CLINICAL ENGINEERING
In Press 1979

December 1978
Final

PHARMACEUTICAL INNOVATION:

APPROACHES TO EVALUATING THE IMPACT OF REGULATION*

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* This material is based upon work supported by the National Science Foundation under grant # 75 19066-00. 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.

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as well as clinical research are now being increasingly regulated. Growing emphasis is also being directed toward postmarketing surveillance and the control of drug utilization.

Measuring innovation

Much has been written on the subject of pharmaceutical innovation but no good scientific measures of innovative output have been developed. After considering many possible measures, we selected and comprehensively developed for the first time one particular measure that did not (except in our pilot project) exist previously--the number of new chemical entities (NCEs; new molecular structures) taken into human testing. While not all NCEs taken into man will turn out to be therapeutic advances, this measure includes all such advances and is a comprehensive measure of innovation at an early point in the pathway of drug development. It is a useful measure since it represents the decision that a compound deserves further testing and investment. It also represents the earliest appearance outside a firm of its innovative output, and in the U.S. it marks the entrance of an NCE into the regulatory pathway. In addition to using this measure of innovation and analyzing it stratified by therapeutic area, we also collected and analyzed data relating to other measures, such as the cost of developing an NCE to the point of approval for U.S. marketing, the national origin of NCEs marketed in the U.S., and the comparative availability of marketed NCEs in the U.S. and U.K.

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Pharmaceutical innovations that lead to advances in medical therapy occur in different ways, including major breakthroughs (e.g., penicillin, levodopa, the β-blockers and the H_2-antagonists); the cumulative effects of relatively minor modifications of an incremental nature (e.g., antihypertensive therapy and cancer chemotherapy); and serendipitous observations of the effect of drugs in man in situations where science and animal models are not yet capable of making reliable predictions (e.g., chlorpromazine as a tranquilizer, iproniazid and imipramine as antidepressants, and allopurinol for gout). The diverse nature of these mechanisms of innovation makes the process highly susceptible to a wide range of external controls such as regulation. The serendipitous (or Oates Type II) pathway of discovery is more important to innovation than is generally realized, and is also the most susceptible to inhibitory regulatory influences.

The legislation and regulations affecting prescription drugs in the U.S. have become increasingly strict since the Food, Drug and Cosmetic Act of 1938, with the pace accelerating particularly since the Drug Amendments of 1962 (Kefauver-Harris Amendments). Recent proposals (e.g., the 1978 Drug Regulation Reform bill and the proposed Bioresearch Monitoring Program regulations) indicate that this trend will continue. In addition to increasing in strength, regulatory controls are covering progressively earlier and more vulnerable stages of the development process so that preclinical toxicology as

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NCE flow in the U.S.

This was the first comprehensive study to use the measure described above to examine the origin and regulatory disposition of NCEs tested in man by all companies in the U.S. and by U.S. companies abroad. Information was obtained on those NCEs taken into human testing from 1963 to 1975 by virtually the entire U.S.-owned pharmaceutical industry and by all foreign-owned firms operating in the U.S., as well as on the regulatory disposition of each of these drugs. The study covered 1,103 NCEs from 36 U.S.-owned and 10 foreign-owned companies.[1]

The further development of NCEs in the U.S., as measured by Investigational New Drug (IND) filings, is concentrated in a small number of firms. Of the 36 U.S.-owned companies that perform research on original NCEs, seven accounted for one-half of the 859 NCEs taken into man, and four of these companies accounted for one-third of the 859.

During the mid-1960s there was a large apparent decline in the number of NCEs tested in man by U.S. companies. The full interpretation of this decline, of its causal relationship to the 1962 Amendments, and the assessment of its exact magnitude, require new data for some years prior to 1963. Since 1966, the rate of testing by U.S.-owned companies has been fairly constant

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at the lower level, the general patterns for the annual number of NCEs taken into man and for the annual number of IND filings being similar. The number of IND filings by foreign-owned firms has remained stable from 1964 (the first year for which we have complete data) through 1974 at a level of about one-third that of the U.S. companies.

Each year an increasing number of NCEs is being sent abroad for initial human testing (in 1973, 34% of U.S.-owned NCEs were first tested abroad by all U.S. companies; the four largest companies studied 50% of their NCEs abroad in that year). Those NCEs that are being brought back to the U.S. for further study are taking longer to do so. Although some industrial research directors have suggested that the trend toward early foreign study of their compounds will decrease as foreign costs and regulatory constraints rise, the latest data (1975) from this study show that the flow abroad is still increasing.

Another important finding of this study concerns the disposition of NCEs within the U.S. regulatory system. Only 12.5% of the INDs filed before 1970 had reached the stage of NDA submission by the time of the survey; beyond that point, however, 88% of the NDA submissions obtained NDA approval given at least five years. Thus, for the almost 90% of the INDs that are terminated, the decisions to do so are made primarily by the companies themselves without direct regulatory intervention. At the NDA stage, where assessment by the FDA is involved, only 12% of the remaining NCEs failed to be approved within five years.

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Our most recent data (the mean for 1974-1975) indicate that the IND and NDA stages now average four years and two years in duration respectively, making a total of six years. In 1975 the IND and NDA time requirements were rising. This trend would be expected to have an impact on the effective patent lives of pharmaceuticals, and thus on the research decisions made by the companies.

Differences were observed between pharmacologic classes of NCEs with respect to the length of time required for clinical investigation and regulatory approval (IND and NDA stages), a fact which implies the existence of scientific, industrial, and/or administrative differences between the various categories. An example of such a difference is that between cardiovascular drugs (which take a relatively long time to reach approval) and drugs for cancer chemotherapy (which take a relatively short time).

The information on investigational compounds obtained and analyzed in this study is the first scientific baseline measure at such an early stage of drug development against which future changes in the research process can be compared; it represents a significant advance over previous analyses employing only data on marketed compounds because by comparing the patterns of IND filings and their fate in the future with the baseline data obtained in this project, one will be able to detect the impact of policy changes approximately six years earlier than was previously possible.

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currently being obtained through an expanded questionnaire on investigational NCEs. At the same time, further necessary data on NCEs that have been marketed since 1962 (including information on the origin, the major research stages, and the regulatory history of each drug) are being obtained through a questionnaire on marketed NCEs.

Comparison of drugs marketed in the U.S. and Britain

We examined the rates and patterns of new drug introductions into the U.S. and Britain from 1972 through 1976 as an update of a previous study by Dr. Wardell that covered the period from 1962 through 1972.[2]

A total of 82 NCEs appeared for the first time in either country during the 1972-1976 period. Only 29% of these became mutually available in both countries, 2.4 times as many becoming available first in Britain as in the U.S. Of the 71% that became exclusively available, 2.6 times as many became available in Britain as in the U.S.

More important than numerical data are the clinical implications of differences between the two countries. The largest differences had narrowed since the previous study, but important categories in which the U.S. still lagged behind Britain in December 1976 included cardiovascular drugs, peptic ulcer treatment, and central nervous system drugs--including therapies for depression, epilepsy, and migraine. In other areas the differences were scattered and,

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while usually in the direction of a British lead, did not present as strong and consistent a pattern as observed previously.

The narrowing of the differences between the U.S. and Britain is due to several factors, the relative contribution of each one being hard to measure. Among the probable causes are the more realistic regulatory practices facilitated by higher quality clinical studies in the U.S., more conservative practices in Britain, actions in the U.S. resulting from the attention drawn by previous studies to the anachronisms that existed here, and industrial changes such as more efficient penetration of the U.S. market by foreign firms.

The therapeutic differences have very substantial consequences for the patients involved in morbidity, mortality, and economic terms. It must be realized that the full effects of recent regulatory changes are not yet fully reflected by our data on the patterns of marketed drugs, because of the long time involved in drug development. Furthermore, it is probable that more detailed study will reveal greater therapeutic differences between the two countries.

National origin of NCEs marketed in the U.S.

The national origin of NCEs introduced onto the U.S. market is a useful measure of pharmaceutical innovation that would reflect the relative strength of U.S. and foreign pharmaceutical industries. The number and nature of drugs originated in a country are important because these measures will reflect the scientific climate, as well

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as regulatory and economic considerations, in that country. Cultural and geographic influences will also be seen if there is an emphasis on certain therapeutic areas or diseases in a particular country. An analysis using this type of measure can provide a useful picture of worldwide innovative activity; furthermore, the findings in one country can also serve as a control for comparisons with another country in assessing the influence of national regulations on innovation. Ideally, the origin of new drugs introduced onto the entire world market should be assessed, but data are available only for certain countries; we focused on the U.S. market.

Two analyses were performed, one defining the "national origin" of an NCE as the location of the laboratory where the drug's pharmacologic activity was discovered, and the other defining it as the nationality of the parent company that owns the drug (i.e., the patent). The three major foreign contributors to the U.S. market have been Switzerland, Britain, and Germany, but the order of their importance has changed over time.

According to both definitions of national origin, the percentage of the total NCE approvals accounted for by U.S.-originated drugs generally declined from the early 1950s through the early 1970s, although with wide fluctuations in certain years--for example, a transient rise around 1970. By "laboratory of origin", the percentage of NCEs originated in the U.S. (using three-year moving averages) declined from a high of 76% in the years centered

example, a transient rise around 1970. By "laboratory of origin", the percentage of NCEs originated in the U.S. (using three-year moving averages) declined from a high of 76% in the years centered

around 1954 to a low of 47% around 1973. By "nationality-of-parent company," data were only available from 1963 to 1975 and the percentage of U.S.-originated drugs ranged from 63% in the years centered around 1964 and 1966 to 38% around 1972. This decline has been followed by a recent rise in the proportion of U.S.-originated NCEs, but not to the level observed previously. These trends are consistent with an early tightening of regulatory policies in the U.S. followed by a more recent tightening of regulatory policies abroad, but alternative explanations are possible.

A similar pattern was observed in both analyses when the percentage of U.S.-originated "significant" NCEs (i.e., those rated by the FDA as representing important or modest therapeutic advances) was calculated.

The existing data do not allow a thorough interpretation of the differences that appear between the analyses based on the two different definitions of "origin". When the parent company and laboratory of origin are in different countries, there may be a relationship between the two companies (e.g., subsidiary) or a compound may have been transferred between them (e.g., by licensing). Although such a distinction could not be made here, data that will clarify this important question are currently being obtained.

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Measures of therapeutic significance of U.S. marketed NCEs

Measures of the therapeutic value of new drugs are necessary for a thorough evaluation of pharmaceutical innovation, but adequate and appropriate measures of this nature have not previously been developed. The purpose of this project was to evaluate and develop the methodology for measuring the medical or therapeutic value of a marketed drug.

We first explored the use of the therapeutic literature as a possible source of information but it became apparent that the literature does not contain the necessary data. One important factor missing from the literature is a measure of the therapeutic impact of medication on a patient's life style and daily activities.

This led us to examine an experimental approach in which assessments were made of the effect of a new anti-inflammatory drug (piroxicam) on patients' lives during an ongoing double-blind, placebo-controlled clinical trial. This novel approach is a valid and useful one, but is not feasible for the assessment of a wide range of drugs, particularly those already marketed.

We therefore went on to explore a third methodological approach, namely a survey of experts to obtain their value ratings of available drugs. We analyzed and extended the methodology required for such a survey, and formulated and tested several versions of a questionnaire in our own medical center. We developed this survey through a pilot stage, in which we obtained ratings from

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78 specialist physicians in most specialty areas at the University of Rochester Medical Center and its associated hospitals. Since this was a pilot survey aimed at improving the existing methodology, the actual results obtained are not of definitive relevance to the assessment of the therapeutic value of individual drugs. With certain modifications, however, the survey approach developed here could be used on a wider (e.g., national) scale.

Economic studies

The cost of developing an NCE is an important influence on innovation and reflects the effects of regulatory policies. Information on the costs of the different stages in the process of drug development has not previously been available. We calculated the expected cost of clinical development of an NCE using information on the costs of a representative sample of NCEs that had been tested in man.[3] The average expenditure on each NCE that entered clinical trials was estimated from these data to be approximately $1 million in 1967 dollars, or $1.8 million in 1976 dollars. These post-IND expenditures are made up mostly of clinical studies, but also include the long-term animal toxicity studies that are carried out concomitantly with human testing. Since about one NCE of every eight that enters clinical trials will eventually reach the market, this figure multiplied by a factor of eight gives the expected post-IND development cost per marketed NCE. The costs of preclinical short-term animal pathology and toxicology tests on

the market, this figure multiplied by a factor of eight gives the expected post-IND development cost per marketed NCE. The costs of preclinical short-term animal pathology and toxicology tests on

those drugs that reached the IND stage (ignoring the comparable costs on those members of the cohort that did not reach the stage of IND filing) averaged $97,500 in terms of 1967 dollars, or $179,000 in 1976 dollars.

Since these expenditures are spread over several years, the outlays were capitalized to the time of marketing approval. The attrition of NCEs from active testing roughly offsets the growth of monthly expenditure per remaining product during the Phase I and Phase II periods with the result that the expected expenditure for clinical trials on a cohort of NCEs remains fairly constant over this period. By the time Phase III is reached, the attrition rate dominates with the result that expected expenditures on the cohort decline. This pattern of expenditures was capitalized to the approval point and, using an 8% rate of interest, the estimated post-IND development and preclinical animal toxicity costs are $13 million in 1967 dollars or $24 million in 1976 dollars for each successful survivor of the cohort.

A substantial additional cost that must be considered for each marketed NCE is the preclinical cost other than the short-term animal pathology and toxicity tests described above. This represents approximately 50% of the total pharmaceutical R&D expenditures. If these additional expenditures are allocated to the NCEs that enter clinical trials and capitalized to the point of approval for marketing, they will add approximately $17 million

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in 1967 dollars to the cost per marketed NCE. Therefore, total R&D costs per marketed NCE capitalized to the point of marketing approval are approximately $30 million in 1967 dollars or $54 million in 1976 dollars.

Another observation in this study was that the expenditures per NCE for clinical testing were greater for the larger firms than for smaller firms. Several industry economists have suggested that this reflected a difference in the nature of the NCEs developed by large and small firms but more data are needed to enable us to interpret this fully.

We also estimated the length of time NCEs remain in active testing. After approximately 15 months, testing had been suspended on one-half of the drugs entering clinical trials. This illustrates the importance of the early human trials as a screening procedure. For those NCEs that dropped out early in the testing, the decision to suspend testing was virtually always based on information obtained in human trials. As products advanced in testing and long-term animal studies were undertaken, however, the information that led to the decision to suspend a drug from further testing was evenly divided between results of clinical trials and the animal studies. Specific details on the reasons for rejection are currently being obtained.

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The effects of a proposed regulatory change that would require all normal animal tests to be completed prior to the start of

testing in human subjects were estimated. For the purpose of analysis we assumed that all testing would be done in the U.S., that the cohort of NCEs entering testing would remain identical and that the decision of a firm to continue or suspend testing following some adverse animal test results would not be changed by the absence of human test results. We found that the increase in the expenditures for animal studies was almost entirely offset by the reduction in clinical testing costs. However, the alteration of the sequence would result in a minimum of a two-year delay in the approval of new products, which will increase the value of the capitalized discovery-phase costs by approximately 15% and will reduce the duration of the effective patent life. These effects on the cost and returns to pharmaceutical R&D in the U.S. would have substantial implications for the amount and location of pharmaceutical R&D. There would be a reduction in the number of humans involved in clinical trials, although most of the reduction would be in low dosage, short-exposure Phase I tests. It should also be noted that this reduction in clinical tests would reduce the opportunities for therapeutic discovery by clinical observation--currently a major pathway of discovery. A full analysis of the impact of the proposed change in policy should compare the possible reduction in harm to test subjects against the delay in introducing therapies, the loss in serendipitous discovery, and our estimate of the reduced economic incentive to innovate.

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Conclusions

Regulation of innovation has been increasing steadily in the U.S. since 1962 and this trend has accelerated rapidly in recent years. In Britain, regulations have also begun to tighten but, because this process started much later in Britain, the level is currently lower there than in the U.S. Due to the length of time involved in drug development, the full effects of recent regulatory changes in either country are not yet visible with the measures of innovation available.

In this study we examined the impact of regulation on pharmaceutical innovation in the U.S. from 1963 to 1975 using one new measure not previously available (the output of new chemical entities) and analyzing several existing measures in more detail than had been done previously. No measure showed innovation in this country to be increasing with time. All measures showed either a decline or no significant change in the level of innovation over time; moreover, those measures in which the change was not statistically significant nevertheless showed a declining trend. A strong movement of early clincial research abroad was shown by U.S. companies since 1969.

Our economic analysis showed that the investment required for a U.S.-owned firm to develop a new drug of its own to the point of marketing in the U.S. is over $50 million, which is considerably higher than previous estimates. The reasons for this difference

a U.S.-owned firm to develop a new drug of its own to the point of marketing in the U.S. is over $50 million, which is considerably higher than previous estimates. The reasons for this difference

include the fact that we capitalized expenditures to the point of marketing approval, we included unsuccessful drugs in the calculations, and we excluded licensed products.

Using the economic and other data, the impact of one suggested regulatory change, that all normal animal tests be completed prior to the start of clinical testing, was evaluated. It was shown that this would have profound consequences on the development process, including a reduction of over 40% in the number of drugs evaluated in man, a 15% increase in research and development costs, and a minimum increase of two years in the development time, with a corresponding reduction in patent protection. The firms' responses to this would probably include reduction of research on financially marginal programs (regardless of their potential medical benefit) and movement of research abroad. A reduction in new-drug research would represent a societal loss since an important pathway of discovery is the serendipitous one, in which major new properties of drugs are discovered only after their introduction into human therapeutics. The significance of these anticipated effects indicates the importance of analyzing the impact of other reguatory proposals on innovation.

While the inhibitory direction of the influence of the regulations on pharmaceutical innovation is clear, we have not been able to measure the precise extent of this influence with the present data. The major problem lies in separating the

regulations on pharmaceutical innovation is clear, we have not been able to measure the precise extent of this influence with the present data. The major problem lies in separating the

specific contributions of factors other than regulation that are also acting to inhibit innovation. The attribution of causal relationships for recent policy changes is helped by our better information on the timing and size of regulatory changes; by the differences between innovation in different therapeutic areas correlated with known differences in governmental policies in these areas; by the international comparative approach; and by the economic analyses. Refinement and continuation of the NCE-IND approach should allow us to detect the impact of policy changes approximately six years earlier than was previously possible (the average length of the IND plus NDA phases in 1974-1975).

Certain other factors, such as the generally increasing amount of scientific evidence required to document safety or efficacy, together with economic considerations, have no doubt contributed to the decline in innovation. However, the results are consistent with the hypothesis that over the past 15 years increased regulation has increased the cost and reduced the amount of pharmaceutical innovation.

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FINAL

METHODOLOGY FOR MEASURING THE EFFECTS OF REGULATION ON PHARMACEUTICAL INNOVATION: REGULATORY DISPOSITION AND NATIONAL ORIGIN OF NEW CHEMICAL ENTITIES IN THE UNITED STATES

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Prepared for an American Chemical Society Symposium on the Effects of Government Regulation on Technological Innovation, Miami Beach, 14 September 1978.

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As long as any disease that is potentially treatable by drugs remains unconquered, there will be a need for pharmaceutical innovation. Among those disease areas that could benefit from pharmaceutical innovation are arthritis, cancer, the muscular dystrophies, and schizophrenia. Despite the advances in drug therapy that have occurred, there is still a pressing need for new and better medicines within many therapeutic areas. Valuable innovations in such areas would offer drugs that are more effective, have fewer or significantly different side effects, and/or are more convenient than existing therapies.

Although the aim of pharmaceutical regulation is to ensure the safety and efficacy of new drugs, regulatory criteria should not be so stringent that they inhibit innovation. In April 1976, the President's Biomedical Research Panel gave the following description of how the regulatory process may act as a roadblock to the development of new drugs.

> "There is a clear impasse arising between society's desire for new and better drugs and the barriers society is erecting to their development and introduction. These barriers, based on a valid desire to improve the standards of safety and efficacy and to insure ethical control in clinical evaluation, increase developmental costs. There is a real danger of bringing the development process and access to clinical resources to a halt."[1]

increase developmental costs. There is a real danger of bringing the development process and access to clinical resources to a halt."[1]

It is important to balance the effects of drug regulation with the need for innovation. As the clinical pharmacologist Walter Modell has said, "Only progress is protection. Without progress we have no protection."[2]

This paper examines the impact of regulation on pharmaceutical innovation in the United States and the methodological problems involved when one attempts to measure pharmaceutical innovation. Data describing the rate and manner of passage of new chemical entities (NCEs) through the U.S. regulatory system and the national origin of NCEs marketed in the U.S. are presented.

Pharmaceutical Regulation in the United States

Legislation.[3] The first major legislation concerning drugs was the Pure Food and Drugs Act of 1906. This Act banned adulterated or misbranded foods and drugs from interstate commerce. Although directed against both impure foods and drugs, its main impact was on foods.

The Food, Drug and Cosmetic Act of 1938 was enacted following the Elixir Sulfanilamide tragedy (in which the untested use of diethylene glycol as a solvent caused the deaths of about 100 people). The aim of this Act was to prevent the marketing of untested, potentially harmful drugs. Its major provision was that the manufacturer was required to demonstrate the safety of a drug to the FDA (in a new drug application or NDA). Unless the FDA

untested, potentially harmful drugs. Its major provision was that the manufacturer was required to demonstrate the safety of a drug to the FDA (in a new drug application or NDA). Unless the FDA

determined within 60 days that safety was not established, a drug could then be marketed. Exemptions to the prohibition against interstate transfer were allowed for drugs intended solely for investigational use by qualified scientific experts.

The next major legislation was also enacted after a tragedy--that of thalidomide. The major provision of the Drug Amendments of 1962 (the Kefauver-Harris Amendments) was that the manufacturer must show substantial evidence of a drug's effectiveness (in addition to its safety) to obtain approval for marketing. Other changes were that positive FDA approval of a drug was required instead of automatic clearance, FDA control over the clinical testing stage was expanded; and the Secretary of HEW could immediately suspend a drug's NDA approval if the drug was found to represent an "imminent hazard" to the public health.

Regulation. The regulations promulgated by the FDA to implement its responsibilities as defined by the legislation have had, and continue to have, a significant impact on pharmaceutical R & D.

Examples of particularly important regulations include the 1970 regulations that defined what constitutes the "well-controlled investigations" needed to provide substantial evidence of effectiveness as required by the 1962 Amendments.

In 1975 regulations came into effect to enhance the acceptance by the FDA of foreign data meeting certain requirements. The aims of these regulations were to eliminate duplicative clinical

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research and to expedite the availability of important new drugs in the United States.

In July 1976, due to concerns over the findings of FDA inspections of certain research laboratories, the Bioresearch Monitoring Program was initiated. Four components of this program relate to drugs: the proposed regulations regarding preclinical testing (Good Laboratory Practices),[4] those proposed for sponsors and monitors of clinical studies,[5] those proposed for clinical investigators,[6] and the proposed regulations pertaining to institutional review boards or IRBs.[7] Implementation of any of the proposed regulations included within this program will raise the cost of developing new drugs and may influence the process of drug development in other ways as well. For example, British pharmaceutical firms have stated that they cannot meet the requirements of the proposed sponsor/monitor regulations in Britain,[8] so presumably clinical data from Britain (and probably from other countries as well) will become unacceptable in support of an NDA if these regulations are implemented as currently proposed. Universities will have severe difficulties in meeting the requirements of, for example, the proposed regulations on Good Laboratory Practices.[9]

Following the appearance of the Final Report of the HEW Review Panel on New Drug Regulation in May 1977, considerable attention was devoted by the FDA and by some members of Congress to

Following the appearance of the Final Report of the HEW Review Panel on New Drug Regulation in May 1977, considerable attention was devoted by the FDA and by some members of Congress to

formulating legislation that would significantly revise pharmaceutical regulation in this country. The outcome was The Drug Regulation Reform Act of 1978 (S.2755, H.R. 11611*), which was introduced in both houses in March 1978.

The Drug Regulation Reform Act (DRRA) represents a complete revision of the Food, Drug and Cosmetic Act of 1938. Although the FDA is currently practicing some of the procedures described in the bill, and would be able to follow others by initiating appropriate regulations, passage of this legislation would clarify and formalize the nature and extent of the authority that Congress intends the FDA to have.

The bill is lengthy and complex. Even among legal and scientific experts there is disagreement as to which aspects of the drug development and approval processes should most appropriately be covered by legislation and which should best be dealt with by regulations. Although this particular bill may not be enacted in 1978, the issues raised during the hearings and debates on it are extremely important and will undoubtedly reappear in future bills.

Since both the 1938 Act and the 1962 Amendments were passed in the wake of tragedies, they were oriented towards risk-avoidance; the FDA is primarily required to prevent harm from drugs and at present has no congressional mandate to promote the improvement of health or to maximize the benefit obtainable from drugs.

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The DRRA recognizes the need to encourage innovation and research and to get new drugs on the market faster. In practice, however, many of its provisions would probably inhibit research and innovation.[10] Significant aspects of the bill include the following*:

1. provisions for limited distribution of a drug;
2. required postmarketing surveillance of a new drug for five years (unless waived by the Secretary of HEW);
3. postmarketing studies of a drug's effectiveness for indications other than those for which approval is sought could be required for uses that are known or could reasonably be expected to occur;
4. continuation of the current requirement for "adequate and well-controlled investigations" as evidence of effectiveness (in contrast to the provision in the Medical Device Amendments of 1976 by which the Secretary may determine whether other valid scientific evidence is adequate to establish the effectiveness of a device);
5. a new definition of safety to mean that the health benefits of a drug must clearly outweigh its risks with regard to society and the public health;

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6. provision for removal of a drug from the market if it represents a substantial risk of illness or injury (this would replace the current provision which requires that a drug be shown to represent an "imminent hazard");
7. provision for the accelerated approval of "breakthrough" drugs if certain requirements are met;
8. the disclosure of all safety and effectiveness data submitted to the FDA (some of which is currently considered as trade secret information);
9. provision for the export of drugs not approved for marketing in this country under certain conditions;
10. expansion of the FDA's jurisdiction to include all drugs (not only those involved in interstate commerce); and
11. provision for drug innovation investigations for the purpose of examining clinical pharmacology, making preliminary assessments of the risks or effectiveness of a drug, or studying the biological mechanisms in humans. The FDA review of such investigations would focus only on the protection of subjects, not on the adequacy of the scientific design. (The aim of this provision is to avoid interfering with the discovery and development of new drugs but the extent to which the provision would achieve this aim has been questioned.)

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the regulatory system, it would be essential to have a thorough evaluation of the present system. Ideally one would like to see a cost/benefit assessment of the current regulations-- cost representing not only economic cost but also the cost of missed innovation, and benefit representing the improved health and safety of the public. One part of this task that our group has approached is a study of the effects of regulation on pharmaceutical innovation. The first problem that must be dealt with in such a study is how to measure innovation.

Nature of Innovation

The present predictive state of pharmacological science is such that the therapeutic or even pharmacologic value of an innovation usually cannot be foretold at the time of its discovery. Thus, a certain amount of innovative activity may never yield real breakthroughs, while certain innovations that may appear scientifically trivial can turn out to be useful contributions to medical progress.

Pharmaceutical innovations that lead to advances in medical therapy occur in a variety of ways. There are dramatic "breakthrough" innovations that depend on a single major concept or discovery, examples being penicillin, levodopa, the β-blockers and the H_2-antagonists. In contrast to these, the cumulative results of several minor or incremental innovations may, when taken

discovery, examples being penicillin, levodopa, the β-blockers and the H_2-antagonists. In contrast to these, the cumulative results of several minor or incremental innovations may, when taken

together over a period of years, constitute a major advance. The areas of antihypertensive therapy and combination chemotherapy for cancer illustrate this type of innovation. Important therapeutic advances may also come about through chance observations of the effects of drugs in man in those situations in which science and animal models are not yet capable of making reliable predictions, such as the use of chlorpromazine as a tranquilizer and of iproniazid and imipramine as antidepressants.

Mechanisms of Innovation

We shall assume, rather arbitrarily for the purposes of this discussion, that the starting point of pharmaceutical innovation is the development of a new biologic concept (or a new approach to an existing concept) that is potentially therapeutically exploitable. Moving from the earliest and most a priori to the later and more empirical methods of drug discovery, the following types of innovation can be distinguished.

1. Synthesis of a new molecular structure (new chemical entity or NCE) with possible biological significance.
2. Discovery of a new pharmacologic action (e.g., the β-blockers and the H_2-antagonists).
3. Structural modification of an existing molecule to improve its therapeutic value, e.g., by making it more effective, less toxic, better absorbed, or longer acting (such

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modification can also lead to the discovery of a new pharmacologic action, as in (2) above, or of new therapeutic effects in man, as in (5) below). An instructive example of the major therapeutic advances that have been obtained by molecular modification is seen in the family of penicillins that followed benzyl penicillin, the original member of the series. In little more than a decade from its first characterization, the original benzyl penicillin molecule was structurally modified to yield phenoxymethyl penicillin (orally active), ampicillin (orally active against gram negative organisms), the penicillinase-resistant penicillins (active against certain resistant organisms, particularly staphylococci), and carbenicillin (active against pseudomonas organisms). These are all relatively trivial modifications of the original benzyl penicillin molecule, the few successes out of competitive programs that synthesized literally thousands of such modified molecules, but they are some of the major therapeutic advances of the antibiotic era.

Similar examples abound in most fields of therapeutics. For example, the major tranquilizer chlorpromazine--the first drug found to have true antipsychotic properties--is a trivial modification of phenothiazine, which was known for decades and used as a de-wormer for livestock. The parent

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phenothiazine, and many of its structural modifications, have no antipsychotic activity at all; it is only certain minor structural modifications that have the essential pharmacologic and therapeutic properties. (Chlorpromazine also happens to be a classic example of the serendipitous empirical-clinical method of discovery of a drug's unique therapeutic value, a method described below.)

4. "Pharmaceutical" modifications of drugs to improve performance, e.g., the production of different formulations or delivery forms. On the overall scale of innovations, these pharmaceutical modifications are generally regarded as being of relatively minor innovative significance; however, some can be of disproportionately large medical value. For example, the simple concept of the depot (long-acting injectable forms of) phenothiazines has improved the long-term treatment of psychotic patients whose disease predisposes to noncompliance with the therapeutic regimen and resultant treatment failure; in some cases the depot form can avert the need for institutionalization. Depot preparations of injectable contraceptives similarly overcome the obvious problem that can result from noncompliance. The Ocusert and Progestasert systems, which deliver drugs locally into particular body compartments (the eye and uterus, respectively) reduce the total systemic burden of

The Ocusert and Progestasert systems, which deliver drugs locally into particular body compartments (the eye and uterus, respectively) reduce the total systemic burden of

a drug, reduce side effects, and provide more uniform and reliable release; the inhaled form of steroids for asthma serves a similar purpose. These are a few of the many examples where pharmaceutical innovations of a relatively modest conceptual or technical nature have nevertheless led to substantial improvements in the quality of medical treatment.

5. Discovery of therapeutic effects in man that may not be predictable from animal models, also known as serendipitous discovery or the "Oates Type II" method of discovery. Examples of major therapeutic advances that have been made in this way include some of the most important therapies of the past three decades: all the major psychotherapeutic drugs (the major tranquilizers and both classes of anti-depressants); the thiazide diuretics; the anti-parkinsonian actions of levodopa and amantadine; the anti-inflammatory actions of steroids and of phenylbutazone; the anti-hypertensive actions of β-blockers methyldopa; the anti-gout action of allopurinol; and the protective effects of β-blockers and platelet modulators against coronary death and myocardial infarction, and against stroke.
6. Discovery of new uses for existing drugs, including those uses discovered as in (5) above.

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innovation, certain principles become apparent. The areas where federal support has been most prominent are in basic research and in large-scale clinical trials. These happen to be areas where the benefits--while very real--are long-term, not immediately apparent ones.

Conversely, the development of specific therapeutic drugs has to a large extent (with the exception of some important areas such as cancer chemotherapy) been achieved by the pharmaceutical industry, without federal funding. For example, the original basic work on β-blockers, new β-agonists, H_2 antagonists, and cromolyn sodium was all done in laboratories of pharmaceutical firms (foreign laboratories, as it happens), and the most important clinical development was also performed by firms abroad. If one traces the research back still further, one can usually find connections with research supported by public funding, but the connection is not an immediate one.

An important trend appears to be developing. Basic research knowledge, once produced, is an international commodity because of the well-developed systems that exist for scientific publication and communication. It is ironic that while most publicly-financed basic knowledge is probably generated by U.S. funding, the U.S. pharmaceutical industry may not be proportionately as prominent in making applied use of this knowledge. It is as if foreign companies are getting "first crack" at these U.S.-originated basic-knowledge opportunities. It is possible that the facility to exploit basic

pharmaceutical industry may not be proportionately as prominent in making applied use of this knowledge. It is as if foreign companies are getting "first crack" at these U.S.-originated basic-knowledge opportunities. It is possible that the facility to exploit basic

knowledge for therapeutic purposes is dependent on the regulatory environments in particular countries.

Measures of Innovation

There are several possible ways of measuring pharmaceutical innovation, but all present technical problems. Two general approaches are the use of absolute measures, using some absolute criterion to measure innovative output, and comparative measures, such as comparing the nature and extent of the output of two different countries. Among the possible absolute measures are the number of new molecular structures (NCEs) synthesized, the novelty of their molecular structure, the novelty of their pharmacologic action, the number of patents issued, the number of NCEs tested in man, the number NCEs submitted for marketing, the number of NCEs marketed, and qualitative measures of the value of marketed NCEs.

Measures such as the number of compounds synthesized and the number of patents issued have been criticized on the grounds that they are more measures of R & D activity (input) rather than of output.[11] Novelty of molecular structure represents a technically difficult assessment which, if performed at the time of synthesis, involves molecules with unknown pharmacologic and therapeutic properties. Novelty of pharmacologic action represents a fundamental measure of at least the <u>potential</u> for therapeutic innovation. In practice, however, this represents a judgmental issue and the

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necessary data on untested or unmarketed drugs would be difficult to obtain.

The problem with using the numbers of NCEs, whether tested in man, submitted for marketing, or marketed, is that these measures consist of numbers alone without interpretation or assessment of therapeutic value. Furthermore, as measures of innovation, they are confounded by regulatory influence during the IND and NDA stages. The therapeutic value of marketed NCEs can be evaluated but the real assessment can only be made some years after a drug has been marketed and its properties fully ascertained (e.g., aspirin's prophylactic effects against myocardial infarction). Therapeutic assessments have been made by the FDA for example,[12] but the methodology for such assessments has not been well-developed.

The measure we have recently developed in some detail is the number of NCEs taken into human testing. This is a valid and useful measure since it represents a firm's decision that a compound is worthy of further testing and investment. It also represents the first appearance of innovative output outside a firm, and in the U.S. it marks the entry of a compound into the regulatory pathway. Although, as described above, this measure of innovation is made before a compound's therapeutic properties are known, it is made at a point when the compound's pharmacologic and toxicologic properties are already defined.

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A further reason for the importance of this measure is the seemingly paradoxical one that some of the most important therapeutic properties of a drug cannot be predicted at the time a drug is first taken into man. In the present rather primitive state of knowledge about structure-activity relationships, our ability to make a priori predictions using such relationships is poor. We therefore depend more than is generally realized on the "Oates Type II" or serendipitous method of discovery, in which major new properties of drugs are discovered only after their introduction into human therapeutics. The more compounds that are studied in man, the more potential there is for this serendipitous method of discovery. Thus, the number of NCEs taken into man for study is one of the more important of the feasible indices of innovation.

The New Drug Approval Process in the United States

The upper portion of Figure 1 depicts the various stages through which a new drug must pass before it can be marketed in the United States. After the preclinical testing phase and initial toxicological studies, a manufacturer may file with the FDA for an investigational new drug exemption (IND) prior to initiating human testing. The clinical investigations are divided into three phases. During Phase I a drug is given to a small number of healthy human volunteers with the principal objectives of looking for evidence of toxicity and determining the basic properties of

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the drug in man. In Phase II studies the drug's effects on a small population of patients with the appropriate disease are examined to determine its therapeutic value and to detect any adverse effects or possible toxicity. Phase III consists of large-scale testing to uncover less common side effects and to approximate more closely the type of drug utilization (e.g., in patients of varying disease severity) that would occur in medical practice if the drug were marketed.

When a manufacturer believes he has adequate evidence to demonstrate the safety and effectiveness of a compound, an NDA is submitted to the FDA. After the NDA has been approved, the drug can be marketed in this country. The term Phase IV is used to denote postmarketing studies that are done to examine the properties of the drug in more widespread or long-term utilization.

Regulatory Disposition of NCEs in the United States

To measure innovation we examined the rate of flow of NCEs into human testing, the earliest point at which reliable information appears outside the pharmaceutical industry and the point at which NCEs enter the regulatory pathway. The rates at which these compounds pass the milestones of the U.S. regulatory pathway (the points of IND filing, NDA submission, and NDA approval) were defined. In addition to the overall analysis, the data were analyzed by individual therapeutic areas. The observed differences between

points of IND filing, NDA submission, and NDA approval) were defined. In addition to the overall analysis, the data were analyzed by individual therapeutic areas. The observed differences between

categories of NCEs imply the existence of scientific, industrial, and/or administrative differences between these categories.

Data were obtained by an exhaustive survey of all pharmaceutical companies operating in the U.S. An NCE was defined as a compound of molecular structure not previously tested in man (excluding new salts or esters, diagnostic agents, and vaccines). For U.S.-owned companies, NCEs taken into man anywhere in the world for the first time from January 1963 (the year the IND requirement was first implemented) to the time of the survey (September 1975) were included. In the case of foreign-owned research-based firms operating in the U.S., we obtained complete data on their U.S. experience with NCEs but not on their worldwide experience.

Information was obtained on a total of 1,103 NCEs, 859 from 36 U.S.-owned companies and 244 from 10 foreign-owned companies.* The portion of the U.S. pharmaceutical industry responsible for the NCEs was highly concentrated; seven companies accounted for one-half of the NCEs and four of these companies accounted for one-third.

The annual rate of NCEs tested in man by U.S. companies rose from 70 in 1963 to a mean of 94 in 1964-1965, then declined sharply to a lower plateau that has been relatively stable (with a mean of 62 NCEs per year) from 1966-1974 (Figure 2).

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* A more detailed description of this study is provided in Wardell, W.M., Hassar, M., Anavekar, S.N., and Lasagna, L.: The rate of development of new drugs in the United States, 1963 through 1975. Clinical Pharmacology and Therapeutics 24:133-145, August 1978.

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The interpretation of this trend is not simple. The values in 1964 and 1965 are relatively high whereas those in 1966-1974 are not very different from 1963. To interpret this, more information for 1963 and prior years is necessary. If 1963 was an "ordinary" year, then the temporary upsurge in 1964 and 1965 needs to be explained but the changes in the later 1960s and early 1970s have been small. If, however, 1963 represents an unusually low year, the subsequent decline from the levels of 1964-1965 has been substantial.

Our best interpretation of the present data, based on answers to questions asked of the firms, is that the 1963 values are artificially low (because of the need then for companies to divert their efforts toward compiling materials for the required retrospective IND filings on drugs already in clinical research), while the 1964-1965 values are artificially rather high (because of a catching-up process).

Analysis by pharmacologic area showed that most NCEs tested by U.S. companies were in the areas of anti-infective drugs (19.4%), psychotropic/neurotropic drugs (14.3%), cardiovascular drugs (14.3%), analgesic/anti-inflammatory drugs (13.0%), and endocrine drugs (11.8%). The strongest time patterns were the large rise and fall in the early years seen overall (as described above) and particularly with anti-infective and cardiovascular compounds, but not with psychotropic/neurotropic, endocrine, or analgesic/anti-inflammatory

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drugs. After 1966 the trends were not strong, but there was a perceptible decline in anti-infective and a rise in endocrine compounds. Psychotropic/neurotropic compounds showed a marked fall between the early and later years studied.

In recent years there has been a large shift in early U.S. drug studies abroad (Figure 3). From 1963 to 1969, an average of only 8% of U.S.-owned NCEs were first studied abroad by the 36 U.S. firms, but this rose to 34% in 1973. (It fell to 31% in 1974 but showed a continuing rise to 47% in our incomplete data for 1975.) The increase in the number of drugs being initially studied abroad was particularly marked within the larger companies; in 1973 the four largest companies first studied 50% of their NCEs abroad. The proportion of drugs first studied abroad also varied by therapeutic area, with gastrointestinal and endocrine drugs having the highest percentages.

The annual rate of IND filings by U.S. companies declined from an average of 87 per year during the two first full years (1964-1965) to a low of 42 in 1972, with a subsequent return to the general levels prevailing in 1967-1970 (Figure 4). The steepest decline occurred between 1965 and 1966; the interpretation of the magnitude of this decline is complicated by factors previously discussed.

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1964 to 1974 (range 14-26). The decline in the rate of total filings was thus due solely to the decline in the U.S. portion. This is consistent with, but does not by itself prove, the hypothesis that an inhibitory influence was acting on U.S. companies but not on foreign companies during this period.

Of those NCEs that entered the U.S. regulatory system, 12.5% of the INDs filed before 1970 (i.e., those which had at least five years to be acted upon) had reached the stage of NDA submission by 1975. Of the NDAs submitted prior to 1970, 88% were successful. The finding that decisions on most INDs that were discontinued before the point of NDA submission were made primarily by the companies themselves has substantial implications for the structure of the regulatory process. Of those compounds that reached the NDA stage, where most of the regulatory assessment by the FDA is involved, only 12% failed to pass in five years. Nevertheless, the NDA review phase occupies a substantial fraction of the total IND-NDA time requirement; for many of the drugs that were ultimately approved, the NDA phase exceeded the length of the IND phase.

The total time required for clinical investigation and approval of a successful NCE in the U.S. (IND and NDA stages) rose from a mean of 31 months in 1966 (17 months IND plus 14 months NDA) to a peak mean of 71 months in 1969 (28 months IND plus 43 months NDA), and has averaged 62 months over the last two complete years (1973-1974; Figure 5). In the last but incomplete year, 1975, the

to a peak mean of 71 months in 1969 (28 months IND plus 43 months NDA), and has averaged 62 months over the last two complete years (1973-1974; Figure 5). In the last but incomplete year, 1975, the

mean time required rose sharply to 82 months (55 months IND plus 27 months NDA), mainly due to the rise in the duration of the IND stage.

The most recent data available on the time requirements and the attrition rates are shown in the bottom portion of Figure 1. The cost estimates provided in the figure are from a study by Hansen,[13] who obtained economic data from U.S. firms on a sample of compounds that were included in the NCE study. He found that, taking failures into account as well as successes, the average cost for a U.S. firm to develop its own NCE to the point of marketing in this country is $54 million in 1976 dollars. This is higher than previous estimates, largely due to capitalization of expenditure flows and exclusion of licensed compounds.

A survival distribution analysis was performed to study the success rates of NCEs in the IND and NDA phases and the amount of time spent in each phase (residence time). There was a trend toward increasing residence times and decreasing success rates with time, but this trend was not significant with the statistical tests employed. The success rates and residence times of U.S. and foreign companies were quite similar in each phase.

The duration of the NDA phase varied significantly between pharmacologic classes. An example from U.S.-owned NCEs was the relatively quick approval of anticancer drugs in contrast to the relatively long times for approval of cardiovascular drugs.

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The duration of the NDA phase for all NCE NDAs (i.e., not just that subset represented by the cohort with new INDs) rose from a mean of approximately 6 months through the latter half of the 1950s to a mean of 44 months in 1969, and then fell rather sharply to a mean of 17 months in 1972 (Figure 6). The reasons for these large changes are not at present clear. Some actions taken by the FDA may have contributed to this shortening of the NDA phase, such as an increased number of Public Health Service physicians assigned to the FDA, an increase in the number of Advisory Committees, and the institution of new internal management systems at FDA. Since 1972, the duration of the NDA phase has been rising again to a value of about two years. This pattern needs further investigation since an understanding of what caused it could help to elucidate the role of regulation versus other factors in the causation of these changes.

This is the first time a data base of this size and degree of comprehensiveness has been compiled on the state of new drug development in any country. We are currently obtaining further information on investigational NCEs, which will include the reasons for termination of clinical research by the firms and full data on licensed compounds. These additional data will clarify some of the trends that have been revealed by the present study, and will allow further analyses to be performed of the reasons behind the observed changes.

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National Origin of NCEs Marketed in the United States[14]*

The national origin of NCEs introduced onto the U.S. market is a key measure of the location of pharmaceutical innovation, and of changes in location. The number and nature of drugs discovered or originated in each country are important because these data reflect the scientific climate, as well as regulatory and economic considerations, in that country. Cultural and geographic influences will also be seen if there is an emphasis on certain therapeutic areas or diseases in a particular country. An analysis using this type of measure can provide a useful picture of worldwide innovative activity; furthermore, the findings in one country can also serve as a control group for making comparisons with another country in assessing the influence of national regulations on innovation. Ideally the origin of new drugs introduced onto the entire world market should be assessed, but data are available only for certain countries; our study focused on the U.S. market.

Two analyses were performed based on data compiled by Paul deHaen[15, 16] and by Harold Clymer.[17] In one analysis the national origin of an NCE was defined as the location of the laboratory where the drug's pharmacologic activity was discovered and in the other the national origin was taken as the nationality of the parent company that owns the drug (i.e., the patent). According to both definitions of national origin, the percentage of U.S. NCE

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* Preliminary results of this study are described in Hassar, M., Clymer, H., Wardell, W., and Lasagna, L.: National origin of new chemical entities (NCEs) admitted to the U.S. market from 1963 to 1974. Clinical Pharmacology and Therapeutics 19:108, January 1976.

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approvals that were accounted for by U.S.-originated drugs generally declined from the early 1950s through the early 1970s, but several transient fluctuations in this pattern were observed. Since there was considerable variability from year to year, three-year moving averages were used rather than yearly figures to represent general time-related trends. By laboratory of origin, the percentage of NCEs originated in the U.S. ranged from a high of 76% in the years centered around 1954 to a low of 47% around 1973 (Figure 7). By nationality of the parent company, for which data were available from 1963 to 1975, the percentage of U.S.-originated NCEs ranged from 63% in the years centered around 1964 and 1966 to 38% around 1972 (Figure 8). This decline has been followed by a recent rise in the portion of U.S.-originated NCEs, but the U.S. has not regained the prominence it had in the earlier years.

A similar pattern was observed in both analyses when the percentages of U.S.-originated "significant" NCEs (i.e., those rated by the FDA as representing important or modest therapeutic advances) over time were calculated.

The three major foreign contributors to the U.S. market by either definition of national origin have been Switzerland, Britain, and Germany; the order of their importance has varied over time however.

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the observed patterns, analysis of the national origin of NCEs using the definitions employed here is not a highly sensitive or specific measure of pharmaceutical innovation. However, the observed trends are consistent with the tightening of regulatory policies first in the U.S. and then subsequently abroad.

We are currently obtaining data that will improve and expand upon these national origin analyses. The new information includes, for each NCE marketed in the U.S. since 1963, the countries of its first chemical synthesis, its first pharmacologic study, and its first administration to man. Information on licensing patterns and on international transfers of drugs at different stages within companies is also being obtained. These data will clarify the observed patterns of national origin and will provide more sensitive measures of international shifts in world pharmaceutical innovative activity.

Comparative Methods of Measuring Innovation: NCEs Marketed in the United States and Great Britain

Since the techniques for measuring pharmaceutical innovation, in particular its scientific and medical value, are not yet well developed, alternative approaches to absolute measures of innovation should be explored. An obvious alternative is the international comparative approach, comparing the performance of drug innovation under the U.S. regulatory system with the performance of drug innovation systems in other countries having

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