a patented invention. Of course, as Judge Learned Hand observed in Cabell v. Markham, 148 F.2d 737, 739 (2d Cir.), aff'd, 326 U.S. 464 (1945):

> [I]t is true that the words used, even in their literal sense, are the primary, and ordinarily the

> most reliable, source of interpreting the meaning of any writing: be it a statute, a contract, or anything else. But it is one of the surest indexes of a mature and developed jurisprudence not to make a fortress out of the dictionary; but to remember that statutes always have some purpose or object to accomplish, whose sympathetic and imaginative discovery is the surest guide to their meaning.

Because Congress has never defined use, its meaning has become a matter of judicial interpretation. Although few cases discuss the question of whether a particular use constitutes an infringing use of a patented invention, they nevertheless convincingly lead to the conclusion that the word "use" in section 271(a) has never been taken to its utmost possible scope. See, e.g., Pitcairn v. United States, 547 F.2d 1106, 192 USPQ 612 (Ct. Cl. 1976), cert. denied, 434 U.S. 1051 (1978) (experimental use may be a defense to infringement); United States v. Univis Lens Co., 316 U.S. 241 (1942) ("An incident to the purchase of any article, whether patented or unpatented, is the right to use and sell it, * * *." Id. at 249); General Electric Co. v. United States, 572 F.2d 745, 198 USPQ 65 (Ct. Cl. 1978) ("[I]t can be properly assumed that as part of the bargain the seller of a device incorporating a patented combination * * * authorizes the buyer to continue to use the device so long as the latter can and does use the elements he purchased from the patentee or licensor." Id. at 784-85, 198 USPQ at 98).

Bolar argues that its intended use of flurazepam hcl is excepted from the use prohibition. It claims two grounds for exception: the first ground is based on a liberal interpretation of the traditional experimental use exception; the second ground is that public policy favors generic drugs and thus mandates the creation of a new exception in order to allow FDA required drug testing. We discuss these arguments seriatim.

B

The so-called experimental use defense to liability for infringement generally is recognized as originating in an opinion written by Supreme Court Justice Story while on circuit in Massachusetts. In Whittemore v. Cutter, 29 F. Cas. 1120, 1121 (C.C.D. Mass. 1813) (No. 17,600), Justice Story sought to justify a trial judge's instruction to a jury that an infringer must have an intent to use a patented invention for profit, stating:

> [I]t could never have been the intention of the legislature to punish a man who constructed such a machine merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects.

Despite skepticism, see, e.g., Byam v. Bullard, 4 F. Cas. 934 (C.C.D. Mass. 1852) (No. 2,262) (opinion by Justice Curtis), Justice Story's seminal statement evolved

until, by 1861, the law was "well-settled that an experiment with a patented article for the sole purpose of gratifying a philosophical taste, or curiosity, or for mere amusement is not an infringement of the rights of the patentee." Poppenhausen v. Falke, 19 F. Cas. 1048, 1049 (C.C.S.D.N.Y. 1861) (No. 11,279). (For a detailed history and analysis of the experimental use exception, see Bee, Experimental Use as an Act of Patent Infringement, 39 J. Pat. Off. Soc'y 357 (1957).) Professor Robinson firmly entrenched the experimental use exception into the patent law when he wrote his famous treatise, W. Robinson, The Law of Patents for Useful Inventions § 898 (1890):

> § 898. No Act an Infringement unless it Affects the Pecuniary Interests of the Owner of the Patented Invention.
>
> [T]he interest to be promoted by the wrongful employment of the invention must be hostile to the interest of the patentee. The interest of the patentee is represented by the emoluments which he does or might receive from the practice of the invention by himself or others. These, though not always taking the shape of money, are of a pecuniary character, and their value is capable of estimation like other property. Hence acts of infringement must attack the right of the patentee to these emoluments, and either turn them aside into other channels or prevent them from accruing in favor of any one. An unauthorized sale of the invention is always such an act. But the manufacture or the use of the invention may be intended only for other purposes, and produce no pecuniary result. Thus where it is made or used as an experiment, whether for the gratification of scientific tastes, or for curiosity, or for amusement, the interests of the patentee are not antagonized, the sole effect being of an intellectual character in the promotion of the employer's knowledge or the relaxation

> afforded to his mind. But if the products of the experiment are sold, or used for the convenience of the experimentor, or if the experiments are conducted with a view to the adaptation of the invention to the experimentor's business, the acts of making or of use are violations of the rights of the inventor and infringements of his patent. In reference to such employments of a patented invention the law is diligent to protect the patentee, and even experimental uses will be sometimes enjoined though no injury may have resulted admitting of positive redress. [Emphasis supplied, footnotes omitted.]

The Court of Claims, whose precedents bind us, on several occasions has considered the defense of experimental use. See Ordnance Engineering Corp. v. United States, 84 Ct. Cl. 1, 32 USPQ 614 (1936), cert. denied, 302 U.S. 708, 37 USPQ 842 (1937); Chesterfield v. United States, 159 F. Supp. 371, 116 USPQ 445 (Ct. Cl. 1958); Douglas v. United States, 181 USPQ 170 (Ct. Cl. Tr. Div. 1974), aff'd, 510 F.2d 364, 184 USPQ 613 (Ct. Cl.), cert. denied, 423 U.S. 825 (1975); Pitcairn v. United States, 547 F.2d 1106, 192 USPQ 612 (Ct. Cl. 1976), cert. denied, 434 U.S. 1051 (1978). Bolar concedes, as it must, that its intended use of flurazepam hcl does not fall within the "traditional limits" of the experimental use exception as established in these cases or those of other circuits. Its concession here is fatal. Despite Bolar's argument that its tests are "true scientific inquiries" to which a literal interpretation of the experimental use exception logically should extend, we hold the experimental use exception to be truly narrow, and we will not expand it under

the present circumstances. Bolar's argument that the experimental use rule deserves a broad construction is not justified.

Pitcairn, the most persuasive of the Court of Claims cases concerning the experimental use defense, sets forth the law which must control the disposition of this case: "[t]ests, demonstrations, and experiments * * * [which] are in keeping with the legitimate business of the * * * [alleged infringer]" are infringements for which "[e]xperimental use is not a defense." 547 F.2d at 1125-1126, 192 USPQ at 625. We have carefully reviewed each of the other Court of Claims cases, and although they contain some loose language on which Bolar relies, they are unpersuasive. The Ordnance Engineering case provides no guidance concerning the boundaries of an appropriately applied experimental use rule other than flatly stating that a device must have been "built for experimental purposes." In Chesterfield, the court's flat declaration that "experimental use does not infringe" is pure obiter dictum. See Pitcairn, 547 F.2d at 1125, 192 USPQ at 625. Douglas has no precedential value here since the Court of Claims never affirmed the part of the trial judge's opinion dealing with experimental use; moreover, Trial Judge Cooper's well-reasoned analysis of the experimental use rule concluded that no case had permitted a pattern of systematic exploitation of a patented invention for the purpose of

furthering the legitimate business interests of the infringer. The authority of Trial Judge Cooper's views rests on his reputation as a fine patent lawyer, and on their own intrinsic persuasiveness.

Bolar's intended "experimental" use is solely for business reasons and not for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry. Bolar's intended use of flurazepam hcl to derive FDA required test data is thus an infringement of the '053 patent./ Bolar may intend to perform "experiments," but unlicensed experiments conducted with a view to the adaption of the patented invention to the experimentor's business is a violation of the rights of the patentee to exclude others from using his patented invention./ It is obvious here that it is a misnomer to call the intended use de minimis. It is no trifle in its economic effect on the parties even if the quantity used is small. It is no dilettante affair such as Justice Story envisioned. We cannot construe the experimental use rule so broadly as to allow a violation of the patent laws in the guise of "scientific inquiry," when that inquiry has definite, cognizable, and not insubstantial commercial purposes.

C

Bolar argues that even if no established doctrine exists with which it can escape liability for patent in-

infringement, public policy requires that we create a new exception to the use prohibition. Parties and amici seem to think, in particular, that we must resolve a conflict between the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301-392 (1982), and the Patent Act of 1952, or at least the Acts' respective policies and purposes. We decline the opportunity here, however, to engage in legislative activity proper only for the Congress.

The new drug approval procedure which existed between 1938 and 1962 was relatively innocuous and had little impact on the development of pioneer prescription new drugs. Section 505 of the FDCA, ch. 675, 52 Stat. 1052 (1938), required the manufacturer of a pioneer new drug to submit to the FDA a New Drug Application (NDA) containing information concerning the safety of the drug. If the FDA did not disapprove the new drug within 60 days after it received the NDA, marketing could begin.

The provisions of the Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780, caused a substantial increase in the time required for development and approval of a pioneer new drug. Beginning in 1962, the amended Section 505 (codified at 21 U.S.C. § 355 (1982)) required an NDA to contain proof of efficacy (effectiveness) as well as safety, and required the FDA affirmatively to approve the NDA rather than just to permit marketing by inaction. A

recent study indicated that it now can take on average from 7 to 10 years for a pharmaceutical company to satisfy the current regulatory requirements. National Academy of Engineering, The Competitive Status of the U. S. Pharmaceutical Industry 79-80 (1983).

Because most FDA-required testing is done after a patent issues, the remaining effective life of patent protection assertedly may be as low as 7 years. Id., citing Statement of William M. Wardell to the Subcommittee on Investigations and Oversight of the Committee on Science and Technology, U. S. House of Representatives, Feb. 14, 1982, at 14. Litigation such as this is one example of how research-oriented pharmaceutical companies have sought to regain some of the earning time lost to regulatory entanglements. They gain for themselves, it is asserted, a de facto monopoly of upwards of 2 years by enjoining FDA-required testing of a generic drug until the patent on the drug's active ingredient expires.

Bolar argues that the patent laws are intended to grant to inventors only a limited 17-year property right to their inventions so that the public can enjoy the benefits of competition as soon as possible, consistent with the need to encourage invention. The FDCA, Bolar contends, was only intended to assure safe and effective drugs for the public, and not to extend a pharmaceutical

company's monopoly for an indefinite and substantial period of time while the FDA considers whether to grant a pre-marketing clearance. Because the FDCA affected prevailing law, namely the Patent Act, Bolar argues that we should apply the patent laws to drugs differently.

Simply because a later enacted statute affects in some way an earlier enacted statute is poor reason to ask us to rewrite the earlier statute. Repeals by implication are not favored. See, e.g., Mercantile National Bank v. Langdeau, 371 U.S. 555, 565 (1963). Thus, "courts are not at liberty to pick and choose among congressional enactments, and when two statutes are capable of co-existence, it is the duty of the courts, absent a clearly expressed congressional intention to the contrary, to regard each as effective." Morton v. Mancari, 417 U.S. 535, 551 (1974). There is no affirmative obligation on Congress to explain why it deems a particular enactment wise or necessary, or to demonstrate that it is aware of the consequences of its action. See Harrison v. PPG Industries, Inc., 446 U.S. 578, 592 (1979). Rather, because "laws are presumed to be passed with deliberation, and with full knowledge of all existing ones on the same subject," T. Sedgwick, The Interpretation and Construction of Statutory and Constitutional Law 106 (2d ed. 1874), we must presume Congress was aware that the FDCA would affect the earning potentiality

of a drug patent, and chose to permit it. Although arguably Title 21 and Title 35 are not laws on the "same subject," we note that during Congress' deliberations on the 1962 amendments to the FDCA, it considered the relationship and interaction of the patent laws with the drug laws. See S. Rep. No. 1744, 87th Cong., 2d Sess., reprinted in 1962 U.S. Code Cong. & Ad. News 2884, 2911-2915.

It is the role of Congress to maximize public welfare through legislation. Congress is well aware of the economic and societal problems which the parties debate here, and has before it legislation with respect to these issues. See H.R. 3605, 98th Cong., 1st Sess. (1983) ("Drug Price Competition Act of 1983") (amending 21 U.S.C. § 355(b) to allow faster marketing of new generic drugs equivalent to approved new drugs); S. 1306, 98th Cong., 1st Sess. (1983) ("Patent Term Restoration Act of 1983") (amending 35 U.S.C. § 155 to add to the patent grant a period of time equivalent to that lost due to regulatory delay), Cong. Rec. S. 6863 (daily ed. May 17, 1983), 26 Pat. Trademark & Copyright J. (BNA) 87-88 (May 26, 1983). No matter how persuasive the policy arguments are for or against these proposed bills, this court is not the proper forum in which to debate them. Where Congress has the clear power to enact legislation, our role is only to in-

terpret and apply that legislation. "[I]t is not our job to apply laws that have not yet been written." Sony Corp. of America v. Universal City Studios, Inc., 52 U.S.L.W. 4090, 4100, 220 USPQ 665, 684 (U.S. Jan. 17, 1984) (No. 81-1687). We will not rewrite the patent laws here.

IV

The district court refused to grant a permanent injunction against Bolar because it believed the law did not require that it find infringement of the '053 patent. Since we hold that there is infringement, Roche is entitled to a remedy. We are not in a position, however, to decide the form of that remedy.

Roche requested us, at first, to remand this case to the district court with instructions to enter a permanent injunction against infringement by Bolar. After the main briefs were filed, but before oral argument, the '053 patent expired. This case is not moot, however, because although the initially requested order no longer is necessary, other remedies can be fashioned to give Roche relief against Bolar's past infringement. Roche requests, for example, an order to confiscate and destroy the data which Bolar has generated during its infringing activity, citing, Pfizer, Inc. v. International Rectifier Corp., 217 USPQ 157 (C.D. Cal. 1982) (granting an injunction of that

nature to remedy infringement done in contempt of a court order).

Statute provides the basis for Roche's request for injunctive relief, 35 U.S.C. § 283:

> The several courts having jurisdiction of cases under this title may grant injunctions in accordance with the principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable.

Section 283, by its terms, clearly makes the issuance of an injunction discretionary: the court "may grant" relief "in accordance with the principles of equity." The trial court thus has considerable discretion in determining whether the facts of a situation require it to issue an injunction. The scope of relief, therefore, is not for us to decide at the first instance, nor is this the time or place for a discourse on the "principles of equity."

Whether an injunction should issue in this case, and of what form it should take, certainly depends on the equities of the case. Bolar, Roche, and amici Pharmaceutical Manufacturers Association and Generic Pharmaceutical Industry Association, each detail the "catastrophic" effect our decision for either party will have on the American public health system. It is true that it "is a principle of general application that courts, and especially courts of equity, may appropriately withhold their aid

where the plaintiff is using the right asserted contrary to the public interest," Morton Salt Co. v. Suppiger Co., 314 U.S. 488, 492 (1941), reh'g denied, 315 U.S. 826 (1942). Since "the standards of the public interest, not the requirements of private litigation, measure the propriety and need for injunctive relief in these cases," Hecht Co. v. Bowles, 321 U.S. 321, 331 (1944), rev'g Brown v. Hecht Co., 137 F.2d 689 (D.C. Cir. 1943), we remand this case to the district court for further proceedings to consider what this interest is and what measures it calls for.

There are other aspects here that might make a tribunal reluctant to select, within the scope of its discretion, relief along the harsher side of the possible scale. The case clearly was regarded by both sides as a test. The good faith with which Bolar acted is undisputed, at least before us. Bolar says it did nothing clandestine, but notified Roche what it was going to do at all times before doing it, so Roche could act promptly to defend what it believed to be its rights. The case may be unlike Pfizer, Inc., supra, in that Bolar scrupulously obeyed all court orders while they were in effect, or so it says, whereas in Pfizer, Inc., the infringer acted in defiance of court decrees. The destruction of material in Pfizer, Inc., was ordered after everything milder had

proved useless. If other measures can be made sufficient, one might well be reluctant to order destruction of the records of research and tests that may embody information that would contribute to the health and happiness of the human race. All this is, of course, for the district judge to consider so far as he finds the factual predicates established.

The actual infringing acts are said to have all occurred in the relatively brief period between vacation of the lower court's restraining order and the expiration of the patent. Counsel for Roche was candid in explaining that he pushed so hard for the harsh relief he did because he thought any money damages would have to be nominal. The correctness of this belief has not been briefed or argued, and we hesitate to state a firm position, but tentatively, at least, we are skeptical. It is clear that the economic injury to Roche is, or is threatened to be, substantial, even though the amount of material used in the tests was small. If the patent law precludes substantial damages, there exists a strange gap in the panoply (in its proper meaning, a suit of armor) of protection the patent statutes place around an aggrieved and injured patentee. The district judge, before getting into the issue of equitable relief, must determine if he can deal with the case by adequate money damages. If he can, the predicate for

equitable relief of a harsh, or even a mild, character is gone.

Counsel are equally mistaken in their apparent belief that once infringement is established and adjudicated, an injunction must follow. In Hecht Co. v. Bowles, supra, the statute, unlike the one we have here, was seemingly mandatory by its language that once a violation was shown, an injunction must follow, and the D. C. Circuit had so held. But the circumstances made an injunction somewhat repugnant. Hecht Co., an unquestionably legitimate and long-established District of Columbia retailer, had got tangled up in the price control regulations of World War II, and its employees had in good faith unwittingly committed some violations. The situation was ironic in that the Hecht Co. had been a leader in extending the patriotic cooperation of the retail trade in application of the unpopular but necessary retail price controls, and had itself offered its own operation for study as illustrating the problems and how they could be solved.

After discovering some loopholes in the statute, in light of the legislative history, Justice Douglas continued at 329:

> We are dealing here with the requirements of equity practice with a background of several hundred years of history. Only the other day we stated that "An appeal to the equity jurisdiction conferred on federal district courts is an appeal to the sound discre-

> tion which guides the determinations of courts of equity." Meredith v. Winter Haven, 320 U.S. 228, 235. The historic injunctive process was designed to deter, not to punish. The essence of equity jurisdiction has been the power of the Chancellor to do equity and to mould each decree to the necessities of the particular case. Flexibility rather than rigidity has distinguished it. The qualities of mercy and practicality have made equity the instrument for nice adjustment and reconciliation between the public interest and private needs as well as between competing private claims. We do not believe that such a major departure from that long tradition as is here proposed should be lightly implied.

While two justices declined to join in the opinion, none expressed themselves in favor of affirming the D. C. Circuit. In short, if Congress wants the federal courts to issue injunctions without regard to historic equity principles, it is going to have to say so in explicit and even shameless language rarely if ever to be expected from a body itself made up very largely of American lawyers, having, probably, as much respect for traditional equity principles as do the courts. If an injunction was not mandatory in Hecht Co. v. Bowles, the more permissive statutory language here makes it a fortiori that an injunction is not mandatory now.

The application of historic equity principles to the case at bar is in the first instance for the district court.

V

Conclusion

The decision of the district court holding the '053 patent not infringed is reversed. The case is remanded with instructions to fashion an appropriate remedy. Each party to bear its own costs.

APPENDIX 4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

July 30, 1984

The Honorable Robert W. Kastenmeier
Chairman, Subcommittee on Courts, Civil
Liberties, & the Administration of Justice
Committee on the Judiciary
House of Representatives
Washington, D. C. 20515

Dear Mr. Kastenmeier:

This is in response to a recent request by Mr. Dave Beier of your Subcommittee staff for information on orphan drugs and approved generic antibiotics.

Since 1962 approximately 350 generic antibiotic applications have been approved. Of those 350 approved applications, 150 have been approved with more than one strength.

With respect to orphan drugs, I am pleased to provide the following information:

- 33 requests for orphan drug designations have been received since October 1983;
- 16 of the designations have been approved (see enclosed list);
- 15 new drug applications (NDA's) for orphan drugs have been received since January 1983;
- 7 NDA's for orphan drugs have been approved for the following conditions:
  1. Chronic urea-splitting urinary infections.
  2. Dissolution of radiolucent gallstones in poor surgical risk patients.
  3. Testicular cancer.
  4. Immunosuppressant in organ transplant recipients.
  5. Hemophilia A.
  6. Hepatic porphyrias.
  7. Severe pain, as in metastatic cancer.

If you have any questions, please let me know.

Sincerely yours,

Robert C. Wetherell, Jr.
Associate Commissioner
for Legislation and Information

Enclosure

ORPHAN DESIGNATIONS
PURSUANT TO SECTION 526
OF THE
ORPHAN DRUG ACT (P.L. 97-414)

Through June 30, 1984

Docket No. 84N-0102

ORPHAN DRUG DESIGNATIONS
THRU JUNE 1984
(Approved for Marketing*)

Sponsor's Name and Address	Name of Drug/Biological Product	Proposed Use
1. Warner-Lambert Co. 201 Tabor Road Morris Plains, NJ 07950	Generic-diaziquone Trade-not established	Treatment of primary brain malignancies (Grade III-IV astrocytomas)
2. Cooper Biomedical, Inc. 3145 Porter Drive Palo Alto, CA 94304	Generic-alpha-1-anti-trypsin (recombinant DNA origin) Trade-not established	Supplementation therapy for alpha-1 antitrypsin deficiency in the ZZ phenotype population
3. Ives Laboratories 685 Third Avenue New York, NY 10017	Generic-hexamethyl-melamine Trade-Hexastat	Treatment of advanced adenocarcinoma of the ovary
4. LyphoMed, Inc. 2020 Ruby Street Melrose Park, IL 60160	Generic-pentamidine isethionate Trade-not established	Pneumocystis carinii pneumonia
5. American McGaw 2525 McGaw Avenue Irvine, CA 92714	Generic-L-carnitine Trade-not established	Genetic carnitine deficiency
6. Fisons Corporation Two Preston Court Bedford, MA 01730	Generic-cromolyn sodium Trade-Cromoral	Mastocytosis
7. A.L. Laboratories, Inc. 452 Hudson Terrace P.O. Box 1621 Englewood Cliffs, NJ 07632	Generic-bacitracin, U.S.P. Trade-not established	Antibiotic-associated pseudomembranous enterocolitis caused by toxins A and B elaborated by Clostridium difficile
8. Alan B. Scott, M.D. 2232 Webster Street San Francisco, CA 94115	Generic-botulinum A toxin Trade-Oculinum	Treatment of strabismus and blepharospasm
9. Abbott Laboratories Pharmaceutical Products Division North Chicago, IL 60064	Generic-hemin Trade-Panhematin*	Amelioration of recurrent attacks of acute intermittent porphyria temporally related to the menstrual cycle in susceptible women and similar symptoms which occur in other patients with acute intermittent porphyria, porphyria variegata and heriditary coproporphyria.

	Sponsor's Name and Address	Name of Drug/Biological Product	Proposed Use
0.	Glaxo, Inc. P.O. Box 13960 Five Moore Drive Research Triangle Park North Carolina 27709	Generic-ethanolamine oleate Trade-not established	Bleeding esophageal varices
1.	Burroughs Wellcome Co. 3030 Cornwallis Road Research Triangle Park North Carolina 27709	Generic-epoprostenol prostacyclin, PGI_2, PGX Trade-Flolan	Replacement of heparin in certain patients requiring hemodialysis dialysis
2.	Johnson and Johnson Baby Products Co. Grandview Road Skillman, New Jersey 08858	Generic-2,3-dimercaptosuccinic Acid (DMSA) Trade-not established	Treatment of lead poisoning in children
3.	Enzon, Inc. 300C Corporate Court South Plainfield, NJ 07080	Generic-PEG-adenosine deaminase (PEG-ADA) Trade-Imudon	For use as enzyme replacement therapy for ADA deficiency in patients with severe combined immunodeficiency (SCID)
4.	Ascot Pharmaceuticals Inc. 7701 N. Austin Avenue Skokie, Illinois 60077	Generic-monooctanoin Trade-Capmul 8210	Dissolution of cholesterol gallstones retained in the common bile duct
5.	Stuart Pharmaceuticals Division of ICI Americas Inc. Wilmington, Delaware 19897	Generic-viloxazine hydrochloride Trade-Vivalan	Treatment of narcolepsy and cataplexy
6.	Pharmaceuticals Division Ciba-Geigy Corporation 556 Morris Avenue Summit, New Jersey 07901	Generic-clofazimine Trade-Lamprene	Treatment of leprosy resistant to Dapsone and the ENL and lepra reaction

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

July 30, 1984

The Honorable Robert W. Kastenmeier
Chairman, Subcommittee on Courts, Civil
Liberties, & the Administration of Justice
Committee on the Judiciary
House of Representatives
Washington, D. C. 20515

Dear Mr. Kastenmeier:

This is in response to a July 25, 1984, request by Mr. Dave Beier of your Subcommittee staff for information regarding the relationship between patent laws and enforcement of the Federal Food, Drug, and Cosmetic (FD&C) Act.

As you may know, in January 1979 the Food and Drug Administration (FDA) published a proposal to amend its public information regulations to include a list of approved prescription drug products for therapeutic equivalence. The term "Approved prescription drug products" refers to prescription drug products approved by FDA through new drug applications (NDA's) or abbreviated new drug applications (ANDA's) under the provisions of section 505 of the FD&C Act (21 U.S.C. 355) or, in the case of antibiotics, through analogous applications, known as Form 5's or Form 6's under section 507 of the FD&C Act (21 U.S.C. 357).

In response to that proposal, FDA received more than 100 comments addressing points covered in the proposal. Among the comments was one that stated that FDA should not evaluate as therapeutically equivalent drug products that infringe patents because including such drugs on the list violates constitutional prinicples as well as patent laws and discourages discovery and disclosure of new inventions. Another comment said that a pharmacist relying on the list may be sued for selling an unlicensed generic product. Therefore, the list should mention that FDA does not consider the patent status of drugs.

After reviewing all comments, including the two mentioned above, FDA published a Final Rule on this subject in the October 31, 1980, Federal Register, Volume 45, No. 213, page 72582. In the preamble to that Final Rule, FDA addressed all the comments, including the two previously mentioned. The preamble stated that "The patent laws do not have any bearing on the enforcement of the Federal Food, Drug, and Cosmetic Act, and the agency does not consider these laws when

reviewing new drug applications and making drug product approval decisions. If a firm submits a new drug application for a patented drug, FDA reviews the application without considering any patent issue. If the application is approvable, it is approved. However, to inform the public of this policy the agency, as requested by the comment, will include a statement in the preface to the List to the effect that the patent status of a drug is not considered by the agency in its review of applications to market drugs." That quote appears on page 72598 of the October 31 Federal Register, a copy of which is enclosed.

This policy, as set out above, has not been revoked or modified since publication in the Federal Register.

Sincerely yours,

Robert C. Wetherell, Jr.
Associate Commissioner
for Legislation and Information

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

August 6, 1984

The Honorable Robert W. Kastenmeier
Chairman, Subcommittee on Courts, Civil
Liberties, & the Administration of Justice
Committee on the Judiciary
House of Representatives
Washington, D. C. 20515

Dear Mr. Kastenmeier:

This is in response to an August 3, 1984, telephone request by Mr. Dave Beier of your Subcommittee staff for information regarding applications for products derived from biotechnology.

At the present time FDA has approved a number of applications for such products. They are:

Manufacturer	Product
Centocor, Inc	Antibody to HB_sAg
Gamma Biologicals, Inc.	Blood Grouping Serum - Anti-M
Ortho Diagnostics, Inc.	Anti-Human Serum - Anti-C3d
Ortho Diagnostics, Inc.	Anti-Human Serum - Anti-C3b, -C3d
Ortho Diagnostics, Inc.	Anti-Human Serum
Chembiomed, Ltd.	Blood Grouping Serum - Anti - A, Anti - B, Anti - Le^a, Anti - Le^b
Eli Lilly	Humulin (insulin)
Eli Lilly	Humulin R (insulin)

In addition, there are two human biological products currently under investigational study.

With respect to veterinary drugs there are currently twelve veterinary products under investigation and one new animal drug application before the Agency for review.

The names of the manufacturers and products that are under investigation, if not already publicly known, are considered to be trade secret and/or confidential commercial information and cannot be disclosed under the requirements of the Federal Food, Drug, and Cosmetic Act.

Sincerely yours,

Robert C. Wetherell, Jr.
Associate Commissioner
for Legislation and Information

DEPARTMENT OF HEALTH & HUMAN SERVICES — Office of the Secretary

Washington, D.C. 20201

The Honorable Peter W. Rodino, Jr.
Chairman, Committee on the Judiciary
House of Representatives
Washington, D.C. 20515

RECEIVED
JUL 25 1984
JUDICIARY COMMITTEE

Dear Mr. Chairman:

There is pending before your Committee H.R. 3605, the "Drug Price Competition and Patent Term Restoration Act of 1984," which was reported on June 21 by the Committee on Energy and Commerce.

Enclosed for your information is a copy of testimony on behalf of the Department on S. 2748 delivered June 28, 1984 before the Senate Committee on Labor and Human Resources by Dr. Mark Novitch, Acting Commissioner of Food and Drugs. Title II of S. 2748 is substantially identical to Title II of H.R. 3605.

To summarize briefly, our testimony raised two major concerns with respect to Title II as drafted. First, we noted that having to determine the regulatory review period for each product for which patent term extension was sought would be burdensome to FDA, and urged that instead the applicant be required to determine the regulatory review period for purposes of the patent term extension, subject to discretionary review by this Department. Second, we also recommended that the provisions for determination of due diligence be deleted; such determination would require additional Departmental resources for no net public benefit, since we believe the overwhelming majority of applicants have in fact exercised due diligence.

We would be pleased to work with your staff to address the concerns we have with H.R. 3605.

Sincerely,

Cynthia C. Root
Deputy Assistant Secretary
for Legislation (Health)

Enclosure

cc: Rep. Kastenmeier
Rep. Fish
Rep. Moorhead

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT

BY

MARK NOVITCH, M.D.

ACTING COMMISSIONER OF FOOD AND DRUGS

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON LABOR AND HUMAN RESOURCES

UNITED STATES SENATE

JUNE 28, 1984

Mr. Chairman:

I am pleased to have this opportunity to discuss our views on S. 2748, the "Drug Price Competition and Patent Term Restoration Act," and on draft legislation on the export of unapproved drugs.

S. 2748 would revise the procedures for new drug applications by authorizing an abbreviated procedure for generic versions of "pioneer" drugs approved after 1962. It would also authorize the restoration of patent time lost due to the premarket requirements of the Federal Food, Drug, and Cosmetic (FDC) Act for drugs, medical devices, food additives and color additives.

As you know, Mr. Chairman, these concepts of an abbreviated approval process for drugs approved after 1962 and patent term restoration are initiatives given high priority by this Administration. We firmly believe that establishing an abbreviated new drug application (ANDA) system is a public health objective whose time has come. As more and more drugs from the post-1962 era come off patent, an ANDA system for these drugs would increase competition, lower drug costs and save American consumers literally hundreds of millions of dollars in the years ahead. And, by preserving incentives for drug development, the companion provision for patent term extension is also in the public interest. Accordingly, we support the concepts in S. 2748 and believe that, with certain technical revisions, the bill would represent a major advance in our nation's health care system.

Let me provide some additional background before I turn to the bill itself.

ANDAs

An ANDA is an abbreviated new drug application for marketing approval for a duplicate version of a drug product that has been approved as safe and effective. An ANDA does not contain the clinical data on human safety and efficacy that were required in the new drug application (NDA) to market the previously approved or "pioneer" drug. It is predicated on the view that the safety and effectiveness of the therapeutic entity have been established.

To require repetition of the costly studies originally needed to establish safety and effectiveness has the effect of barring the introduction of most generic equivalents. Without an ANDA procedure, the requirement for NDAs has the effect of a secondary patent which protects the pioneer indefinitely from generic competition. Moreover, a requirement for duplicative clinical studies is scientifically unnecessary.

The Food and Drug Administration (FDA) has long recognized the value of an ANDA system. ANDAs have been used by FDA under the Drug Efficacy Study Implementation (DESI) program for the approval of generic versions of drugs first approved only for safety between 1938 and 1962, the year in which Congress amended the FDC Act to require that drugs be shown to be effective as well as safe. A similar procedure has not been established for post-1962 drugs. In recent years, however, the patents have expired for many post-1962 drugs. As a result, generic drug manufacturers have become increasingly interested in changing FDA's drug approval system to eliminate the current requirement for the

submission of full reports of safety and effectiveness studies for generic drug products.

To give you some idea of the impact a post-1962 ANDA system would have, by the end of 1985 there will be approximately 160 drugs approved since 1962 that will have come off patent, and that number will grow by over 30 percent by the year 1990. A number of drugs about to come off patent are also among the nation's top selling prescription products. Of the post-1962 drugs coming off patent by the end of next year, six are among the nation's top ten sellers in terms of retail sales. That number, too, will grow over the next several years.

A post-1962 ANDA procedure would be consistent with a number of FDA programs that have aided the marketing of generic drugs. In addition to the pre-1962 ANDA procedure under the DESI program, FDA has permitted generic applicants for post-1962 drug products to rely on reports of studies published in the open scientific literature, the so-called paper NDA process. However, adequate literature is available for relatively few post-1962 drugs.

For these reasons, the Committee is to be commended for introducing this important legislation.

S. 2748 (Title I)

Let me now turn to the specific bill. We believe that with a few technical modifications S. 2748 would contain the essential ingredients for balancing many complex and competing considerations surrounding an equitable ANDA system. If adopted, these modifications would not upset

the careful balance that S. 2748 is intended to achieve. Our concerns go primarily to the manner in which FDA would be asked to implement the post-1962 ANDA system. To gain the desired benefits, the system needs to be manageable and workable. That is our main concern and I would like to summarize our recommendations for you.

1. The Bill Would Create a Burdensome Backlog of Applications

S. 2748 would immediately open to ANDA eligibility all drug products approved from 1962 through 1982 that are no longer protected by patent. We foresee a difficult period arising from this in which our current review resources could not handle the incoming applications. Within the first six months of enactment we might receive 900 applications, followed by 400 applications during the next six months. Thousands more would follow during the next several years.

Our objective is to deal with these applications in the most efficient and productive manner possible. To that end, we are already evaluating the resource implications and gearing up, to the extent possible, to implement this legislation. However, Mr. Chairman, you should be aware that we would be unable to act on each application within the 180 day time-frame specified in the bill if we were confronted by the staggering volume of applications that we anticipate receiving.

To remedy this situation, we recommend that the bill establish an orderly phase-in of eligibility for ANDAs. One possibility is to begin with drugs in order of initial approval. Another is to begin with drugs that represent the greatest prescribing volume. In

any event, we would aim to open the process to all drugs in the shortest possible time and we would be pleased to work with the Committee to achieve an equitable and workable solution.

2. Different Active Ingredients Should Not Be Specifically Authorized

Second, we recommend deletion of provisions in S. 2748 that permit ANDAs for new combination drugs. We believe that, as a rule, ANDAs should be limited to drugs which have the same active ingredients as the pioneer drugs. There may be rare instances in which the public interest is served by permitting ANDAs for combinations which have not been previously approved. But overall, we do not believe that it is in the public interest to encourage the proliferation of new combinations without adequate clinical testing for safety and effectiveness.

We would be pleased to work with the Committee to develop a procedure to approve new combinations in those limited circumstances where public health and scientific considerations make such approvals appropriate.

3. Linking Effective Date of Approval to Patent Status of the Pioneer Drug Has Resource Implications

S. 2748 ties ANDA and paper NDA approval to the patent status of the pioneer drug. The effective date of FDA's approval of an ANDA or paper NDA would vary, depending on whether the pioneer patent had expired or was still running or whether the patent status of the pioneer was being litigated.

As a result, FDA would be responsible for delaying the effective date of approvals pending resolution of such matters as civil litigation or requests for reexamination of patentability to the Patent Office, and for delaying the effective date of the approval of subsequent generic applications until the first generic drug involved in a patent challenge had been marketed for 180 days.

Although these provisions are not intended to require judgmental determinations with respect to patent status, the new and complex recordkeeping that would be required would have resource implications for the Agency and would also embroil us in the substance of patent controversies. For example, a successful litigant in a patent suit would learn of a court decision before FDA could be officially notified and, from our experience, would pressure the Agency to issue an approval prior to the official notification, or perhaps simply market the product, leaving us with an enforcement problem.

We understand that the purpose of these provisions is to prevent the marketing of duplicate products before issues concerning the pioneer's patent status are resolved. Mechanisms are available, however, to protect patent rights which need not involve the limited resources of FDA. In our view the requirement in S. 2748 that ANDA and paper NDA applicants must provide notice of their intentions to the patent holder should be adequate to protect the patent status of the pioneer product. This notification, which would precede ANDA or paper NDA approval in every case by six months or more, should enable the pioneer manufacturer to protect its patent rights through judicial remedies.

4. Veterinary Drugs Should Be Included

S. 2748 would provide patent protection for pioneer veterinary drugs but would not authorize an abbreviated application procedure for generic versions of these products. We believe that veterinary drugs should be included. A post-1962 abbreviated new animal drug application policy would essentially eliminate the need to reprove that which has already been established. The benefits of such a policy would accrue primarily as savings through the increased availability of lower-priced generic animal drug products. Less expensive drugs available to the livestock producer and the veterinarian should result in savings in the cost of food and savings in health care for companion animals.

I would note that the animal drug provisions in Title II are inconsistent with those contained in H.R. 5529, a bill designed to extend patents for both agricultural and chemical products, and that the United States Department of Agriculture has officially notified Congressman Kastenmeyer of its support for the bill. While FDA has not been asked to provide its views on H.R. 5529, we encourage the Congress to review the possibility of reconciling these differences as quickly as possible in order to enact the most meaningful set of legislative changes.

PATENT RESTORATION

Turning now to patent restoration, it is well-known that products requiring FDA premarket approval sometimes entail high development costs, the risk of failure and small potential markets. And as an

additional disincentive, innovators typically lose years of patent exclusivity because of testing requirements and regulatory review.

We are mindful of the paradox that the careful and time-consuming scientific review needed to confirm safety and effectiveness may be reducing initiatives to develop drugs that come to FDA for review. Streamlining the regulatory process will help. However, our premarket approval system must continue to be thorough enough to assure the safety and efficacy of new drugs and devices and the safety and functionality of food and color additives, even if that means living with a process that takes longer than we would ideally prefer. We want to encourage innovation, but not at the expense of safety. Consequently, the Department of Health and Human Services supports patent extension legislation as a means of encouraging innovative research.

Title II of S. 2748

As with the ANDA portion of S. 2748, we believe the patent restoration provisions in the bill reflect a major step toward equitable legislation in this area. We do have some concerns that we would like to share with you, however, about the impact that this legislation would have on the operation of FDA.

We also understand that the Patent and Trademark Office of the Department of Commerce has some concerns, which Commissioner Mossinghoff described in yesterday's hearing on H.R. 3605, House companion bill to S. 2748, which we would commend to the Committee's attention.

45-024 O - 85 - 14

1. FDA Need Not Determine the Regulatory Review Period for Every Product

S. 2748 would require an applicant for patent extension to submit to the Commissioner of Patents a brief description of the applicant's activities during the premarket regulatory review period and the dates of certain significant milestones that occurred during this period. The Commissioner of Patents would be required to send a copy of the application containing this information to the Secretary of Health and Human Services, who would be required within 30 days to determine the applicable regulatory review period.

Having to determine and confirm the regulatory review period for each product would be burdensome to FDA because the Agency would have to store and retrieve information in a form which otherwise would be of little or no utility to it. We believe this burden could be eliminated by requiring the applicant, rather than FDA, to determine the regulatory review period in its application to the Commissioner of Patents. The formula for doing so is provided in the bill, and the applicable dates would be well known to the applicant.

The applications could be made available to FDA for inspection or audit at FDA's discretion on the same enforcement basis that other reports, such as income tax filings, are regulated. Since the patent term extension is added on to the end of the patent term, we can perceive no public health reason to require FDA to determine the regulatory review period under a restrictive 30-day time schedule. The regulatory review period may be adequately determined and validated

through a submission by the applicant and a discretionary review by FDA.

2. The Determination of "Due Diligence" Should Be Deleted

S. 2748 would require the Secretary to determine whether an applicant acted with "due diligence" during the regulatory review period if the Secretary were petitioned to do so within 180 days after a patent extension determination is published. If the Secretary were to find that an applicant did not act with due diligence for some period of time, the amount of patent extension that the applicant would be entitled to could be reduced.

The concept of "due diligence" is a laudable attempt to make patent restoration as fair as possible by disallowing time during which the development of a product was not vigorously pursued. However, we believe that the overwhelming majority of applicants would be entitled to the five-year maximum allowable patent restoration in S. 2748. This is true because the regulatory review period will generally be longer than necessary to confer the full extension period even assuming a reasonable attempt by both the applicant and FDA to assure prompt evaluation of the applications. A deduction for lack of due diligence would reduce the time that may be counted toward patent restoration down toward this five-year maximum, but probably not below it. Nonetheless, under the bill, FDA would be required to promulgate regulations, review petitions, prepare due diligence determinations and conduct hearings. As a practical matter, therefore, it appears that a complex system would be established that would require FDA resources to

implement and maintain for no net public benefit. We therefore strongly urge that this feature of the bill be deleted.

EXPORT OF UNAPPROVED DRUGS

I turn my comments next to the issue of the export of unapproved new drugs. We appreciate receiving a draft of proposed legislation that would authorize such export. Before commenting specifically on the draft, however, I would first like to put this issue into some perspective.

As the Subcommittee recognizes, the FDC Act does not presently permit the export of unapproved new human and animal drugs except for certain carefully controlled exports for investigational use abroad. Similarly, the Public Health Service Act does not permit the export of unlicensed biologicals.

The Department of Health and Human Services (DHHS) and the FDA have in the past been asked to consider statutory amendments to permit the export of unapproved new drugs and unlicensed biologicals. For example, the proposed Drug Regulation Reform Act of 1978 contained a provision for the export of unapproved new drugs. Although the Department has no current legislative initiative on this subject, we will be pleased to work with you in providing comments on the current proposal or any other specific proposal this committee should advance.

Let me now take a few moments and discuss our current thinking on this issue. We believe we have an excellent precedent right in the FDC Act, that being the provision authorizing the export of unapproved medical devices. We believe that provision contains adequate public health safeguards, and our experience with medical device exports under this provision of the FDC Act has been quite favorable. For example, we are not processing approximately 250-300 export requests per year under the medical device provision. We will be happy to provide more specific information regarding our export experience with medical devices for the record, if you feel that would be useful.

The Medical Device Amendments of 1976 permit the export of certain classes of medical devices, including unapproved medical devices, if they:

(1) accord to the specifications of the foreign purchaser;

(2) are not in conflict with the laws of the country to which they are intended for export;

(3) are labeled on the outside of the shipping package that they are intended for export;

(4) are not sold or offered for sale in domestic commerce: and

(5) if the Secretary of DHHS determines that their export would not be contrary to the public health and safety; and

(6) that their export has the approval of the country to which they are intended to export.

The most important public health safeguards in the medical device provision are the last two I mentioned, namely, concern over public health and safety and the approval of the importing country. Untimately, however, we believe that the governments of other nations are the proper authorities to assess their own health needs, the diseases and health-related characteristics of their populations, the nature of their health care delivery systems, the availability of treatment alternatives, and all of the many other factors that go into risk/benefit decisions. We support, and would continue to support, international efforts to assure that all nations have access to information to assist in those risk/benefit determinations.

In this regard, the Adminstration supports international efforts to share information and to improve the ability of all nations to make their own risk/benefit decisions regarding drugs. FDA shares with

other countries information regarding drug approvals and withdrawals, as well as concerns we may have with respect to specific drugs. The United States has actively participated in the World Health Organization's (WHO) Certification Scheme for Pharmaceuticals Moving in International Commerce. This system, adopted by WHO in 1975 and currently agreed to by over 80 countries, permits an importing country to obtain from the government of an exporting country current information on the quality and approval status of a drug in the country of export.

The United States is also involved in other international activities for ensuring the flow of information on the safety and efficacy of pharmaceutical products. These activities include regular submissions of information as well as notifications of significant regulatory actions on drugs to the WHO for subsequent dissemination in WHO's Drug Information Circular and the WHO Drug Information Bulletin. The United States also serves as a National Collaborating Center for the WHO International Drug Monitoring Scheme. In addition, the United States participates in the biennial International Conferences of Drug Regulatory Authorities, which provides a forum for the exchange of drug information and discussions of regulatory actions. The first such conference was hosted by the United States in Annapolis, Maryland in

1980 and the second conference was held in Rome, Italy in 1982. The third has just been held in Sweden.

Thus, we believe that the safeguards described above relating to medical devices, together with WHO's information dissemination efforts, in which we actively cooperate, would provide an appropriate measure of control over the export of unapproved new drugs and unlicensed biologicals, while at the same time permitting the governments of other nations to exercise their own risk/benefit decisions with respect to the pharmaceuticals they believe are suitable for use in their countries.

Now let me turn to the draft legislative proposal at hand. We support its intent, and we especially support the reliance placed on requiring assurance that the drug may be lawfully offered for use in that country. As noted above, this has proven to be quite workable in the export of unapproved medical devices. There are some aspects of the draft bill that do cause us some concern, however. Let me outline them for you briefly.

1. Development of the List of Countries Eligible to Receive Drug Products Not Approved in the United States.

We understand the objectives of the draft's requirement that we establish a list of foreign countries with adequate regulatory systems in place to approve drugs. While such a list could be developed, we believe that for us to sit in judgment of our sister regulatory agencies around the world would place us in the very difficult diplomatic position of publicly assessing the suitability of public health safeguards in other countries. We believe the governments of other nations are in the best position to assess their own health needs.

Mr. Chairman, the system devised by the Congress to authorize the export of unapproved medical devices, the key elements of which I described earlier, is sound and efficient, and deserves the Committee's consideration.

2. Labeling Provisions

A more technical point is that the provision for foreign language labeling is not feasible from an administrative standpoint. The draft would allow the pre-export notification to FDA for a drug not approved in the United States to contain non-English labeling from a listed country and a non-English translation of that labeling for an unlisted country. The Agency would, therefore, be required to check the adequacy of the labeling in multiple languages. This provision should be changed to require that the pre-export notification to FDA contains certified English translations of all labels submitted.

3. Definition of "Banned" Drugs

One of the conditions to be met in order for a product to be exported to listed or unlisted countries raises the concept of a drug that is "banned" in the United States, a concept which has not been defined in either the draft or existing law for drugs. The current statutory scheme for drugs and biologics in the United States results in essentially two categories: those that are approved or licensed and those that are not. For a relatively small number of those that are not approved or licensed, the FDA has refused approval or has withdrawn approval. If the concept of a "banned" drug is to be retained, it should probably include, at a minimum, products for which FDA has formally withdrawn approval or suspended licensure under the normal statutory procedures for withdrawing approval of such application as well as under the "imminent hazard" provision of the FDC Act.

4. Dissemination of Significant Information on Drugs

As I discussed earlier, we already have mechanisms in place to provide important regulatory information to foreign governments and WHO. Specific legislation to do so is, therefore, unnecessary. To expand this effort as described in the draft to include information on all drug approvals and all labeling revisions, and sending this regularly to over 160 member countries of WHO, would be extremely burdensom. I also do not believe that even WHO would have the resources to perform such a function.

In closing, Mr. Chairman, I can only emphasize that, with the few technical amendments that I have discussed with you today, the Department supports S. 2748. We will also work with the Committee to help develop legislation regarding the export of unapproved drug products.

That concludes my prepared statement, Mr. Chairman. I will be glad to answer any questions you may have.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 2 1 1984

The Honorable Robert W. Kastenmeier
Chairman, Subcommittee on Courts, Civil Liberties,
and the Administration of Justice
Committee on the Judiciary
House of Representatives
Washington, D.C. 20515

Dear Mr. Kastenmeier:

This is in response to a request from Mr. David W. Beier, III, Assistant Counsel of the Subcommittee, for information on the number of new drug applications approved from 1979 to date.

Enclosed is a listing of all new drug applications (NDA) approved from 1979 through May 1984. The NDA number, generic name, trade name, dosage form, applicant name, indication and approval date are included in the list.

Mr. Beier also requested that we identify the new chemical entities that were approved during that time.

The classification nomenclature we use is new molecular entity, not new chemical entity. The classification description attached to the list defines a new molecular entity which, in the list, is designated by the number "1". The letter designation refers only to therapeutic potential. All other numerical designations are for non new molecular entities.

If you have any questions regarding this list, please let me know.

Sincerely yours,

Robert C. Wetherell, Jr.
Associate Commissioner
for Legislation and Information

Enclosure

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFI-CATION	APPROVAL DATE
January 1979							
17-989	Carboprost Tromethamine	Prostin M 15	Injection	Upjohn	Abortifacient	1-C	1-9-79
18-025	Furosemide Injection USP	None	Injection	International Medication Systems	Diuretic agent	5-C	1-10-79
17-941	Pseudoephedrine HCl	Sudafed S.A.	Capsule	Burroughs-Wellcome	Nasal and eustachian tube decongestant	5-C	1-15-79
18-181	Clotrimazole	Mycelex	Solution	Dome Labs	Topical antifungal agent	5-C	1-15-79
18-183	Clotrimazole	Mycelex	Cream	Dome Labs	Topical antifungal agent	5-C	1-15-79
February 1979							
17-385	Electrolyte and Dextrose Injection	PLASMA-LYTE 56 and 5% Dextrose	I.V. Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-P	2-1-79
17-390	Electrolyte and Dextrose Injection	PLASMA-LYTE-M and 5% Dextrose	I.V. Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-P	2-1-79
17-438	Electrolyte Solution	PLASMA-LYTE	I.V. Solution (in flexible container)	Travenol Labs	Fluid and electrolyte replenishment	5-C-P	2-1-79
17-634	Dextrose and Potassium Chloride Injection	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-P	2-1-79
17-378	Electrolyte Solution	PLASMA-LYTE 148	I.V. Solution (in flexible container)	Travenol Labs	Fluid and electrolyte replenishment	5-C-P	2-2-79
17-451	Electrolyte and Dextrose Injection	PLASMA-LYTE 148 and 5% Dextrose	I.V. Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-P	2-2-79

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
February 1979 (cont.)							
17-484	Electrolyte and Dextrose Injection	5% Dextrose and Electrolyte No. 48	I.V. Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-P	2-2-79
17-648	Sodium Chloride and Potassium Chloride Injection	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid and electrolyte replenishment	5-C-P	2-2-79
18-008	Dextrose, Sodium Chloride and Potassium Chloride Injection	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-P	2-2-79
18-016	Sodium Chloride Injection	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid replenishment	5-C-P	2-2-79
18-037	Dextrose, Sodium Chloride and Potassium Chloride Injection	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-P	2-2-79
18-058	Gallium Citrate Ga 67	None	Injection	Mallinckrodt	Diagnostic agent for Hodgkin's disease, lymphomas & bronchogenic carcinoma	5-C	2-2-79
17-862	Metoclopramide	Reglan	Injection	A.H. Robins	Gastric smooth muscle stimulant	1-B	2-7-79
18-230	Clotrimazole	Mycelex G	Vaginal Cream	Dome Labs	Treatment of vulvovaginal candidiasis	5-C	2-16-79
17-971	Lithium Carbonate	Eskalith	Tablet	Smith Kline & French	Treatment of manic episodes of manic-depressive illness	5-C	2-26-79
18-182	Clotrimazole	Gyne-Lotrimin	Vaginal Tab.	Dome Labs	Treatment of vulvovaginal candidiasis	5-C	2-27-79

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
March 1979							
50-530	Cephradine	Velosef	Tablet	E.R. Squibb & Sons	Antibiotic (semi-synthetic cephalosporin)	3-C	3-9-79
17-130	Sodium Heparin Injection USP	None	Injection	Bel-Mar Labs	Anticoagulant therapy	5-C	3-21-79
18-121	Chymotrypsin	Catarase	Ophthalmic Solution	Cooper Labs	For enzymatic zonulysis prior to intracapsular lens extraction	5-C	3-27-79
April 1979							
18-090	Sodium Chloride	None	I.V. Solution (in flexible container)	Abbott Labs	Fluid and electrolyte replenishment	5-C-P	4-4-79
50-521	Cefaclor Monohydrate	Ceclor	Capsule	Eli Lilly	Antibiotic (semi-synthetic cephalosporin)	1-C-U	4-4-79
50-522	Cefaclor	Ceclor	Oral Suspension	Eli Lilly	Antibiotic (semi-synthetic cephalosporin)	2-C-U	4-4-79
17-992	Human Growth Hormone	Crescormon	Injection	Swedish Independent Development Corp.	Treatment of growth failure due to pituitary hormone deficiency	5-C	4-6-79
18-089	Betamethasone Benzoate	Benisone/Flurobate	Ointment	Warner-Chilcott	Topical anti-inflammatory	5-C	4-6-79
17-917	Quinidine Gluconate	Duraquin	Sustained Release Tablet	Parke Davis	Anti-arrhythmic agent	5-C	4-11-79
18-074	Phendimetrazine Tartrate	None	Timed Release Capsule	Vitarine	Anorexigenic agent	5-C	4-16-79
18-027	Lithium Carbonate	Lithotabs	Tablet	Rowell Labs	Antimanic agent	5-C	4-27-79

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
May 1979							
18-103	Ticrynafen	Selacryn	Tablet	Smith Kline & French	Antihypertensive agent with uricosuric properties	1-B-U	5-2-79
18-004	Hydroxyprogesterone Caproate	NONE	Injection	Maurry Biological	Progestagen	5-C	5-11-79
18-024	Nalbuphine HCl	Nubain	Injection	Endo Labs	Narcotic Analgesic	1-C	5-15-79
18-203	Intravenous Fat Emulsion	Liposyn 10%	Infusion	Abbott	Parenteral nutrition	1-C-U*	5-16-79
June 1979							
18-184	Sodium Chloride Injection	0.45% Sodium Chloride Injection	I.V. Solution (in flexible container)	McGaw Labs	Fluid & electrolyte replenishment	5-C-MPU	6-8-79
50-519	Tobramycin Sulfate	Nebcin	Infusion	Eli Lilly	Antibiotic (aminoglycoside)	3-C-U	6-11-79
16-792	Trimipramine Maleate	Surmontil	Capsule	Ives Labs	Antidepressant	1-C	6-12-79
18-031	Propranolol HCl and Hydrochlorothiazide	Inderide	Tablet	Ayerst Labs	Antihypertensive	4-C	6-15-79
18-186	Sodium Lactate Injection USP	1/6 Molar Sodium Lactate Injection	I.V. Solution (in flexible container)	McGaw Labs	Fluid & electrolyte replenishment	5-C-MPU	6-18-79
17-884	Lactulose	Chronulac	Syrup	Merrell-National	Laxative	5-C	6-20-79
18-141	Technetium Tc 99m Medronate	Technetium Tc 99m Medronate Kit	Injection	Diagnostic Isotopes	Diagnostic for bone imaging	5-C-U	6-26-79
17-891	Heparin Sodium Injection USP	Heparin Sodium Injection	Injection	Inolex	Anticoagulant	5-C	6-27-79

* Contains 10% Safflower oil whereas NDA 17-643 Intralipid 10% contains 10% Soybean oil.

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
June 1979 (Cont.)							
18-229	Dextrose and Sodium Chloride Injection USP	10% Dextrose and 0.45% Sodium Chloride Injection	I.V. Solution (in flexible container)	McGaw Labs	Fluid, electrolyte & caloric replenishment	5-C-PU	6-29-79
July 1979							
18-206	Norgestrel, Ethinyl Estradiol and Ferrous Fumarate	Lo/Ovral-28 and Ferrous Fumarate	Tablet	Wyeth Labs	Oral contraceptive	3-C	7-26-79
August 1979							
18-156	Ringer's Solution NF	None	Irrigation Solution (in flexible container)	McGaw Labs	Urologic irrigation	5-C-PU	8-6-79
18-161	0.25% Acetic Acid USP	None	Irrigation Solution (in flexible container)	McGaw Labs	Urologic irrigation	5-C-PU	8-6-79
17-984	Diazepam	Valcaps	Capsule	Hoffman-La Roche	Anti-anxiety agent	3-C-U	8-8-79
18-205	Copper IUD	Tatum-T	IUD	Searle Labs	Contraception	5-C	8-16-79
18-096	2.5% Dextrose and 0.45% Sodium Chloride Injection USP	None	I.V. Solution (in flexible container)	Abbott Labs	Fluid, electrolyte & caloric replenishment	5-C-PU	8-17-79
18-055	2/3 Dextrose 5% in 1/3 strength Saline	None	I.V. Solution (in flexible container)	Abbott Labs	Fluid, electrolyte & caloric replenishment	5-C-PU	8-20-79
17-465	5% Dextrose Injection USP	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid & caloric replenishment	5-C-PU	8-23-79

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
August 1979 (Cont.)							
17-477	0.9% Sodium Chloride Injection USP	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid & electrolyte replenishment	5-C-PU	8-23-79
17-504	10% Dextrose Injection USP	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid & caloric replenishment	5-C-PU	8-23-79
17-509	5% Dextrose and 0.45% Sodium Chloride Injection USP	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-PU	8-23-79
17-587	5% Dextrose and 0.2% Sodium Chloride Injection USP	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-PU	8-23-79
17-590	Electrolytes and Dextrose Injection	Plasma-Lyte 56 in 5% Dextrose	I.V. Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-PU	8-23-79
17-591	5% Dextrose and 0.33% Sodium Chloride Injection USP	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-PU	8-23-79
17-593	5% Dextrose in Lactated Ringer's Injection	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-PU	8-23-79
17-595	Lactated Ringer's Injection USP	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-PU	8-23-79
17-597	10% Dextrose and 0.9% Sodium Chloride Injection USP	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-PU	8-23-79

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
August 1979 (Cont.)							
17-616	5% Dextrose and 0.9% Sodium Chloride Injection USP	None	I.V Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-PU	8-23-79
17-620	5% Dextrose and Electrolytes Injection	5% Dextrose with Electrolyte No. 48	I.V. Solution (in flexible container)	Travenol Labs	Fluid, electrolyte & caloric replenishment	5-C-PU	8-23-79
17-621	0.45% Sodium Chloride in Water	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid & electrolyte replenishment	5-C-PU	8-23-79
17-521	50% Dextrose Injection USP	None	I.V. Solution (in flexible container)	Travenol Labs	Fluid & caloric replenishment	5-C-PU	8-28-79
18-080	10% Dextrose Injection USP	None	I.V. Solution (in flexible container)	Abbott Labs	Fluid & caloric replenishment	5-C-PU	8-28-79
18-256	5% Dextrose in Ringer's Injection	None	I.V. Solution (in flexible container)	McGaw Labs	Fluid, electrolyte & caloric replenishment	5-C-PU	8-28-79
18-124	Technetium Tc 99m Medronate	AN-MDP Kit	Injection	Ackerman Nuclear	Radiodiagnostic bone imaging agent	5-C-U	8-29-79
September 1979							
50-508	Cyclacillin	Cyclapen	Oral Suspension	Wyeth Labs	Antibiotic	1-C	9-14-79
50-509	Cyclacillin	Cyclapen	Tablet	Wyeth Labs	Antibiotic	3-C	9-14-79
18-264	Dantrolene Sodium	Dantrium	Injection	Norwich-Eaton	Skeletal muscle relaxant	3,6-A-U	9-18-79

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
October 1979							
50-505	Gentamicin Sulfate	Garamycin	Intrathecal Injection	Schering Corp.	Antibiotic (aminoglycoside)	3-C-TU	10-1-79
17-871	Metyrosine	Demser	Capsule	Merck Sharp & Dohme	Treatment of pheochromocytoma	1-B	10-3-79
18-116	Amcinonide	Cyclocort	Topical Cream	Lederle	Topical anti-inflammatory	1-C-U	10-18-79
18-154	Minoxidil	Loniten	Tablet	Upjohn	Treatment of severe hypertension	1-B-TU	10-18-79
18-150	Thallous Chloride Tl 201	Thallous Chloride Tl 201	Injection	Mallinckrodt	Radiodiagnostic for myocardial perfusion imaging	5-C	10-23-79
18-039	Loxapine HCl	Loxitane I.M.	Injection	Lederle	Treatment of the manifestations of schizophrenia	3-C	10-26-79
18-084	Tolmetin Sodium	Tolectin DS	Capsule	McNeil Labs	Treatment of rheumatoid arthritis and osteoarthritis	3-C-MU	10-30-79
November 1979							
18-307	Potassium Iodide	Thyro-Block	Tablet	Wallace Labs	Thyroid blocking in a radiation emergency	3-A-RSU	11-9-79
18-308	Potassium Iodide	Thyro-Block	Solution	Wallace Labs	Thyroid blocking in a radiation emergency	3-A-RSU	11-9-79
18-211	Oxybutynin Chloride	Ditropan	Syrup	Marion Labs	Anticholinergic agent	3-C-U	11-29-79
50-529	Erythromycin Ethyl Succinate and Sulfisoxazole Acetyl	Pediazole	Oral Suspension	Ross Labs	Antibiotic for acute otitis media	3,4-C-U	11-29-79
18-144	Prazepam	Centrax	Capsule	Warner-Lambert/ Parke Davis	Anti-anxiety agent	3-C	11-30-79

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
December 1979							
18-344	Purified Pork Insulin	Regular Iletin II	Injection	Eli Lilly	Diabetes Mellitus	3-C-U	12-5-79
18-345	Isophane Purified Pork Insulin	NPH Iletin II	Injection	Eli Lilly	Diabetes Mellitus	3-C-U	12-5-79
18-346	Protamine Zinc Purified Pork Insulin	Protamine Zinc Iletin II	Injection	Eli Lilly	Diabetes Mellitus	3-C-U	12-5-79
18-347	Zinc Purified Pork Insulin	Lente Iletin II	Injection	Eli Lilly	Diabetes Mellitus	3-C-U	12-5-79
18-063	Nadolol	Corgard	Tablet	E.R. Squibb	Angina Pectoris	1-C	12-10-79
18-064	Nadolol	Corgard	Tablet	E.R. Squibb	Antihypertensive	6-C	12-10-79
17-624	Isoflurane	Forane	Liquid for Inhalation	Ohio Medical	General anesthesia	1-B	12-18-79
50-484	Daunorubicin HCl	Cerubidine	Injection	Ives Labs	For remission induction in acute non-lymphocytic leukemia	1-B-T	12-19-79
17-938	Molindone HCl	Moban	Tablet and Solution	Endo Labs	Management of the manifestations of schizophrenia	3-C-U	12-28-79
17-874	Scopolamine	Transderm-V	Patch	Alza Corp.	Prevention of nausea and vomiting associated with motion sickness	3-B-P	12-31-79

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
January 1980							
18-175	Absorbable Suture/Dyed	Vicryl	Suture	Ethicon	Absorbable surgical suture	3-C-MPU	1-3-80
18-176	Absorbable Suture/Undyed	Vicryl	Suture	Ethicon	Absorbable surgical suture	3-C-MPU	1-3-80
18-254	Dextrose 5% in Ringer's Injection	None	I.V. Solution (in flexible container)	Abbott	Fluid, electrolyte and caloric replenishment	5-C-MPU	1-15-80
50-533	Doxycycline Hyclate	Vibra-Tabs	Tablet	Pfizer	Antibiotic	3-C	1-15-80
18-193	Purified Pork Insulin	Insulin Nordisk Quick	Injection	Nordisk Insulin	Diabetes Mellitus	5-C-MU	1-16-80
18-194	Isophane Purified Pork Insulin	Insulin Nordisk NPH	Injection	Nordisk Insulin	Diabetes Mellitus	5-C-MU	1-16-80
18-195	Isophane Purified Pork Insulin and Purified Pork Insulin	Insulin Nordisk Mixtard	Injection	Nordisk Insulin	Diabetes Mellitus	5-C-MU	1-16-80
18-234	Halcinonide	Halciderm 0.1%	Cream	E.R. Squibb	Corticosteroid-responsive dermatoses	5-C-U	1-24-80
February 1980							
18-099	Chlorpheniramine Maleate and Phenylpropanolamine HCl	Contac Continuous Action Decongestant	Capsule	Menley & James	Decongestant/Antihistamine	5-C	2-4-80
18-233	Sterile Water for Injection, USP	None	I.V. Solution (in flexible container)	Abbott	For the aseptic preparation of parenteral solutions	5-C-MPU	2-18-80
18-313	Sterile Water for Irrigation, USP	None	Irrigation (in flexible container)	Abbott	Irrigation	5-C-MPU	2-28-80

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
February 1980 (cont.)							
18-314	0.9% Sodium Chloride Irrigation, USP	None	Irrigation Solution (in flexible container)	Abbott	Irrigation	5-C-MPU	2-22-80
18-315	Aminoacetic Acid Irrigation, USP	Glycine Irrigation 1.5%	Irrigation Solution (in flexible container)	Abbott	Urologic irrigation	5-C-MPU	2-22-80
18-316	Sorbitol and Mannitol	Sorbitol-Mannitol Irrigation	Irrigation Solution (in flexible container)	Abbott	Urologic irrigation	5-C-MPU	2-22-80
17-343	Nitrofurazone Ointment, N.F.	Actin-N	Soluble Dressing in Gauze Pad	Chesebrough-Pond's	Topical antibacterial	5-C	2-25-80
March 1980							
18-381	Purified Pork Insulin	Actrapid	Injection	Novo Labs	Diabetes mellitus	5-C-MU	3-17-80
18-382	Prompt Purified Pork Insulin Zinc Suspension	Semitard	Injection	Novo Labs	Diabetes mellitus	3-C-MU	3-17-80
18-383	Purified Pork Insulin Zinc Suspension	Monotard	Injection	Novo Labs	Diabetes mellitus	5-C-MU	3-17-80
18-384	Purified Pork & Beef Insulin Zinc Suspension	Lentard	Injection	Novo Labs	Diabetes mellitus	4-C-MU	3-17-80
18-385	Extended Purified Beef Insulin Zinc Suspension	Ultratard	Injection	Novo Labs	Diabetes mellitus	3-C-MU	3-17-80
18-309	Desoximetasone	Topicort LP Emollient	Cream	Hoechst-Roussel	Relief of inflammatory manifestations of corticosteroid responsive dermatoses	3-C-M	3-28-80

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
April 1980							
18-208	Lithium Carbonate	Pfi-Lith	Capsule	Pfizer	Treatment of manic episodes of manic-depressive illness	5-C	4-2-80
18-299	Trifluridine	Viroptic	Ophthalmic Solution	Burroughs-Wellcome	Treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to Herpes simplex, types 1 and 2	1-B	4-10-80
18-246	Sterile Water for Irrigation, USP	None	Irrigation (in semi-rigid container)	Cutter Labs	Irrigation	5-C-MPU	4-16-80
18-247	Sodium Chloride Irrigation, USP	None	Irrigation (in semi-rigid container)	Cutter Labs	Irrigation	5-C-MPU	4-16-80
18-245	Oxytocin Injection, USP (Synthetic)	Syntocinon	Injection	Sandoz	For the medical induction of labor	5-C	4-17-80
18-258	5% Dextrose in Acetated Ringer's Injection	None	I.V. Solution (in semi-rigid container)	McGaw Labs	Fluid, electrolyte and caloric replenishment	5-C-MPU	4-17-80
18-337	Acetaminophen	Acetaminophen Uniserts	Rectal Suppository	Upsher-Smith	Non-narcotic analgesic	5-C	4-22-80
18-243	Oxytocin Injection, USP (Synthetic)	None	Injection	Wyeth Labs	For the medical induction of labor	5-C	4-29-80
18-358	2.5% Dextrose Injection, USP	None	I.V. Solution (in semi-rigid container)	McGaw Labs	Fluid and caloric replenishment	5-C-MPU	4-29-80

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
May 1980							
18-239	Dipivefrin HCl	Diopine	Ophthalmic Solution	Allergan	Control of intraocular pressure in chronic open-angle glaucoma	3-B	5-2-80
18-251	Ringer's Injection, USP	None	I.V. Solution (in flexible container)	Abbott	Electrolyte replenishment	5-C-MPU	5-16-80
17-850	Potassium Chloride	Klotrix	Controlled Release Tablet	Mead Johnson	Potassium supplement	5-C	5-22-80
18-300	Chlorhexidine Gluconate	Hibistat	Topical Solution	ICI Americas	Antimicrobial hand wash	3-C	5-23-80
18-362	5% Dextrose and 0.45% Sodium Chloride with 0.15%, 0.224% or 0.3% Potassium Chloride Injection	None	I.V. Solution (in flexible container)	Abbott	Fluid, electrolyte & caloric replenishment	5-C-PU	5-29-80
18-365	5% Dextrose and 0.225% Sodium Chloride with 0.15% Potassium Chloride Injection	None	I.V. Solution (in flexible container)	Abbott	Fluid, electrolyte & caloric replenishment	5-C-PU	5-29-80
18-371	5% Dextrose with 0.15% or 0.3% Potassium Chloride Injection	None	I.V. Solution (in flexible container)	Abbott	Fluid, electrolyte & caloric replenishment	5-C-PU	5-29-80
17-863	3% Sorbitol Solution	None	Irrigation Solution (in flexible container)	Travenol	Urologic irrigation	5-C-MP	5-30-80
17-864	0.45% Sodium Chloride in Water	None	Irrigation Solution (in flexible container)	Travenol	Irrigation	5-C-MPU	5-30-80

NDAs APPROVED

[illegible]	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
May 1980 (Cont.)							
17-865	1.5% Aminoacetic Acid, USP	None	Irrigation Solution (in plastic container)	Travenol	Urologic irrigation	5-C-MP	5-30-80
17-866	Sterile Water for Irrigation, USP	None	Irrigation Solution (in flexible container)	Travenol	Irrigation	5-C-MPU	5-30-80
17-867	0.9% Sodium Chloride Irrigation, USP	None	Irrigation Solution (in flexible container)	Travenol	Irrigation	5-C-MPU	5-30-80
17-943	Trimethoprim	Proloprim	Tablet	Burroughs-Wellcome	Treatment of initial urinary tract infections due to susceptible organisms	3-C-U	5-30-80
50-518	Meclocycline Sulfosalicylate	Meclan	Cream	Johnson & Johnson	Treatment of acne vulgaris	1-C-U	5-30-80
June 1980							
17-952	Trimethoprim	Trimpex	Tablet	Hoffman-La Roche	Treatment of initial urinary tract infections due to susceptible organisms	5-C-U	6-2-80
50-526	Erythromycin	Staticin	Topical Solution	Westwood Pharm.	Treatment of acne vulgaris	3-C-U	6-3-80
50-532	Erythromycin	Ilotycin	Topical Solution	Eli Lilly	Treatment of acne vulgaris	3-C-U	6-3-80
18-279	Potassium Chloride	K-Tab	Controlled Release Tablet	Abbott	Potassium supplement	3-C	6-9-80
18-297	Allopurinol	Lopurin	Tablet	Generic Pharm.	Treatment of hyperuricemia	5-C-U	6-10-80

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
June 1980 (Cont.)							
18-404	0.25% Acetic Acid Irrigation, USP	None	Irrigation Solution (in flexible container)	Abbott	Urologic irrigation	6-C-P	6-10-80
18-088	Krypton Kr 81m Gas	MPI Krypton Kr 81m Gas Generator	Inhalation	Medi-Physics	Radiodiagnostic agent for pulmonary ventilation	2-B-U	6-12-80
18-476	Protamine Zinc Purified Beef Insulin Suspension	Protamine Zinc & Iletin II (Beef)	Injection	Eli Lilly	Diabetes mellitus	3-C-U	6-12-80
18-477	Purified Beef Insulin Zinc Suspension	Lente Iletin II (Beef)	Injection	Eli Lilly	Diabetes mellitus	3-C-U	6-12-80
18-478	Purified Beef Insulin Suspension	Regular Iletin II (Beef)	Injection	Eli Lilly	Diabetes mellitus	3-C-U	6-12-80
18-479	Isophane Purified Beef Insulin Suspension	NPH Iletin II (Beef)	Injection	Eli Lilly	Diabetes mellitus	3-C-U	6-12-80
17-968	Testosterone Cypionate & Estradiol Cypionate	Depo-Testadiol	Injection	Upjohn	Treatment of symptoms associated with menopause in patients not responding to estrogen alone	5-C	6-13-80
17-986	Prazosin HCl & Polythiazide	Minizide	Capsule	Pfizer	Antihypertensive/diuretic	4-C	6-13-80
18-067	Cinoxacin	Cinobac	Capsule	Eli Lilly	Treatment of initial and recurrent urinary tract infections due to susceptible organisms	1-C-U	6-13-80
18-153	Beclomethasone Dipropionate	Beclovent	Aerosol Inhaler	Glaxo Labs	Corticosteroid for control of symptoms of bronchial asthma	5-C-MU	6-24-80
18-006	Meclofenamate Sodium	Meclomen	Capsule	Parke Davis	Relief of symptoms of acute & chronic rheumatoid arthritis & osteoarthritis	1-C-U	6-25-80

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
July 1980							
18-248	Oxytocin Injection, USP	None	Injection	Invenex Labs	For the medical induction of labor	5-C	7-9-80
18-372	5% Dextrose Injection, USP	None	I.V. Solution (in semi-rigid container)	Cutter Labs	Fluid & caloric replenishment	5-C-P	7-9-80
18-399	5% Dextrose and 0.2% Sodium Chloride, USP	None	I.V. Solution (in semi-rigid container)	Cutter Labs	Fluid, electrolyte & caloric replenishment	5-C-P	7-9-80
18-400	5% Dextrose and 0.45% Sodium Chloride, USP	None	I.V. Solution (in semi-rigid container)	Cutter Labs	Fluid, electrolyte & caloric replenishment	5-C-P	7-9-80
50-537	Clindamycin Phosphate	Cleocin T	Topical Solution	Upjohn	Treatment of acne vulgaris	3-C	7-9-80
18-376	2.5% Dextrose and 0.9% Sodium Chloride, USP	None	I.V. Solution (in semi-rigid container)	McGaw Labs	Fluid, electrolyte & caloric replenishment	5-C-P	7-11-80
18-386	10% Dextrose and 0.2% Sodium Chloride, USP	None	I.V. Solution (in semi-rigid container)	McGaw Labs	Fluid, electrolyte & caloric replenishment	5-C-P	7-11-80
18-417	Lactated Ringer's Injection, USP	None	I.V. Solution (in semi-rigid container)	Cutter Labs	Fluid & electrolyte replenishment	5-C-PU	7-11-80
18-069	Oxamniquine	Vansil	Capsule	Pfizer	Treatment of Schistosoma mansoni	1-A-NSU	7-23-80
18-140	Lorazepam	Ativan	Injection	Wyeth Labs	Presurgical anti-anxiety agent	3-C	7-25-80

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFI-CATION	APPROVAL DATE
July 1980 (Cont.)							
18-249	Sodium Lactate Injection, USP, 1/6 Molar	None	I.V. Solution (in flexible container)	Abbott	Fluid & electrolyte replenishment	5-C-MP	7-25-80
August 1980							
18-252	Multiple Electrolytes	Isolyte S	I.V. Solution (in semi-rigid container)	McGaw Labs	Fluid & electrolyte replenishment	5-C-MP	8-5-80
18-312	Calcifediol	Calderol	Capsule	Upjohn	Management of metabolic bone disease associated with chronic renal failure in patients undergoing renal dialysis	1-C	8-5-80
18-380	0.45% Sodium Chloride	None	Irrigation Solution (in flexible container)	Abbott	Irrigation	5-C-P	8-5-80
50-528	Cefadroxil Monohydrate	Duricef	Tablet	Mead Johnson	Semi-synthetic cephalosporin antibiotic for treatment of susceptible organisms	3-C-U	8-6-80
18-274	Multiple Electrolytes with 5% Dextrose	Isolyte with 5% Dextrose	I.V. Solution (in semi-rigid container)	McGaw Labs	Fluid, electrolyte & caloric replenishment	5-C-MPU	8-11-80
18-280	Ritodrine HCl	Yutopar	Injection & Tablet	Duphar Labs	Management of preterm labor	1-A	8-24-80
18-406	0.9% Sodium Chloride	PhysioSol	Irrigation Solution (in flexible container)	Abbott	Irrigation	5-C-P	8-25-80
17-980	Mazindol	Mazanor	Tablet	Wyeth Labs	Anorexigenic agent	5-C-U	8-28-80

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
September 1980							
18-379	Dextrose and Electrolytes	Inpersol with 1.5% or 4.5% Dextrose	Irrigation Solution (in flexible container)	Abbott	Peritoneal dialysis	5-C-PU	9-3-80
18-164	Naproxen Sodium	Anaprox	Tablet	Syntex	Non-steroidal anti-inflammatory agent	5-C-MU	9-4-80
18-268	5% Dextrose, Sodium Chloride and Potassium Chloride	None	I.V. Solution (in semi-rigid container)	McGaw Labs	Fluid, electrolyte & caloric replenishment	5-C-MPU	9-5-80
50-527	Cefadroxil Monohydrate	Duricef	Oral Suspension	Mead Johnson	Antibiotic (semi-synthetic cephalosporin)	3-C-U	9-12-80
17-659	Metaproterenol Sulfate	Alupent	Inhalation Solution	Boehringer-Ingelheim	Bronchodilator	3-B-U	9-18-80
18-075	Potassium Chloride	Timcap	Controlled Release Capsule	Berlex Labs	Potassium replenishment	5-C	9-18-80
18-021	Amoxapine	Asendin	Tablet	Lederle	Antidepressant	1-C	9-22-80

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
October 1980							
18-269	Multiple Electrolytes with 5% Dextrose	Isolyte E	I.V. Solution (in semi-rigid container)	McGaw Labs	Fluid, electrolyte & caloric replenishment	5-C-MPU	10-3-80
18-270	Multiple Electrolytes with 5% Dextrose	Isolyte M	I.V. Solution (in semi-rigid container)	McGaw Labs	Fluid, electrolyte & caloric replenishment	5-C-MPU	10-3-80
18-271	Multiple Electrolytes with 5% Dextrose	Isolyte R	I.V. Solution (in semi-rigid container)	McGaw Labs	Fluid, electrolyte & caloric replenishment	5-C-MPU	10-3-80
18-273	Multiple Electrolytes with 5% Dextrose	Isolyte H	I.V. Solution (in semi-rigid container)	McGaw Labs	Fluid, electrolyte & caloric replenishment	5-C-MPU	10-3-80
18-238	Potassium Chloride	Micro-K Extencaps	Controlled Release Capsule	A.H. Robins	Potassium replenishment	3-C	10-17-80
50-542	Amoxicillin	Amoxil	Chewable Tablet	Beecham Labs	Antibiotic (semi-synthetic)	3-C-U	10-21-80
18-236	Zomepirac Sodium	Zomax	Tablet	McNeil Labs	For relief of mild to moderately severe pain	1-B-U	10-28-80
18-202	Aminoglutethimide	Cytadren	Tablet	Ciba-Geigy	Suppression of adrenal function in selected patients with Cushing's Syndrome	6-B-U	10-29-80
50-502	Sisomicin Sulfate	Siseptin	Injection	Schering	Antibiotic (aminoglycoside)	1-C-U	10-29-80
18-191	Pseudoephedrine Sulfate	Afrinol Repetabs	Controlled Release Tablet	Schering	Decongestant	5-C-U	10-30-80

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
November 1980							
18-101	Amantadine HCl	Symmetrel	Tablet	Endo Labs	Anti-Parkinsonian and antiviral agent	3-C-U	11-3-80
18-261	Oxytocin	Pitocin	Injection	Parke-Davis	Medical induction of labor	5-C	11-19-80
17-812	Lithium Carbonate, USP	None	Capsule	Philips Roxane Labs	Treatment of manic episodes of bipolar disorder	5-C	11-26-80
18-353	Metronidazole HCl	Flagyl I.V.	Injection	Searle	Treatment of serious infections due to susceptible anaerobic bacteria	3-B-U	11-28-80
18-429	Crystalline Amino Acid Solution - Renal Formula	Aminosyn-RF	I.V. Solution	Abbott	Source of protein in patients with potentially reversible acute renal failure, unable to eat, with limited access to dialysis	3-C-U	11-28-80
December 1980							
17-543	Maprotiline HCl	Ludiomil	Tablet	Ciba-Geigy	Anti-depressant	1-C	12-1-80
18-237	Calcium Heparin	Calciparine	Injection	Choay Labs	Anticoagulant	2-C-M	12-12-80
18-539	Purified Pork and Beef Insulin Injection	Regular Iletin II Pork and Beef Suspension	Injection	Lilly Research	Diabetes Mellitus	3-C-U	12-12-80
18-540	Purified Pork and Beef Insulin Suspension	Lente Iletin II Pork and Beef Suspension	Injection	Lilly Research	Diabetes Mellitus	3-C-U	12-12-80
18-541	Isophane Purified Pork and Beef Insulin Suspension	NPH Iletin II Pork and Beef Suspension	Injection	Lilly Research	Diabetes Mellitus	3-C-U	12-12-80

NDAs APPROVED

NDA#	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFI-CATION	APPROVAL DATE
December 1980 (Cont.)							
18-542	Protamine, Zinc Purified Pork and Beef Insulin Suspension	Protamine, Zinc and Iletin Pork and Beef Suspension	Injection	Lilly Research	Diabetes Mellitus	3-C-U	12-12-80
18-555	Ritodrine HCl	Yutopar	Tablets	Merrell-National	Premature labor	5-C-M	12-12-80
18-580	Ritodrine HCl	Yutopar	Injection	Merrell-National	Premature labor	5-C-M	12-12-80
50-541	Tobramycin	Tobrex	Ophthalmic Solution	Alcon Labs	Antibiotic (aminoglycoside)	3-C-U	12-12-80
18-388	0.2% and 0.4% Lidocaine in 5% Dextrose Solution	None	Injection	Abbott	Cardiac arrhythmia	4-C-P	12-14-80
50-520	Bacampicillin HCl	Spectrobid	Tablets	Pfizer	Antibiotic (semi-synthetic)	1-C-M	12-22-80
18-421	Lithium Citrate	Lithium Citrate	Syrup	Philips Roxane Labs	Anti-manic agent	5-C	12-23-80
17-854	Metoclopramide	Reglan	Tablets	A. H. Robins	Motility stimulant	3-C-M	12-30-80

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
January 1981							
18-449	Intravenous Fat Emulsion	Intralipid 20%	I.V. Emulsion	Cutter Labs	Parenteral nutrition	3-C-MU	1-23-81
50-536	Erythromycin	Eryc	Capsule (containing enteric-coated pellets)	Faulding Medical	Antibiotic	3-C-MU	1-26-81
18-375	Hexachlorophene	Turgex	Aerosol foam	Xttrium	Bacteriostatic surgical skin cleanser	3-C	1-29-81
18-418	Ergoloid mesylates	Hydergine	Oral liquid	Sandoz	Dementia	3-C	1-30-81
February 1981							
18-543	Lidocaine Hydrochloride, U.S.P.	None	Sterile Powder (for dilution in I.V. solution)	International Medication Systems	Acute management of ventricular arrythmias	3-B	2-9-81
18-107	Technetium 99m Medronate	MDP-Squibb	Injection	E.R. Squibb & Sons	Diagnostic for bone imaging	5-C-U	2-17-81
18-321	Technetium 99m Oxidronate	Osteoscan-HDP	Injection	Procter & Gamble	Diagnostic for bone imaging	5-C-U	2-18-81
18-173	Cyclothiazide	Fluidil	Tablet	Adria Labs	Diuretic/Anti-hypertensive	3-C	2-24-81
18-535	Metolazone	Diulo	Tablet	Searle	Diuretic/Anti-hypertensive	5-C	2-24-81
18-163	Temazepam	Restoril	Capsule	Sandoz	Insomnia	1-C	2-27-81

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
March 1981							
50-547	Cefotaxime sodium	Claforan	Injection	Hoechst-Roussel	Antibiotic (semi-synthetic cephalosporin)	1-S	3-11-81
18-179	Diazepam	Valrelease	Slow-release capsule	Hoffmann-LaRoche	Anti-anxiety agent	3-C	3-12-81
18-462	Ringer's Irrigation, U.S.P.	None	Irrigation solution (in flexible container)	Abbott	Irrigation	5-C	3-21-81
17-807	Iron Dextram Injection, U.S.P.	Proferdex	Injection	Fisons	Iron deficiency	5-C	3-26-81
18-397	Chlorpheniramine maleate/ pseudoephedrine sulfate	Chlor-Trimeton Repetabs	Long acting Tablets	Schering	Antihistamine/nasal decongestant	5-C	3-31-81

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	[illegible]
April 1981							
18-343	Captopril	Capoten	Tablet	E.R. Squibb & Sons	Antihypertensive agent (for those who have failed to respond to previous multidrug regimens)	1-B-MU	4-[illegible]
18-461	Lidocaine Hydrochloride and 5% Dextrose Injection	None	I.V. Solution (in flexible container)	Travenol	Acute management of ventricular arrhythmias	3-C-P	4-[illegible]
May 1981							
17-559	Albuterol	Proventil	Oral inhalation aerosol	Schering	Relief of bronchospasm in patients with reversible obstructive airway disease	1-B-MSU	5-[illegible]
18-473	Albuterol	Ventolin	Oral inhalation aerosol	Glaxo, Inc.	Relief of bronchospasm in patients with reversible obstructive airway disease	5-B-MSU	5-[illegible]
18-014	Dopamine Hydrochloride	None	Injection	International Medication Systems	Correction of hemodynamic imbalances present in the treatment of shock (an inotropic agent increasing cardiac output)	5-C	5-[illegible]

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROV DATE
18-132	Dopamine Hydrochloride	None	Injection	Abbott	Correction of hemodynamic imbalance present in the treatment of shock (an inotropic agent increasing cardiac output)	5-C	5-19-
18-139	Dopamine Hydrochloride	Dopastat	Injection	Parke-Davis	Correction of hemodynamic imbalances present in the treatment of shock (an inotropic agent increasing cardiac output)	5-C	5-19-
18-242	Sulfamethoxazole and trimethoprim	SMZ/TMP	Tablet	Brocraft	Treatment of urinary tract infection due to susceptible organisms. Also for the treatment of documented *Pneumocystis carinii* pneumonitis	5-C-U	5-19-
18-267	Furosemide Injection, U.S.P.	None	Injection	Elkins-Sinn, Inc.	Diuretic agent	5-C-U	5-19-
18-197	Ibuprofen	Rufen	Tablet	Boots	Relief of signs and symptoms of rheumatoid arthritis and osteoarthritis. Also for the relief of mild to moderate pain.	5-C-M	5-21-

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROV/ DATE
17-675	Bethanidine Sulfate	Tenathan	Tablet	A.H. Robins	Antihypertensive	1-C-M	5-29-8
18-009	Saralasin Acetate	Sarenin	Infusion	Norwich-Eaton	Detection of angiotensin II - dependent hypertension	1-C-RU	5-29-8
18-290	Secretin	Secretin-Kabi	Injection	Kabi Group, Inc.	1) Diagnosis of pancreatic exocrine disease 2) Diagnosis of Gastrinoma Zollinger-Ellison Syndrome) 3) As an adjunct in obtaining disquamated pancreatic cells for cytopathologic examination	1-B-M	5-29-8
June 1981							
18-363	Hexachlorophene	Hexascrub	Brush-sponge	Professional Disposables, Inc.	Bacteriostatic surgical skin cleanser	5-C-P	6-2-8
18-533	Ketoconazole	Nizoral	Tablet	Janssen	Antifungal agent	1-A-U	6-12-8
18-590	5% Dextrose and 0.9% Sodium Chloride Injection, USP	None	I.V. Solution (in semi-rigid container)	Cutter Labs	Fluid, electrolyte & caloric replenishment	5-C-PU	6-17-8
18-592	0.9% Sodium Chloride Injection, USP	None	I.V. Solution (in semi-rigid container)	Cutter Labs.	Fluid & electrolyte replenishment	5-C-PU	6-17-8

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPR. DATE
18-503	0.45% Sodium Chloride Injection, USP	None	I.V. Solution (in semi-rigid container)	Cutter Labs.	Fluid & electrolyte replenishment	5-C-PU	6-17
18-504	10% Dextrose Injection, USP	None	I.V. Solution (in semi-rigid container)	Cutter Labs.	Fluid & caloric replenishment	5-C-PU	6-17
18-505	Sterile Water for Injection, USP	None	I.V. Solution (in semi-rigid container)	Cutter Labs.	For the aseptic preparation of parenteral solutions	5-C-PU	6-17
18-501	5% Dextrose and 0.3% Sodium Chloride Injection, USP	None	I.V. Solution (in semi-rigid container)	Cutter Labs.	Fluid, electrolyte & caloric replenishment	5-C-PU	6-22
18-374	Sulfamethoxazole and Trimethoprim	Bactrim	Infusion	Hoffman-LaRoche	Treatment of *Pneumocystis carinii* pneumonitis and shigellosis. Also for the treatment of urinary tract infections due to susceptible organisms.	3-B-MU	6-23
18-452	Sulfamethoxazole and Trimethoprim	Septra	Infusion	Burroughs-Wellcome	Treatment of *Pneumocystis carinii* pneumonitis and shigillosis. Also for the treatment of urinary tract infections due to susceptible organisms.	3-C-MU	6-23

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NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
18-524	Prompt Purified Beef Insulin Zinc Suspension	Purified Semilente Beef Insulin	Injection	E.R. Squibb	Diabetes Mellitus	5-C-U	6-29-8
18-525	Purified Beef Insulin Zinc Suspension	Purified Lente Beef Insulin	Injection	E.R. Squibb	Diabetes Mellitus	5-C-U	6-29-8
18-526	Isophane Purified Beef Insulin Suspension	Purified NPH Beef Insulin	Injection	E.R. Squibb	Diabetes Mellitus	5-C-U	6-29-8
18-527	Extended Purified Beef Insulin Zinc Suspension	Purified Ultralente Beef Insulin	Injection	E.R. Squibb	Diabetes Mellitis	5-C-U	6-29-8
18-528	Purified Pork Insulin Injection	Purified Regular Pork Insulin	Injection	E.R. Squibb	Diabetes Mellitis	5-C-U	6-29-8

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
July 1981							
18-398	Dopamine Hydrochloride	None	Injection	Elkins-Sinn	Correction of hemodynamic imbalances present in the treatment of shock (an inotropic agent increasing cardiac output)	5-C	7-6-81
18-115	Phenylpropanolamine HCl and Chlorpheniramine Maleate	Triaminic-12	Sustained Release Tablet	Dorsey Labs	Nasal decongestant/anti-histamine	5-C-U	7-23-8
18-310	Isosulfan Blue	Lymphazurin	Injection	Hirsch Industries	Contrast agent for the delineaion of lymphatic vessels	1-C-U	7-29-8
18-623	Isophane Purified Pork Insulin Suspension	Protaphane NPH Pork Suspension	Injection	Novo Labs	Diabetes Mellitus	5-C-U	7-30-8

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVA DATE
August 1981							
18-485	Verapamil	Isoptin	Injection	Knoll Pharm.	Supraventricular tachy-arrythmias	1-[redacted]	8-12-81
18-076	Iodoxamate Meglumine	Cholovue	Injection	E.R. Squibb & Sons	Radiopaque diagnostic agent for cholecystochol-angiography	2-C	8-14-81
18-077	Iodoxamate Meglumine	Cholovue	Infusion	E.R. Squibb & Sons	Radiopaque diagnostic agent for cholecystochol-angiography	3-C	8-14-81
18-499	5% Dextrose in Lactated Ringer's Injection	None	I.V. Solution (in semi-rigid container)	Cutter Labs	Fluid, electrolyte and caloric repienishment	5-C	8-14-81
18-240	Atenolol	Tenormin	Tablet	ICI Americas	Antihypertensive agent (beta-blocker)	1-C-H	8-19-81
18-423	Chlorhexidine Gluconate	Hibiclens	Brush-Sponge	ICI Americas	Bacteriostatic surgical skin cleanser	5-C	8-27-81
18-487	Furosemide	None	Tablet	Mylan	Diuretic agent	5-C-U	8-27-81
18-389	Methyldopa	Aldomet	Oral Suspension	Merck Sharp & Dohme	Antihypertensive agent	3-C-U	8-28-81

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPR DA
September 1981							
18-450	Nitroprusside Sodium	Nitropress	Infusion (powder for reconstitution	Abbott Labs.	Immediate reduction of blood pressure during hypertensive crises.	5-C	9-8
50-549	Mezlocillin Sodium	Mezlin	Injection	Miles Pharm.	Antibiotic (semi-synthetic broad spectrum penicillin)	1-C-U	9-2
17-736	Halazepam	Paxipam	Tablet	Schering Corporation	Anti-anxiety agent	1-C	9-2
18-148	Flunisolide	Nasalide	Nasal Solution	Syntex	Relief of symptoms of seasonal or perennial rhinitis	1-B-UR	9-2
18-521	Beclomethasone Dipropionate	Vancenase	Aerosol, Nasal Inhaler	Schering Corporation	Relief of symptoms of seasonal or perennial rhinitis in those cases poorly responsive to convential treatment	3-B-UR	9-2
18-537	Nitroglycerin	Tridil	Injection	American Critical Care	Treatment of hypertension & for the induction of controlled hypotension during surgery	3-B	9-3
18-584	Beclomethasone Dipropionate	Beconase	Aerosol, Nasal Inhaler	Glaxo, Incorporated	Relief of symptoms of seasonal or perennial rhinitis in those cases poorly responsive to conventional therapy	5-C-UR	9-3

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
October 1981							
18-200	Amiloride HCl	Midamor	Tablet	Merck Sharp & Dohme	Antihypertensive agent	[illegible]	10-5-81
18-201	Amiloride HCl and Hydrochlorothiazide	Moduretic	Tablet	Merck Sharp & Dohme	Antihypertensive/Diuretic agent	4-C	10-5-81
18-336	Sodium Chloride, Potassium Chloride, Magnesium Sulfate, Sodium Phosphate, & Potassium Phosphate	Tis-u-Sol	Irrigation Solution (in plastic container	Travenol	Irrigation	5-C-MPU	10-6-81
18-531	Nitroglycerin	None	Injection	Abbott Labs	Treatment of hypertension & for the induction of controlled hypotension during surgery	5-C	10-6-81
50-550	Moxalactam Disodium	Moxam	Injection	Eli Lilly	Antibiotic	[illegible]	10-6-81
18-276	Alprazolam	Xanax	Tablet	Upjohn	Anti-anxiety agent	1-C	10-16-81
18-484	Alprostadil (PGE_1)	Prostin VR Pediatric	Injection	Upjohn	Palliative therapy to maintain the ductus arteriosus in neonates	[illegible]	10-16-81

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
18-569	Furosemide, U.S.P.	None	Tablet	Cord Labs	Diuretic agent	5-C-U	10-19-81
18-588	Nitroglycerin	Nitrostat	Injection	Warner-Lambert	Treatment of hypertension & for the induction of controlled hypotension during surgery	5-C	10-26-81
18-614	Intravenous Fat Emulsion	Liposyn 20%	I.V. Emulsion	Abbott Labs	Parenteral nutrition	3-C-MU	10-26-81
18-469	Sodium Chloride, Potassium Chloride, Sodium Phosphate, Sodium Bicarbonate, Hydrochloric Acid and/or Sodium Hydroxide, Calcium Chloride Magnesium Chloride, Dextrose & Glutathione	BSS Plus	Intraocular Irrigation	Alcon Labs	Irrigating solution during intraocular surgical procedures	3-C	10-28-81
18-557	Sulfadoxine and Pyrimethamine	Fansidar	Tablet	Hoffmann-LaRoche	Antimalarial	1,4-B-U	10-28-81
18-460	Sodium Acetate, Sodium Chloride, Calcium Chloride Magnesium Chloride, Sodium Lactate, Sodium Bisulfite & Dextrose	Dialyte with Dextrose	Dialysis solution (in plastic container)	American McGaw	Peritoneal dialysis	3-C-PU	10-29-81
18-517	Metronidazole	None	Tablet	Zenith Labs	Antiprotozoal (Trichomonas)	5-C-U	10-30-81
18-333	Sucralfate	Carafate	Tablet	Marion	Short term treatment of duodenal ulcer	1-B	10-31-81

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
November 1981							
18-440	Multiple vitamins (A,B_1, B_2,B_6,B_{12},C,D,E, Niacin, Panothenic acid, Biotin and Folic Acid)	M.V.C. 9 + 3	Injection	Lypho-Med	Vitamin dificiencies in patients receiving parenteral nutrition	5-C	11-6-81
18-498	Amcinonide	Cyclocort	Topical Ointment	Lederle	Relief of inflammatory manifestations of corticosteroid-responsive dermatoses	3-C-U	11-13-81
18-017	Timolol maleate	Blocadren	Tablet	Merck Sharp and Dohme	1) antihypertensive agent 2) to reduce cardiovascular mortality in patients who have survived the acute phase of a myocardial infarction.	3-A	11-25-81
50-555	Tobramycin	Tobrex	Ophthalmic Ointment	Alcon	Antibiotic (aminoglycoside)	3-C-U	11-25-81
18-571	Terbutaline sulfate, U.S.P.	Brethine	Injection	Ciba-Geigy	Bronchodilator	5-C	11-30-81

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
December 1981							
18-061	Timolol Maleate and Hydrochlorothiazide	Timolide	Tablet	Merck Sharp & Dohme	Antihypertensive/Diuretic	4-C	12-11-81
18-281	Carbamazepine	Tegretol	Chewable Tablet	Ciba-Geigy	Epilepsy and trigeminal neuralgia	3-C-U	12-14-81
18-422	Gemfibrozil	Lopid	Capsule	Warner-Lambert	Antihyperlipidemic (Type IV)	1-C	12-21-81
18-045	Estramustine Phosphate Sodium	Emcyt	Capsule	Hoffmann-LaRoche	Antineoplastic agent	1-C	12-24-81
18-207	Trazodone Hydrochloride	Desyrel	Tablet	Mead Johnson	Anti-depressant	1-C	12-24-81
18-296	Ceruletide	Tymtran	Injection	Adria	Diagnostic adjunct in oral cholecystography	1-C-M	12-24-81
18-657	Metronidazole	Flagyl	I.V. Solution (in flexible container)	Searle	Anti-infective	5-C-P	12-24-81
18-401	Buprenorphine Hydrochloride	Buprenex	Injection	Eaton	Narcotic analgesic	1-C	12-29-81
50-545	Piperacillin Sodium	Pipracil	Injection	Lederle	Antibiotic (semi-synthetic aminobenzyl-penicillin)	1-B-U	12-29-81
18-160	Ethynodiol Diacetate and Ethinyl Estradiol	Demulen 1/35 - 28 Day	Tablet	Searle	Oral Contraceptive	3-C	12-30-81
18-168	Ethynodiol Diacetate and Ethinyl Estradiol	Demulen V35 - 21 Day	Tablet	Searle	Oral Contraceptive	3-C	12-30-81

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
18-304	Bupivacaine Hydrochloride	Sensorcaine	Injection	Astra	Local Anesthetic	5-C-U	12-30-81
50-548	Cephradine	Velosef	Tablet	E.R. Squibb & Sons	Antibiotic (semi-synthetic cephalosporin)	3-C	12-30-81
18-482	Nifedipine	Procardia	Capsule	Pfizer	Anti-anginal	1-S-N	12-31-81

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
January 1982							
18-621	Nitroglycerin	Nitro-bid	Injection	Marion Labs	Treatment of hypertension & for the induction of controlled hypotension during surgery	5-C	1-5-82
18-354	Norethindrone & Ethinyl Estradiol	Ortho-Novum 10/11	Tablet	Ortho	Oral Contraceptive	3-C	1-11-82
18-272	Technetium Tc 99m Gluceptate	TechneScan Gluceptate Kit	Injection	Mallinckrodt	Diagnostic for kidney and brain imaging	5-C-U	1-27-82
18-110	Thallous Chloride Tl 201	None	Injection	Diagnostic Isotopes	Radiodiagnostic for myocardial perfusion imaging	5-C-U	1-29-82
18-558	Lithium Carbonate, USP	None	Tablet	Philips Roxane	Treatment of manic episodes of Bipolar Disorder	5-C	1-29-82

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
February 1982							
17-707	Pentetate Indium Disodium In 111	MPI Indium DTPA In 111	Intrathecal Injection	Medi-Physics	Radiodiagnostic for cisternography	1-C	2-18-82
18-494	Lactated Ringer's Irrigation	None	Irrigation Solution (in plastic container)	Travenol	Irrigation	5-C	2-19-82
18-495	Ringer's Irrigation	None	Irrigation Solution (in plastic container)	Travenol	Irrigation	5-C	2-19-82
18-497	0.45% Sodium Chloride Solution, U.S.P.	None	Irrigation Solution (in plastic container)	Travenol	Irrigation	5-C	2-19-82
18-508	Sodium Chloride, Potassium Chloride, Magnesium Sulfate, Sodium Phosphate & Potassium Phosphate	Tis-u-Sol	Irrigation Solution (in plastic container)	Travenol	Irrigation	5-C	2-19-82
18-522	1.5% Aminoacetic Acid Irrigation, U.S.P.	None	Irrigation Solution (in plastic container)	Travenol	Irrigation	5-C	2-19-82
18-523	0.25% Acetic Acid Irrigation, U.S.P.	None	Irrigation Solution (in plastic container)	Travenol	Irrigation	5-C	2-19-82
18-551	Potassium Iodide	None	Solution	Philips Roxane	Thyroid blocking in radiation emergency	5-C	2-19-82
18-185	Indomethacin	Indocin SR	Sustained release Capsule	Merck Sharp & Dohme	Non-steroidal anti-inflammatory agent	3-C-M	2-23-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
18-578	Silver Sulfadiazine	None	Topical Cream	Travenol	Topical antibacterial	5-C-U	2-25-82
18-420	Furosemide, U.S.P.	None	Injection	Parke-Davis	Diuretic agent	5-C-U	2-26-82
18-608	Multiple Electrolytes	Cardioplegic Solution	Solution (in flexible container)	Abbott	To induce cardiac arrest during open heart surgery	3-A	2-26-82
18-660	Fat Emulsion	10% Travamulsion	I.V. Emulsion	Travenol	Parenteral nutrition	5-C-U	2-26-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
March 1982							
18-620	Metronidazole	None	Tablet	Premo	Antiprotozoal (Trichomonas)	5-C	3-4-82
18-593	Verapamil	Isoptin	Tablet	Knoll	Anti-anginal	3-B	3-8-82
18-327	Xenon Xe 133 Gas	None	Gas for Inhalation	Mallinckrodt	Radiodiagnostic	5-C-U	3-9-82
18-520	Miconazole Nitrate	Monistat	Vaginal suppository	Ortho	Treatment of vulvovaginal candidiasis	3-C	3-15-82
18-467	Technetium Tc 99m Disofenin	Hepatolite kit	Injection	New England Nuclear	Diagnostic for hepato-biliary imaging	1-B	3-16-82
18-361	Clomiphene Citrate, U.S.P.	Serophene	Tablet	Plantex-U.S.A.	Treatment of ovulatory failure in patients desiring pregnancy	5-C	3-22-82
18-506	Azatadine maleate and Pseudoephedrine sulfate, U.S.P.	Trinalin	Long acting Tablets	Schering	Antihistamine/Decongestant	4-C	3-23-82
18-561	70% Dextrose Injection, U.S.P.	None	I.V. Solution (in flexible container)	Abbott	Fluid and caloric replenishment	5-C-U	3-23-82
18-562	40% Dextrose Injection, U.S.P.	None	I.V. Solution (in flexible container)	Abbott	Fluid and caloric replenishment	5-C-U	3-23-82
18-563	50% Dextrose Injection, U.S.P.	None	I.V. Solution (in flexible container)	Abbott	Fluid and caloric replenishment	5-C-U	3-23-82
18-564	20% Dextrose Injection, U.S.P.	None	I.V. Solution (in flexible container)	Abbott	Fluid and caloric replenishment	5-C-U	3-23-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
18-629	5% Dextrose, 0.33% Sodium Chloride and Potassium Chloride	None	I.V. Solution (in flexible container)	Travenol	Fluid, electrolyte and caloric replenishment	5-C	3-23-82
50-556	Bacampicillin HCl	Spectrobid	Oral Suspension	Pfizer	Antibiotic (semi-synthetic penicillin)	3-C-U	3-23-82
18-152	Lithium Carbonate	Eskalith	Controlled release tablet	Smith Kline & French	Anti-manic agent	5-C	3-29-82
18-586	Desoximetasone	Topicort	Topical Gel	Hoechst-Roussel	Relief of inflammatory manifestations of corticosteroid-responsive dermatoses	3-C-U	3-29-82
18-604	Acyclovir	Zovirax	Ointment	Burroughs Wellcome	Management of herpes genitalis	1-B-U	3-29-82
18-029	Methylphenidate HCl	Ritalin	Sustained release tablet	Ciba Geigy	Attention deficit disorders and narcolepsy	5-C-U	3-30-82
18-514	Hydrocortisone Butyrate	Locoid	Topical Cream	Gist-Brocades	Relief of inflammatory manifestations of corticosteroid-responsive dermatoses	2-C-U	3-31-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
April 1982							
18-232	Aminophylline, U.S.P.	Somophyllin	Rectal solution	Fisons	For relief and/or prevention of symptoms from asthma & reversible bronochospasm	5-C-U	4-2-82
18-147	Piroxicam	Feldene	Capsule	Pfizer	Nonsteroidal anti-inflammatory, analgesic, antipyretic for relief of symptoms of rheumatoid and osteoarthritis	1-C-U	4-6-82
18-250	Benoxaprofen	Oraflex	Tablet	Eli Lilly	Nonsteroidal anti-inflammatory, analgesic, antipyretic for relief of symptoms of rheumatoid and osteoarthritis	1-C-U	4-19-82
18-445	Diflunisal	Dolobid	Tablet	Merck Sharp & Dohme	Nonsteroidal anti-inflammatory, analgesic, antipyretic for relief of symptoms of osteoarthritis and mild to moderate pain	1-B	4-19-82
18-405	Norethindrone Acetate, U.S.P.	Aygestin	Tablet	Ayerst	Progestational agent for treatment of secondary amenorrhea, endometriosis & abnormal uterine bleeding due to hormonal imbalance	5-C	4-21-82
18-609	Heparin Sodium in 0.9% Sodium Chloride Injection	None	I.V. Solution (in plastic container)	Travenol	Anticoagulant	5-C-P	4-28-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
May 1982							
18-582	Amino Acids, Glycerol and Electrolytes	PeriphrAmine	Injection	American McGaw	Parenteral nutrition	3-C-U	5-6-82
17-853	Albuterol Sulfate	Proventil	Tablet	Schering	Relief of bronchospasm in patients with reversible obstructive airway disease	3-C	5-7-82
17-961	Streptozocin	Zanosar	Injection (sterile power for re-constitution)	Upjohn	Metastatic islet cell carcinoma of the pancreas	1-C	5-7-82
18-662	Isotretinoin	Accutane	Capsule	Hoffmann-LaRoche	Treatment of severe recalcitrant cystic acne	1-A	5-7-82
18-668	Levonorgestrel & Ethinyl Estradiol	Nordette	Tablet	Wyeth	Oral contraceptive	3-C	5-10-82
18-369	Furosemide	None	Tablet	Chelsea Labs	Diuretic agent	5-C	5-14-82
18-669	Niclosamide	Niclocide	Chewable Tablet	Miles Pharmaceuticals	Anthelmintic	1-A-U	5-14-82
17-944	Dimercaptosuccinic Acid	MPI DMSA Kidney Reagent (Technetium Tc 99m Succimer Kit)	Injection	Medi-Physics	Combined with Technetium Tc 99m to form a radio-diagnostic in evaluating renal parenchymal disorders	1-C-U	5-18-82
18-598	Sulphamethoxazole & Trimethoprim	None	Tablet	Premo	Treatment of urinary tract infections due to susceptible organisms	5-C	5-19-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
18-512	Sorbitol Irrigation	None	Irrigation Solution (in plastic bottles)	Travenol	Urologic Irrigation	5-C-U	5-27-82
18-671	Sodium Iodide I^{123}	None	Capsule	Benedict Nuclear Pharmaceuticals	Radiodiagnostic in evaluating thyroid function	5-C-U	5-27-82
18-596	Cromolyn Sodium, U.S.P.	Intal	Nebulizer Solution	Fisons	Management of bronchial asthma	3-B	5-28-82
18-667	Furosemide	None	Injection	Abbott	Diuretic agent	5-C	5-28-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
June 1982							
18-519	Citric Acid, Sodium Carbonate, Magnesium Oxide	Irrigating Solution G	Irrigation Solution (in plastic bottle)	Travenol	Dissolution of calculi within the urinary tract	5-C	6-21-82
18-632	Sterile water for Injection, U.S.P.	None	I.V. Solution (in plastic container)	Travenol	Vehicle for the asceptic preparation of parenteral solutions	5-C-PU	6-30-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
July 1982							
18-439	Multiple vitamins	MVC Plus	Injection	Ascot	Vitamin deficiencies in patients receiving parenteral nutrition	5-C	7-13-82
18-655	Disopyramide Phosphate	Norpace CR	Controlled Release Capsule	Searle	Cardiac arrythmias	3-C	7-20-82
18-670	Furosemide	None	Injection	Wyeth	Diuretic agent	5-C	7-20-82
18-782	Levonorgestrel & Ethinyl Estradiol	Nordette-28	Tablet	Wyeth	Oral contraceptive	5-C	7-21-82
18-118	Digoxin	Lanoxicaps	Capsule (solution in soft gelatin)	Burroughs Wellcome	Heart failure, atrial fibrillation and flutter, paroxysmal atrial tachycardia	3-C	7-26-82
18-649	Theophylline in 5% Dextrose Injection	None	I.V. Solution (in plastic container)	Travenol	Relief and/or prevention of symptoms from asthma and reversible bronchospasm	4-C	7-26-82
18-415	Furosemide	None	Tablet	Lederle	Diuretic agent	5-C	7-27-82
18-581	Sodium Nitroprusside	None	Injection	Elkins-Sinn	For immediate reduction of blood pressure in hypertensive crises	5-C	7-28-82
18-507	Furosemide	None	Injection	Lypho-Med	Diuretic agent	5-C	7-30-82
18-679	Trimethoprim	None	Tablet	Biocraft	Treatment of urinary tract infections due to susceptible organisms	5-C	7-30-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
August 1982							
18-613	Malathion	Prioderm	Topical Lotion	Purdue Frederick	Treatment of head lice & their ova	1-C	8-2-82
18-335	Methylene Diphosphonic Acid	Amer-Scan MDP Kit	Injection	Amersham	Radiodiagnostic (after reconstitution with Sodium Pertechnetate Tc 99m) for skeletal imaging to detect altered osteogenesis.	5-C	8-5-82
18-676	Amino Acids	HepatAmine	Injection	American McGaw	Parenteral nutrition	3-C	8-3-82
18-674	Metronidazole	Metro I.V.	Injection	American McGaw	Treatment of serious infections caused by susceptible anaerobic bacteria	5-C	8-31-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
September 1982							
18-456	Miconazole Nitrate	Micatin	Topical Spray Powder	Ortho	Antifungal agent	3-C	9-2-82
18-457	Miconazole Nitrate	Micatin	Topical Powder	Ortho	Antifungal agent	3-C	9-2-82
18-285	Pindolol	Visken	Tablet	Sandoz	Antihypertensive agent	1-C	9-3-82
50-562	Azlocillin Sodium	Azlin	Injection	Miles	Infections caused by susceptibile strains of Pseudomonas aeruginosa	1-C	9-3-82
18-227	Etomidate	Amidate	Injection	Abbott	General anesthetic	1-C	9-7-82
18-587	Guanabenz Acetate	Wytensin	Tablet	Wyeth	Antihypertensive agent	1-C	9-7-82
18-599	Metronidazole	None	Tablet	Chelsea	Treatment of trichomoniasis and amebiasis	5-C	9-17-82
18-764	Metronidazole	None	Tablet	Danbury Pharmacal	Treatment of trichomoniasis and amebiasis	5-C	9-17-82
18-458	Pentazocine Hydrochloride & Acetaminophen	Talacen	Tablet	Winthrop	For the relief of mild to moderate pain	4-C	9-23-82
18-123	Gonadorelin Hydrochloride	Factrel	Injection (powder for reconstitution)	Ayerst	Diagnostic for evaluating hypothalamic-pituitary gonadotropic function	1-B	9-30-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
October 1982							
18-536	Xenon Xe 127	None	Gas for inhalation	Mallinckrodt	Radioactive diagnostic for the evaluation of pulmonary function and lung imaging.	1-C	10-1-82
18-658	Dextromethorphan resin complex	Delsym	Sustained Release Oral Suspension	Pennwalt	Antitussive	3-C	10-8-82
18-664	Potassium Iodide	Iostat	Tablet	Anbex, Inc.	Thyroid blocking in radiation emergency	5-C	10-14-82
18-603	Acyclovir Sodium	Zovirax	Powder for Injection	Burroughs Wellcome	Treatment of herpes simplex and herpes genitalis	2,3-A	10-22-82
18-740	Metronidazole	None	Tablet	Cord	Antiprotozoal (Trichomoniasis)	5-C	10-22-82
18-801	Sterile Water for Injection, USP	None	Injection	Abbott	For diluting or dissolving drugs for injection	5-C	10-27-82
18-802	Bacteriostatic Water for Injection, USP	None	Injection	Abbott	For diluting or dissolving drugs for injection	5-C	10-27-82
18-780	Human Insulin, Regular	Humulin R	Injection	Eli Lilly	Diabetes Mellitus	1-C	10-28-82
18-781	Human Insulin, Isophane (NPH) Suspension	Humulin N	Injection	Eli Lilly	Diabetes Mellitus	3-C	10-28-82
18-590	Aminocaproic Acid	None	Injection	Elkins-Sinn	Treatment of excessive bleeding due to hyperfibrinolysis	5-C	10-29-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
18-652	Hydrocortisone Butyrate	Locoid	Topical Ointment	Gist-Brocades	Relief of inflammatory & pruritic manifestations of corticosteroid-responsive dermatoses.	2,3-C	10-29-82
18-800	Bacteriostatic Sodium Chloride 0.9%	None	Injection	Abbott	For diluting or dissolving drugs for injection	5-C	10-29-82
18-803	Sodium Chloride 0.9% Injection	None	Injection	Abbott	For diluting or dissolving drugs for injection	5-C	10-29-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
November 1982							
18-602	Diltiazem	Cardizem	Tablet	Marion Labs	Anti-anginal	1-C	11-5-82
18-744	Dextrose & Potassium Chloride Injection	None	I.V. Solution (in plastic container)	American McGaw	Caloric and Electrolyte Replenishment	5-C-P	11-9-82
18-721	Ringer's Injection, USP	None	I.V. Solution (in plastic container)	American McGaw	Electrolyte Replenishment	5-C-P	11-9-82
18-722	Sodium Chloride & Potassium Chloride Injection	None	I.V. Solution (in plastic container)	American McGaw	Electrolyte Replenishment	5-C-P	11-9-82
18-663	Chymopapain	Chymodiactin	Injection	Smith Labs	Treatment of herniated lumbar intervertebral discs	1-A	11-10-82
17-892	Triazolam	Halcion	Tablet	Upjohn	Insomnia	1-C	11-15-82
50-551	Cefoperazone Sodium	Cefobid	Powder for Injection	Pfizer	Semisynthetic cephalosporin antibiotic	1-C	11-18-82
18-228	Etomidate	Hypnomidate	Injection	Janssen	General Anesthetic	5-C	11-23-82
18-725	Acetated Ringer's Injection	None	I.V. Solution (in plastic container)	American McGaw	Electrolyte Replenishment	5-C-P	11-29-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
December 1982							
18-799	Pralidoxime Chloride	Protopam	Injection	Ayerst	Antidote for chemical nerve agents having anticholinergic activity	3-C-P	12-13-82
18-702	Alclometasone Dipropionate	Vaderm	Topical Ointment	Schering	Relief of inflammatory & prurtic manifestations of corticosteroid-responsive dermatoses	1-C	12-14-82
18-707	Alclometasone Dipropionate	Vaderm	Topical Cream	Schering	Relief of inflammatory prurtic manifestations of corticosteroid-responsive dermatoses	3-C	12-14-82
18-298	Clemastine Fumarate & Phenylpropanolamine HCl	Tavist D	Sustained Release Tablet	Dorsey Labs	Relief of symptoms associated with allergic rhinitis	3,4-C	12-15-82
18-733	Pentazocine HCl & Naloxone HCl	Talwin Nx	Tablet	Sterling	Analgesic	4-B	12-16-82
18-751	Econazole Nitrate	Spectazole	Topical Cream	Ortho	Antifungal	1-C	12-23-82
18-681	Lactated Ringer's	None	Irrigation Solution	American McGaw	Irrigation	5-C-U	12-27-82
18-757	Sodium Cellulose Phosphate	Calcibind	Oral Powder	University of Texas, Health Science Center	Treatment of hypercalciuria Type I with recurrent calcium nephrolithiasis	1-A	12-28-82
18-104	Guanadrel Sulfate	Hylorel	Tablet	Upjohn	Antihypertensive Agent	1-C	12-29-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
18-714	Praziquantel	Biltricide	Tablet	Miles	Antischistosomal	1-A	12-29-82
18-320	Diethylpropion Hydrochloride	Tenucap	Controlled-Release Tablet	Merrell Dow	Anorectic Agent	3-C	12-30-82
18-548	Thallous Chloride	None	Injection	Amersham	Radiodiagnostic for myocardial perfusion imaging	5-C-U	12-30-82
18-748	Ciclopirox Olamine	Loprox	Topical Cream	Hoechst-Roussel	Antifungal Agent	1-C	12-30-82

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
January 1983							
18-615	Sulfamethoxazole & Trimethoprim	Sulfatrim	Oral Suspension	National Pharmaceutical Maufacturing Co	Urinary tract infections due to susceptible organisms	5-C	1-7-83
18-795	Hydrocortisone Butyrate	Locoid	Topical Cream	Dermatological Products of Texas	Relief of inflammatory & prurtic manifestations of corticosteroid-responsive dermatoses	5-C	1-7-83
18-595	Sterile Water for Injection, USP	None	I.V. Solution (in plastic container)	Travenol	Vehicle for asceptic preparation of parenteral solutions	5-C-PU	1-17-83
18-706	Ergoloid Mesylates	Hydergine	Liquid Capsules	Sandoz	Treatment of symptoms of idiopathic decline in mental capacity in the elderly	3-C	1-18-83
18-062	Albuterol Sulfate	Proventil	Syrup	Schering	Relief of bronchospasm in patients with reversible obstructive airway disease	3-C	1-19-83

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
January 1983 (Cont.)							
18-774	Nitroglycerin	Nitrol	Injection	Kremers-Urban	Treatment of hypertension & for the induction of controlled hypotension during surgery	5-C	1-19-83
18-812	Sulfamethoxazole & Trimethoprim	SMZ-TMP	Oral Suspension	Biocraft Labs	Treatment of urinary tract infections due to susceptible organisms	5-C	1-28-83
18-419	Furosemide, USP	None	Tablet	Parke-Davis	Diuretic agent	5-C	1-31-83

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
February 1983							
18-635	5% Dextrose in Ringer's Injection	None	IV Solution (in plastic container)	Travenol	Fluid, caloric & electrolyte replenishment	5-C	02-07-83
18-648	Ringer's Injection	None	IV Solution (in plastic container)	Travenol	Fluid and electrolyte replenishment	5-C	02-07-83
18-370	Furosemide	None	Tablet	Superpharm	Diurectic agent	5-C	02-10-83
18-566	5% Dextrose & 0.45% Sodium Chloride and Potassium Chloride	None	IV Solution (in plastic container)	Travenol	Fluid, caloric & electrolyte replenshment	5-C	02-10-83
18-758	Intravenous Fat Emulsion	20% Travamulsion	IV infusion	Travenol	Source of calories and essential fatty acids in in parenteral nutrition	5-C	02-15-83
18-567	5% Dextrose 0.2% Sodium Chloride and Potassium Chloride	None	IV Solution (in plastic container)	Travenol	Fluid, caloric & electrolyte replenishment	5-C	02-16-83
18-818	Metronidazole	None	Tablet	Barr Labs	Treatment of trichomiasis and amebiasis	5-C	02-16-83

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
February 1983							
18-630	0.9% Sodium Chloride and Potassium Chloride	None	IV Solution (in plastic container)	Travenol	Fluid & electrolyte replenishment	5-C	02-17-83
18-682	Tioconazole	Trosyd	Topical cream	Pfizer	Anti-fungal agent	1-C	02-18-83
18-225	Bumetanide	Bumex	Tablet	Hoffmann-LaRoche	Diurectic agent	1-C	02-28-83
18-226	Bumetanide	Bumex	Injection	Hoffmann-LaRoche	Diurectic agent	3-C	02-28-83
50-544	Netilmicin sulfate	Netromycin	Injection	Schering	Antibiotic (semi-synthetic aminoglycoside)	1-C	02-28-83

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
March 1983							
18-871	Metronidazole	Protostat	Tablets	Ortho	Trichomoniasis	5-C	3-2-83
18-723	Divalproex Sodium (Sodium valproate & valproic acid)	Depakote	Enteric-coated Tablet	Abbott Labs	Simple (petit mal) and complex absence seizures	3-C	3-10-83
18-549	Dopamine Hydrochloride	None	Injection	Bristol	Hypotension & Shock	5-C	3-11-83
18-306	Cromolyn Sodium	(No trade name established)	Nasal Solution	Fisons	Allergic rhinitis	3-B	3-18-83
18-642	Betamethasone Valerate	Beta-val	Topical Cream	Lemmon	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses	5-C-U	3-24-83
18-263	Technetium Tc 99m Albumin Colloid Kit	Microlite	Injection	New England Nuclear	Radiodiagnostic imaging agent for visualization of the reticuloendothelial (RE) system, of the liver, spleen and bone marrow	3-C	3-25-83
18-821	Metoclopramide Hydrochloride	Reglan	Syrup	AH Robins	Gastrointestinal motility stimulant	3-C	3-25-83
50-540	Cefmandole Sodium	Mandol	Injection	Eli Lilly	Antibiotic (semi-synthetic cephalosporin)	2-C	3-30-83

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
April 1983							
18-683	Nonoxynol-9	Today	Vaginal Sponge	VLI Corporation	Vaginal Contraceptive	3-C	04-01-83
18-920	Multiple Vitamins	Pediatric M.V.I	Injection	USV	Vitamin deficiencies in patients receiving parenteral nutrition	4-B	04-06-83
18-553	Propranolol HCl	Inderal	Long Acting Capsule	Ayerst	Hypertension, Angina Pectoris, Hypertrophic Subaortic Stenosis & Migraine	3-C	04-19-83
18-986	Pralidoxime Chloride	None	Injection	Survival Technology	Antidote for chemical nerve agents having anticholinergic activity	5-C-P	04-26-83

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
May 1983							
18-893	Sodium Acetate, USP	None	Injection	Abbott	Source of sodium for the treatment of hyponatremia	5-C	05-04-83
18-852	Sulfamethoxazole/ Trimethoprim	None	Tablet	Danbury Pharmacal	Urinary tract infections due to susceptible organisms	5-C	05-09-83
18-854	Sulfamethoxazole/ Trimethoprim	None	Tablet (Double strength)	Danbury Pharmacal	Urinary tract infections due to susceptible organisms	5-C	05-09-83
18-89[illegible]	Sodium Phosphates, USP	None	Injection	Abbott	Source of phosphate for the treatment of hypophosphatemia	5-C	05-10-83
18-647	Nadolol/ Bendroflumethiazide	Corzide	Tablet	E.R. Squibb & Sons	Anti-hypertensive agent	4-C	05-25-83
18-904	Citric Acid, Sodium Carbonate, & Magnesium Oxide	Urologic G Irrigation	Irrigation Solution (semi-rigid container)	Abbott	Bladder irrigation to dissolve calculi of phosphatic origin	5-C-P	05-27-83
18-749	Acetohydroxamic Acid	Lithostat	Tablet	Uro-Research Inc.	Adjunctive therapy to decrease urinary ammonia & alkalinity in patients with chronic urea-splitting urinary infection	1-A-H	05-31-83

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
June 1983							
18-713	Clotrimazole	Mycelex	Oral Troches	Miles	Treatment of oral candidiasis	3-C	06-17-83
18-933	Multiple Vitamins	M.V.I.	Injection	USV	Vitamin deficiencies in patients receiving parenteral nutrition	3-C	06-20-83
18-856	Dopamine Hydrochloride	None	IV	Astra Labs	Hypotension & Shock	5-C	06-28-83
18-703	Ranitidine	Zantac	Tablet	Glaxo	Short-term treatment of duodenal ulcer	1-C	06-28-83
18-868	Furosemide	None	Tablet	Kalapharm	Diurectic agent	5-C	06-28-83
18-465	Fat Emulsion	Soyacal 10%	I.V. Infusion	Alpha Therapeutic	Source of calories and essential fatty acids in parenteral nutrition	5-C	06-29-83
18-786	Fat Emulsion	Soyacal 20%	I.V. Infusion	Alpha Therapeutic	Source of calories and essential fatty acids in parenteral nutrition	5-C	06-29-83
18-840	Dextrose, Lactic Acid, Sodium Hydroxide, Potassium Chloride, Postassium Phosphate, Sodium Chloride	Dextrose W/ Electrolytes # 75	I.V. Solution (in plastic container)	Travenol	Fluid, caloric & electrolyte replenishment	5-C-P	06-29-83
18-761	Metaproterenol Sulfate	Alupent	Inhalation Solution	Boehringer Ingelheim	Relief of bronchospasm in patients with reversible obstructive airway disease	3-C	06-30-83
18-839	Betamethasone Valerate	Betaderm	Topical cream	T.J. Roaco, Ltd	Relief of inflammatory and prurtic manifestations of corticosteroid-responsive dermatoses	5-C-U	06-30-83

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
July 1983							
18-576	Doxylamine Succinate	(No trade name established)	Tablets	Beecham	To help reduce difficulty in falling asleep	5-C	07-05-83
18-538	Indapamide	Lozol	Tablets	USV Labs	Antihypertensive/Diurectic	1-C-M	07-06-83
18-342	Leucovorin Calcium	Wellcovorin	Tablets	Burroughs Wellcome	Antidote for hematologic toxicity caused by folic acid antagonists	3-C	07-08-83
18-741	Betamethasone Dipropionate	Diprolene	Topical Ointment	Schering	Relief of the inflammation & pruritic manifestations of corticosteroid-responsive dermatoses	3-C	07-27-83
18-513	Chenodiol	Chenix	Tablets	Rowell Labs	For dissolution of radiolucent gallstones in poor-surgical-risk patients	1-A-M	07-28-83

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
August 1983							
18-726	Hydrocortisone Valerate	Westcort	Topical Ointment	Westwood	Corticosteroid-responsive dermatoses	3-C	8-08-83
18-845	Metronidazole	None	Tablets	Par Pharmaceutical	Treatment of trichomoniasis, amebiasis & anaerobic infections	5-C	8-18-83
18-930	Metronidazole	None	Tablets	Par Pharmaceutical	Treatment of trichomoniasis, amebiasis & anaerobic infections	5-C	8-23-83
18-807	Sodium Chloride, Sodium Acetate, Calcium Chloride, Magnesium Chloride, Sodium Bisulfite and Dextrose	Dialyte Concentrates	Peritoneal Dialysis Solution (in plastic container)	American McGaw	Peritoneal Dialysis	5-C-P	8-26-83
18-672	Nitroglycerin	Nitronal	Injection	G Pohl-Boskamp	Control of blood pressure in perioperative hypertension	5-C	8-30-83
18-777	Human Insulin Zinc Suspension (Lente)	Monotard Human	Injection	Squibb/Novo	Diabetes Mellitus	3-C	8-30-83
18-778	Human Insulin, Regular	Actrapid Human	Injection	Squibb/Novo	Diabetes Mellitus	3-C	8-30-83
18-860	Betamethasone Valerate	None	Topical Cream	Pharmaderm/Byk-Gulden	Corticosteroid-responsive dermatoses	5-C-U	8-31-83
18-861	Betamethasone Valerate	None	Topical Cream	E Fougera/Byk-Gulden	Corticosteroid-responsive dermatoses	5-C-U	8-31-83
18-862	Betamethasone Valerate	Betatrex	Topical Cream	Savage Labs/Byk-Gulden	Corticosteroid-responsive dermatoses	5-C-U	8-31-83

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
August 1983(cont)							
18-863	Betamethasone Valerate	Betatrex	Topical Ointment	Savage Labs/Byk-Gulden	Corticosteroid-responsive dermatoses	5-C-U	8-31-83
18-864	Betamethasone Valerate	None	Topical Ointment	Pharmaderm/Byk-Gulden	Corticosteroid-responsive dermatoses	5-C-U	8-31-83
18-865	Betamethasone Valerate	None	Topical Ointment	E Fougera/Byk-Gulden	Corticosteroid-responsive dermatoses	5-C-U	8-31-83
18-866	Betamethasone Valerate	None	Topical Lotion	E Fougera/Byk-Gulden	Corticosteroid-responsive dermatoses	5-C-U	8-31-83
18-867	Betamethasone Valerate	Betatrex	Topical Lotion	Savage Labs/Byk-Gulden	Corticosteroid-responsive dermatoses	5-C-U	8-31-83
18-870	Betamethasone Valerate	None	Topical Lotion	Pharmaderm/Byk-Gulden	Corticosteroid-responsive dermatoses	5-C-U	8-31-83

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
September 1983							
17-813	Chlordiazepoxide	Librelease	Capsules	Hoffman-La Roche	Relief of short-term anxiety disorders and preoperative apprehension	3-C	9-12-83
50-560	Ceftizoxime Sodium	Cefizox	Injection	Smith Kline & French Labs	Anti-bacterial used for treatment of urinary tract infections	1-C	9-15-83
18-900	Metronidazole	Metro I.V.	Injection	American McGaw	Treatment of serious infections caused by anaerobic bacteria	5-C	9-29-83
18-826	Dopamine 5% Dextrose Injection	None	Injection	Abbott	Agent for hypotension & shock	5-C	9-30-83

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
October 1983							
18-763	Desoximetasone	Topicort	Topical Cream	Hoechst-Roussel	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses	3-C	10-03-83
50-558	Cefuroxime Sodium	Zinacef	Injection	Glaxo	Antibiotic (semi-synthetic cephalosoporin)	1-C	10-19-83
18-814	Heparin Sodium & Dextrose	None	I.V. Solution (in plastic container)	Travenol	Anticoagulant therapy	5-C-P	10-31-83
18-899	Sodium Acetate Sodium Chloride Potassium Chloride Calcium Chloride Magnesium Chloride	Isolyte E	I.V. Solution (in plastic container)	American McGaw	Electrolyte & fluid replenishment	5-C-P	10-31-83

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
November 1983							
19-022	Sodium Chloride 3% and 5%	None	I.V. Solution (in plastic container)	Travenol	Electrolyte replenishment	5-C-P	11-01-83
18-768	Etoposide	VePesid	Injection	Bristol	Antineoplastic agent	1-A	11-10-83
50-573	Cyclosporine	Sandimmune	Injection	Sandoz	Immunosuppressant used to prevent organ transplant rejection	1-A-U	11-14-83
50-574	Cyclosporine	Sandimmune	Oral Solution	Sandoz	Immunosuppressant used to prevent organ transplant rejection	3-A-U	11-14-83
18-889	Metronidazole	None	Injection	Abbott	Treatment of serious infections caused by anaerobic bacteria	5-C	11-18-83
18-890	Metronidazole	None	Injection	Abbott	Treatment of serious infections caused by anaerobic bacteria	5-C	11-18-83
18-831	Atracurium Besylate	Tracrium	Injection	Burroughs-Wellcome	Neuromuscular blocking agent	1-B	11-23-83
18-790	Furosemide	None	Tablets	Barr	Diuretic agent	5-C	11-29-83
18-579	Furosemide	None	Injection	Natcon Chemical	Diuretic agent	5-C	11-30-83
18-413	Furosemide	None	Tablets	Zenith	Diuretic agent	5-C	11-30-83

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATION	CLASSIFICATION	APPROVAL DATE
December 1983							
18-685	Aluminum Hydroxide & Magnesium Trisilicate	Gaviscon/ Gaviscon-2	Chewable Tablets	Marion Labs	Antacid	4-C	12-09-83
18-816	Miconazole Nitrate	Micatin	Topical Powder	Ortho	Antifungal agent	3-C	12-13-83
50-576	Nystatin	Nilstat	Topical Powder	Lederle	Antifungal agent	3-C	12-22-83
18-166	Oxprenolol Hydrochloride	Trasicor	Capsules	Ciba-Geigy	Antihypertensive agent	1-C	12-28-83
18-366	Bentiromide	Chymex	Oral Solution	Adria Labs	Screening test for pancreatic exocrine insufficiency	1-C	12-29-83

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	[redacted]	CLASSIFICATION	APPROVAL DATE
January 1984							
19-165	M-140S Protamine Zinc Insulin (Beef)	None	Injection	Eli Lilly	litus	5-C	01-03-84
19-166	M-240 Regular Insulin (Beef)	None	Injection	Eli Lilly	litus	5-C	01-03-84
19-167	M-340S NPH Insulin (Beef)	None	Injection	Eli Lilly	litus	5-C	01-03-84
19-168	M-440S Lente Insulin (Beef)	None	Injection	Eli Lilly	litus	5-C	01-03-84
18-050	Phenylpropanolamine Hydrochloride	Corsym	Oral suspension	Pemwalt		5-C	01-04-84
19-034	Hydromorphone HCl	Dilaudid-HP	Injection	Knoll Labs		3-B	01-11-84
18-612	Nicotine Resin Complex	Nicorette	Chewing Gum	Dow Chemicals	Aid	1-C	01-13-84
18-792	6.5% Amino Acids	Neopham 6.5%	I.V. Solution	Cutter-Vitrum Inc.	trition	3-C	01-17-84
18-625	Chymopapain	Discase	Injection	Travenol	herniated vertebral	5-C-S	01-18-84
18-916	Heparin Sodium	None	Injection	Abbott		5-C-P	01-31-84

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
February 1984							
18-813	Clotrimazole	Lotrimin Lotion	Topical Lotion	Schering Corp.	Anti-fungal agent	3-C	02-17-84
18-753	Furosemide	None	Tablet	IMS Ltd.	Diuretic agent	5-C	02-28-84

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIFICATION	APPROVAL DATE
March 1984							
19-077	Sterile Water for Injection, USP	None	Injection	American McGaw	Diluent for other parentral drugs.	5-C-P	3-02-84
18-938	Desmopressin Acetate	DDAVP Injection	Ampuls	Armour	Anti-diuretic used to treat moderate *hemophillia*.	3-B	3-30-84
18-907	Metronidazole	Redi-Infusion	Vial	Elkins-Sinn	Treatment of serious infections caused by susceptible anaerobic bacteria.	5-C	3-30-84
18-967	Lidocaine HCl & 5% Dextrose Injection	None	Injection	American McGaw	Anesthetic	5-C	3-30-84
18-704	Metoprolol	Lopressor	Injection	Ciba-Geigy	Anti-hypertensive (Beta-Blocker)	3-B	3-30-84
18-925	Verapamil HCl	Calan I.V.	Vials	Searle	Supraventricular Tachy-Arrhythmias	5-C	3-30-84
19-038	Verapamil HCl	Calan I.V.	Syringes	Searle Pharms	Supraventricular Tachy-Arrhythmias	5-C	3-30-84

NDAs APPROVED

NDA #	GENERIC NAME	TRADE NAME	DOSAGE FORM	APPLICANT	INDICATIONS	CLASSIF-ICATION	APPROVAL DATE
April 1984							
18-985	Norethindrone & Ethinyl Estradiol	Ortho-Novum 7/7/7	Tablets	Ortho	Oral Contraceptive	3-C	04-04-84
19-004	Norethindrone & Ethinyl Estradiol	Ortho-Novum 7/14	Tablets	Ortho	Oral Contraceptive	3-C	04-04-84
19-006	Multi-Electrolytes in plastic container	Isolyte S	Injection	American McGaw	Electrolyte & fluid replacement	5-C-P	04-04-84
18-921	Lactated Ringer's Irrigiation in Plastic Container	None	Irrigation Solution	Travenol	Irrigation solution	5-C	04-06-84
18-901	Essential Amino Acids with Histidine	Aminess 5.2%	Injection	Cutter-Vitrum	Parenteral nutrition	5-C	04-06-84
18-849	Fluocinonide	Lidex 0.05%	Topical Solution	Syntex	Corticosteroid responsive dermatoses	3-C	04-06-84
18-977	Norethindrone & Ethinyl Estradiol	Tri-Norinyl 21 & 28 Day	Tablets	Syntex	Oral contraceptive	3-C	04-11-84
18-858	Indomethacin	None	Capsules	Mylan	Anti-inflammatory	5-C	04-20-84
18-776	Vecuronium Bromide	Norcuron (NC-45)	Injection	Organon Inc.	Neuromuscular blocking agent	1-S	04-30-84