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CONTROLS OF DRUG UTILIZATION: NATIONAL AND INTERNATIONAL IMPLICATIONS

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The increasing number of national and international studies of drug utilization, such as those presented at this symposium, implies that some attention will be given to the results of such studies. Under many medical and regulatory systems, this means that some form of control will be exerted or attempted, and indeed many programs already exist to control the utilization of therapeutic drugs. In this paper I shall examine the purpose, mechanisms, achievements and implications of drug utilization control mechanisms. A more detailed account of this topic has recently been published in the form of an international comparison (1).

The study of drug utilization controls deals mainly with controls over drug use *after* the point of marketing. It deals with systems for distributing and paying for drugs, therapeutic practices, physician prescribing, and patient compliance. The systems that regulate research on drugs prior to their approval for the market are also important, however, because to a regulatory agency, the way a drug is likely to be used once marketed may determine whether it will be allowed on the market at all.

Over the past decade, the control over the use of therapeutic drugs by physicians and patients has been gaining momentum in most countries with two general aims: improvement of the quality of drug prescribing and reduction of drug costs.

BACKGROUND TO CONTROL OF DRUG USE

Quality of Use

The recent increase in attention to the quality of drug use has two distinct aspects. The first is a desire to improve the standards of drug prescribing and use. With the limited evidence available, it would seem that the quality of medical care could be improved if standards of drug utilization were improved, but the extent of this potential improvement in relation to other remediable deficiencies in health care is not known.

The second aspect of the quality of drug use focuses on a regulatory agency's approval of a drug for the market. In the present scheme, a regulatory agency must address the problem of having to grant approval despite uncertainty about how the drug will actually be used in medical practice and what the total impact of such

approval of a drug for the market. In the present scheme, a regulatory agency must address the problem of having to grant approval despite uncertainty about how the drug will actually be used in medical practice and what the total impact of such

use, for good or ill, will be. The marketing of a newly approved drug occurs with great intensity: the drug moves almost overnight from scientifically controlled study in a few hundred or thousand patients with no commercial promotion, to maximal promotion and relatively uncontrolled treatment situations that may involve several million patients in the first year of marketing alone. Faced with such uncertainties, there is a natural tendency for a regulatory agency to err on the side of conservatism. In the U.S., for example, former FDA Commissioner Dr. Alexander Schmidt described some drugs as being held to ransom in the regulatory process because of doubts about how they would be used if approved for release (2), and the recently-introduced Drug Regulation Reform bill (1978) seeks to apply unlimited utilization controls to drugs of high risk that would otherwise not be permitted on the market at all (3).

One way to improve the knowledge about the use and impact of new drugs would be to use postmarketing surveillance (PMS) to avoid prolonged premarketing barriers. Virtually all parties to the process of drug development have agreed that improved PMS is desirable, but the technical problem of devising an effective, and cost-effective, system remains. In response to a challenge from Senator Edward Kennedy, an independent Joint Commission on Prescription Drug Use has been set up in the U.S. with industrial and other funding to consider all aspects of drug utilization. This commission may recommend utilization controls if the quality of drug use is deemed to be significantly deficient.

Drug Costs

The other reason for controls is to constrain the cost of prescription drugs. The cost of health care in general has caused increasing concern in all countries, and particularly in the United States as that nation considers some sort of national health insurance scheme. In this context, prescription drugs have received more and earlier attention than have other components of health care, even though they account for somewhat less than 10 percent of the total cost of health care.* In countries with a national health service where the government pays for all or most prescription drugs, cost-constraint programs have been in operation for many years, and several cost-control initiatives have been implemented in recent years in the U.S. (such as the Maximum Allowable Cost, or MAC, program) in a manner similar to existing programs in other countries.

MEASURING THE IMPACT OF UTILIZATION CONTROLS

Control of Drug Costs

Although the expenditure on drugs can be readily constrained by a control system, two questions have not been satisfactorily answered. The first is whether the total cost of administering a control scheme can be offset by the actual saving in drug costs. There is evidence that at least in some cases, such as the Manitoba system in Canada, the saving may be less than the cost of administering the system (4).

The second question relates to the overall effect of savings in drug costs on the total cost of health care. Since the drug component is a relatively small per-

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centage of the total, even a large reduction in drug expenditures could not reduce total health care costs substantially. It is possible that cost constraints on drugs could change health care delivery patterns into more expensive modes (for example, by lengthening the time of hospitalization), or could prolong a patient's loss of earnings. (It is also possible that the opposite would happen.) The actual effects of drug cost-constraint systems are unknown and, until hard data are obtained to answer these questions, it is not valid to assume that cost constraints on drugs will actually constrain the total cost of health care.

Control of the Quality of Prescribing

The use of utilization controls to improve the quality of prescribing has important implications for both the quality of therapeutics and the regulation of new-drug development.

Utilization controls would deserve serious consideration if it could be shown that they improve the quality of therapeutics both for individual patients and for society as a whole (for example, if they generally structure drug use to "beneficial" indications without denying care to those patients who would benefit from an unapproved use).

Control of utilization has reduced the inappropriate use of toxic drugs in the case of chloramphenicol restrictions in New Zealand and Sweden (1), for example, but in most situations the outcome, in terms of risks and benefits, has not been fully examined. Indeed, there is usually no procedure for examining the outcome in those situations where most controls are exerted, such as admission of drugs to formularies (1). Most schemes that are intended to alter benefit-risk ratios are implemented through the special use of existing cost-control systems, but in many systems neither the net cost savings nor the full medical benefits have been assessed in relation to the disadvantages.

In the case of the regulation of drugs in the U.S., both past and present FDA commissioners have stated that if the agency knew drug use would be confined to specific and restricted indications, it would be more ready to approve new drugs. There is, however, a risk that these restrictions would simply add new postmarketing hurdles to the existing premarketing ones, thus defeating the aims of the exercise.

Impact on Research

Another very important influence of drug utilization controls is on research. Tight controls on drug utilization would, if they have the same substantial impacts on the world's main drug markets as they have had in other countries (1), raise the prospect of a radical, and so far generally unanticipated, change in the structure of drug research.

The prospective returns on investment in research by profit-making companies are very likely to be reduced by utilization controls, both those aimed directly at drug costs as well as those intended to improve prescribing. If this occurs in the main world markets (themselves the main drug-developing countries), the level of industrial investment in research and development will necessarily decline and research investment will be reduced or redirected into products with less likelihood of being controlled. The implementation of both types of controls in the United States would be the first serious attempt in history to control utilization in the world's largest single market. If, as a result, the private sector's investment in research and development (R&D) should fall, there would be a delay before the impact of this decline would be recognized. This delay in recognition

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would be due to the rudimentary state of our ability to measure the level of research and to quantify the therapeutic innovations that result, and to the length of time that must elapse between research investment and any measurable outcome from it (5). There could be a significant shortfall in R&D investment and a very large decrease in research output before society became aware of the difference. The ultimate result might be government intervention to make up the shortfall in research although recent figures for worldwide governmental expenditures on research hardly encourage optimism about such action. In the interim, the years of delay in therapeutic progress could be very costly to patients. This cost must be weighed against any short-term saving on drug costs (if saving does in fact outweigh the cost of controls) and the putative improvement in the quality of prescribing that are the aims of existing and planned utilization control systems.

Research in vaccines and antisera has special relevance to the future structure of the drug R&D effort. For a number of reasons government participation in this type of research in the U.S. has been increasing and that of commercial producers declining. The *Reports and Recommendations* of the National Immunization Work Groups in March 1977 describes the problem as a threat to maintaining the production and supply of vaccines, and concludes that unless the problems they describe "are dealt with effectively, production and supply as well as research and development of present and potential vaccines and serums could be threatened, despite the absence of a current crisis" (6).*

The area of vaccines is one in which the government has already been involved and in which the discovery procedures and likelihood of results are far more predictable than is the case with drugs. The special problems of R&D and production that are now seen with vaccines may thus be the first indication of what may occur for other pharmaceuticals as the decline in return on R&D is accentuated by utilization controls.

CONCLUSIONS

Most utilization-control systems have originated for the purpose of constraining drug costs under third-party payment schemes (7). In some countries these control systems have easy access to large computerized data bases that already exist for purposes of reimbursement and accounting and that typically have information for each prescription identifying the kind and amount of drugs used, the prescribing physician, and the dispensing pharmacist. Some systems have, in addition, information on the patient's identity and the medical indication for which the drug was prescribed. These systems are readily adaptable to setting up and enforcing elaborate utilization controls. Criteria can be set for the identity and quantity of drug, the condition for which it is prescribed, the type of physician or pharmacist, and the patient, or any combination of these. Failure to meet all the criteria can be made grounds for rejecting reimbursement of the prescription's cost by the third-party payer. These systems thus have the potential for complete control over the way in which reimbursable drugs are used. In some countries, the systems have been adapted to varying extents to improve the quality of utilization of therapeutic drugs. More recently, it has been proposed to use utilization control schemes to control at least the early stages of drug use after

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*Since their report was published, one of the major remaining vaccine producers has decided to cease production of vaccines. Subsequently it was noted that "only one firm, Merck, is currently producing live measles, rubella, and mumps virus vaccines, compared with seven producers within the past 15 years." (*F-D-C Reports*, vol. 39, 11 April 1977, p. T&G-6.)

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marketing. For this purpose, the premarketing investigation of a drug's development is integrated with its early postmarketing experience.

In some countries both main objectives of utilization control are merged within one system. For example, a country with a structured health service and a national formulary may implement constraints on utilization, under the rules of third-party reimbursement, in order to monitor the early progress of a drug after it has been approved for marketing.

In the United States the two functions of cost constraint and improving the quality of prescribing have in the past been kept separate, with the FDA confining its attention to matters of science and, more recently, to quality of prescribing. In the past year, however, the FDA has moved sharply and enthusiastically into cost-containment activities (8). Certain parts of currently proposed bills would further involve the FDA in cost-containment activities. For example, its rulings on the therapeutic equivalence of different products would imply a guarantee of bioequivalence that is needed and used in the MAC program. Cost containment is a new role for FDA, and one not envisioned among its original functions.

There are large differences between the systems in countries that are solely drug consumers and those that are also drug developers. The former perceive utilization controls largely as cost-control weapons that enable the consumer David to fight the Goliath of the multinational pharmaceutical industry. In contrast, the drug-developing countries are less likely to control domestic drug costs, probably because to do so might damage the export prices obtainable for the same drugs.

Although the objective of most utilization-control systems is to save money, there has not yet been a good demonstration of the saving related to even this narrow objective (taking into account the cost of administering the system) (9). Nor has there been a cost-benefit study in a wider sense that weighs the cost of illness against the cost of drug therapy and the saving achieved by utilization constraints. The cost of illness and the cost-savings achieved by effective therapy have seldom been measured by anyone and obviously need research.

In improving drug utilization, the main alternatives to compulsory forms of control are voluntary processes such as peer review and education. The Scandanavian countries, for example, feel that postgraduate education of physicians is the preferred way to improve prescribing.

Other alternatives include better information for the patient. One channel for this is the patient package insert (PPI), two of which already exist in the U.S. (for oral contraceptives and for estrogens used postmenopausally), and two others (for progestogens and for intrauterine devices) have been ordered by FDA. This is in general a desirable trend but more research is needed to determine the most effective type of PPI. There has been little objective study of what information, and how much, should be included or excluded to benefit the patient most; nor is there any information about how much improvement in the quality of drug use will result from different levels of information.

Another alternative to stricter regulation is stricter legal liability of a manufacturer for his products (10, 11). The consequences and public policy implications are far-reaching but have not been fully explored. The liability issues that have arisen as a result of the 1976 swine flu program in the United States are believed by some to imperil all future national immunization programs in that country. To date, 1,483 claims have been filed against the U.S. government seeking damages of $775 million for alleged injuries from swine flu immunization (12). (The original cost of the program itself was a little over $100 million.)

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Utilization-control systems, in addition to any direct effect on drug prescribing, provide a means of enforcing other influences on the drug market, including generic substitution and price controls. Along with other regulations, such as the compulsory licensing of patents in some countries (for example, Canada), these mechanisms will make it possible for third-party payers to control the pharmaceutical companies' returns on investment in drug research. Such controls already exist in some of the drug-consumer countries, but since these are small individual markets the full impact on expected return on investment has not been felt. The real impact will occur as the drug-developing countries impose utilization controls. When this happens, it will signal the beginning of a major change in the entire structure of therapeutic R&D, including a fundamental rearrangement of the relations between the functions of the public and private sectors in this endeavor.

The magnitude—even the existence—of this potential problem is not generally appreciated. The full public policy implications of the impact on therapeutic progress have scarcely begun to receive attention. One indication of the scope of the problem is the extremely small number of countries that are now responsible for originating nearly all new therapeutic drugs (13).

At present, with applied drug development largely in the hands of the private sector, decisions to fund projects that could yield better drugs depend in large part on the anticipated returns from sales to tomorrow's patients, while the funds for implementing these decisions come from profits on sales of existing drugs to today's patients. Controls on the profits from today's new drugs and hence on the return on investment in therapeutic drug R&D inevitably raise the important public policy question of who will fund drug research and development in the future. The answers will determine the structure and future of drug (and device) research. The serious problems with vaccine R&D in the United States illustrate what could happen to such research in the future.

In view of existing U.S. and foreign experience, I would suggest the following objectives for sound public policy decisions regarding utilization controls.

1. The goals of any proposed utilization-control system, or of any particular aspect of such a system, should be clearly defined. Formal evaluation should be part of the design and implementation of the system in order to determine whether the stated goals are actually being achieved. In particular, evaluation should also seek to detect and measure any undesired effects, especially on R&D.

2. For any system that is designed to constrain drug costs, the evaluation should, at a minimum, measure the total amount actually saved on drugs and compare it with the total cost of setting up, implementing, and administering the cost-constraint system.

3. Formal and more extensive cost-benefit analyses should be undertaken to assess the total medical impact of utilization-control systems as measured by rates of mortality and morbidity, gain or loss of earnings, and comparative total cost of all forms of treatment for each disease in question.

4. Detailed attention should be given to the effects of utilization controls (particularly cost constraints) on the expected rate of return from research and on the discovery and development of drugs and medical devices in the future.

5. In the overall task of improving utilization, alternatives to regulation need careful consideration. Continuing education of physicians and patients is one realistic alternative approach to improving utilization, although a clear distinction needs to me made between education aimed at cost constraint and edu-

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cation aimed at improving the quality of prescribing.

The papers presented at this symposium have generally dealt with national and international data on the utilization of drugs within particular therapeutic categories. Few of the reports that are available on this subject include a convincing explanation of the reasons for any observed differences in patterns of utilization between countries, or of the therapeutic consequences that result. Although it would be extremely difficult to dissect the precise contribution of specific factors to the observed patterns, the types of drug utilization controls that exist in the different countries would be among the important determinants. As I have described in this paper, the nature and implementation of drug utilization controls have very important implications for the quality of drug therapy available to patients, the cost of drugs, and the nature and future of drug research.

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A Close Inspection of the 'Calm Look'

Rhetorical Amblyopia and Selective Amnesia at the Food and Drug Administration

William M. Wardell, MD, PhD

Playing such simplistic numbers games is misleading and only clouds the issue.

HENRY E. SIMMONS, MD, Director, FDA Bureau of Drugs (criticizing the use of Paul deHaen's numbers to assess national systems of drug regulation), February 1973[1]

I am somewhat weary of the drug-introduction numbers game being played by Government, industry, and a lot of other people. Unfortunately, I am an unwitting contributor to this number juggling on the introduction of new drugs in this country and abroad because many of the data used by all sides are mine.

PAUL DEHAEN, head of Paul deHaen, Inc[2]

The major constraint on pharmaceutical innovation in the U.S. today is probably the IND regulations coupled with the institutional review committee requirement.

J. RICHARD CROUT, MD, Director, Bureau of Drugs, December 1975[3]

It is very clear that certain drugs that are good drugs and properly should be approved in a modern country are approved somewhat later [in the United States than, for instance, in Britain]. . . . I think we have made a number of improvements in recent years in the review time, I can document that. . . . [However] within the last year we have also had an increasing backlog, and I think we are going in the wrong direction again [emphasis mine].

J. RICHARD CROUT, MD, Director, Bureau of Drugs, January 1978[4]

CONNOISSEURS of vintage political pharmacology from the Food and Drug Administration experienced a strong sense of déjà vu on reading Commissioner Donald Kennedy's recent article "A Calm Look at 'Drug Lag.' "[5] Like his two immediate predecessors in office, Dr Kennedy incants the now ritual oath seemingly required of a new FDA Commissioner: The drug lag does not exist; nevertheless I will abolish it. Dr Kennedy's article is part of a new FDA campaign[6] to exorcise the drug lag by dialectic[7-10] (remarks before the Food and Drug Law Institute, December 1977) if it cannot be abolished by deeds. Unlike his predecessors, Dr Kennedy feels the need for a new drug law to accomplish this.

CONTRADICTIONS

Dr Kennedy's two predecessors recanted their disavowal of the drug lag on leaving office (A. M. Schmidt, Feb 9, 1977; C. C. Edwards, Sept 18, 1975). Dr Kennedy has spared us the wait, having partially recanted on several occasions already. For example, on Oct 27, 1977, he said:

I think there is no question that the Drug Lag exists although it is substantially less serious than the Food and Drug Administration's severest critics make it out to be.[11]

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The contradiction in Dr Kennedy's various statements is due to the fact that he *needs* the drug lag to justify his proposed new law, since one of the legislation's claimed purposes is to abolish the lag. As he stated in October 1977:

Some historical inflexibilities in our drug laws may be contributing some unnecessary delay and procedural stiffness to the new drug approval process, and that is part of the reason we are proposing the first major revisions in the drug laws since the Kefauver-Harris amendments of 1962.[10]

Dr Kennedy cannot have his cake and eat it too; if the drug lag has vanished, then so has one of his justifications for a new drug law.

Given the Commissioner's doublethink about the drug lag, where do his superiors at the Department of Health, Education, and Welfare (DHEW) and his scientific advisors at FDA's Bureau of Drugs stand on this issue? Both, it turns out, acknowledge that there is a drug lag.

At DHEW, Secretary Joseph Califano[12] recently cited the following problems with the regulation and approval of new drugs among the reasons he claimed necessitate a new drug law:

The problem of lengthy—and often repetitive—review procedures to get a drug on the market. Applications for approval of new drugs average 34 volumes, take years to process, and cost millions of dollars to complete. . . . Because it is difficult to remove a drug from the market, our only responsible course has been to be extraordinarily conservative in the approval process—which aggravates the problems of delay I have already mentioned [empha-

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sis mine].

We need a system that will allow us to put promising drugs on the market faster, without compromising safety, and that will encourage competition, not stifle it. We must look for ways to provide clear guidance and to accelerate the approval process without loss of quality.

At the FDA's Bureau of Drugs, Director Richard Crout not only admits that a drug lag exists, but opines that it may now be getting worse.[4] The FDA has in fact acknowledged the drug lag as a problem since September 1974 when, at hearings of the Senate Health Subcommittee, Dr Crout retracted the strenuous denial of the problem that had been the previous policy of Commissioner Edwards and his Bureau of Drugs director, Dr Henry Simmons. Dr Crout's prepared statement for the hearings contained the following:

Mr. Chairman, I am pleased to have the opportunity to appear before your Subcommittee to discuss the "drug lag" from the viewpoint of the Food and Drug Administration (FDA).

Let me begin by stating that there is no question that a "drug lag" exists in the United States in the sense that a significant number of drugs marketed in foreign countries are not available here. . . .

There is, therefore, a societal cost for strong effectiveness and labeling requirements in that drugs are introduced more slowly into this country than certain other countries. It is important that we maintain balance and perspective on this problem so that the overall net effect is beneficial to the health of the American public. We strongly believe that this is the case now. The "drug lag" is, therefore, a real phenomenon and worth continuing attention; but when reviewed in perspective, it must be appreciated that it does not involve any drugs which are important therapeutic gains and is an expected consequence of high regulatory standards. . . .

For some time, the Agency has been under criticism by the medical profession and the drug industry for its alleged failure to approve drugs which are available in other countries. To the extent that this failure of timely approval is due to administrative delays in the FDA, the Agency has reappraised its way of doing things. We believe we have done this honorably in the past several years with resulting important gains in internal procedures and the quality of decisions.[13]

The actual hearing record contains these exchanges:

Senator Edward Kennedy. *You are aware of what Mr. Simmons said last year before Senator Nelson. . . . He said in our judgment there is no condition amenable to drug therapy which cannot be treated as effectively in the United States as anywhere in the world, and that the American public is not being deprived of safe and efficacious drugs. . . . Dr. Crout, what do you have to say?*

Dr Crout. *We would modify that statement today, as my statement here indicates. . . .*

I think we would just be blind to the truth to say that there are not some drugs overseas that will be beneficial in this country, and we have a responsibility in the Food and Drug Administration to make sure they get here. . . .

We have the highest standards for effectiveness and safety in the world. We are proud of it. We do not want to change the situation but, as I pointed out, a cost of that is that some drugs of value to patient care get here later than they do in other countries. . . .

Senator Kennedy. *How many drugs did the FDA approve in the cardiovascular area since 1963? . . .*

Dr Crout. *The data cited by Dr. Wardell are correct.* There were no approvals of hypertensive drugs in the first decade after the [1962 Kefauver-Harris Drug] amendments. There were no approvals in the cardiovascular area in the years between 1967 and 1972, *and that is one of the causes of much of the concern by physicians and so on about the drug lag business* [*emphasis mine*].[13]

But let us ignore all these contradictions and proceed to examine the analysis of the drug lag that Dr Kennedy presents. The plan of his "calm look" article is as follows:

1. An attempt to impugn the integrity of those who assert that there is, or ever has been, a drug lag.

2. An attempt to disprove the notion of a US drug lag by pointing out that drug introduction dates are asynchronous across countries (the "asynchrony argument").

3. Use of the asynchrony argument, combined with the world slowdown in pharmaceutical innovation, to claim that the US slowdown is simply part of a global trend. This begs the question of whether the United States lags behind other countries.

4. Attribution of the slowdown in US and world pharmaceutical innovation to what may be termed the "knowledge depletion" hypothesis, further diverting attention from the drug lag issue.

5. Taking credit for some alleged benefits of the drug lag in terms of risk avoidance, apparently without concern for the fact that this tacitly acknowledges that the drug lag does exist.

6. A final cautious admission that the FDA's practices have slowed the passage of drugs through the system, this being used to justify the proposed new drug law.

Even at a casual glance, the aforementioned plan demonstrates some doubtful overall logic. I will now examine the details of Dr Kennedy's argument in the same sequence as they appeared in his article.

OBFUSCATION, SMEAR TACTICS, AND STRAW MEN

Obfuscation

Although Dr Kennedy has previously decried the use of the term "drug lag" without a definition,[6-9,14,15] nowhere in his article does he define it himself. It is a simple matter to state the important questions in the drug lag issue: Are there unnecessary delays in the process of drug development and regulation in the United States? Are new drugs being approved for use consistently later in the United States than in other medically advanced countries? If so, what are the reasons, and are there significant therapeutic consequences?

While a numerical summary is a useful starting point, the answers to these questions cannot be found in raw, uninterpreted numbers such as the deHaen data, however skillfully they are juggled; that strategem was deservedly repudiated by the FDA's Dr Simmons[1] and by Mr deHaen himself[2] five years ago. Nor can the fact that drugs are introduced asynchronously into a number of countries be an answer to the question of how the United States compares with other countries; that tactic actually obscures the real questions.

A valid approach is first to compare the United States in detail with Great Britain, the country with medical standards most similar to ours and the only other English-speaking country performing drug development on a substantial scale. After performing such a comparison, one might pick the next most important country whose therapeutics one understands and perform a similar systematic comparison. The question

Agency has reappraised its way of doing things. We believe we have done this honorably in the past several years with resulting important gains in internal procedures and the quality of decisions.[13]

The actual hearing record contains these exchanges:

Senator Edward Kennedy. *You are aware of what Mr. Simmons said last year*

lags behind other countries.

4. Attribution of the slowdown in US and world pharmaceutical innovation to what may be termed the "knowledge depletion" hypothesis, further diverting attention from the drug lag issue.

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is, how does the *United States* compare with each of the other countries *not*, how does each country compare with the others. Dr Kennedy's use and analysis of multicountry numbers obscure this main question. I will discuss his analysis in more detail.

Smear Tactics

Dr Kennedy opens with the smear tactic first used by former Commissioner Edwards in attempting to rebut the Dripps Committee in 1972, namely, that the idea of the drug lag (and even the term itself) was invented by the pharmaceutical industry, implying that anyone who believes in, uses, or endorses the notion is ipso facto part of that industry. Commissioner Kennedy has used this tactic in at least seven speeches or papers since June 1977.[6,7,9,10,14-16] It is well known at the FDA that the charge is factually incorrect. The first published use of the term "drug lag" was in a paper delivered at the Fifth International Pharmacology Congress at San Francisco in July 1972,[17] at which Dr Richard Crout occupied most of the discussion period delivering a response from the FDA.

Many eminent scientists in the academic and medical communities, together with professional societies and at least one prestigious government panel, have expressed concern about the problem of drug lag and the FDA's delaying effects.

One of the first academic groups to express concern was the Dripps Committee. On Feb 29, 1972, the late Dr Robert Dripps, Vice-President for Medical Affairs at the University of Pennsylvania, wrote to Congressman Paul G. Rogers to voice his concern that "the procedures by which new drugs are evaluated and approved for use in this country is [sic] causing us to fall behind in this important area of medical science." The cosignatories were 21 other distinguished medical scientists who were deans or departmental chairmen of medical schools or directors of medical research institutes. They represented some of the most notable figures in American therapeutic research, including five Albert Lasker Award winners and a Nobel laureate.

Many experts in the academic and medical communities have voiced similar and more specific concerns about their own particular therapeutic areas. These areas include cardiovascular therapy,[18-22] respiratory therapy,[23-25] gastrointestinal therapy,[26-27] psychiatry,[28-30] cancer chemotherapy (E. J. Freireich, Oct 1, 1976), and epilepsy.[31] National private disease-oriented societies and certain divisions of the National Institutes of Health (NIH) have also chafed at the FDA's delays and inhibitory effects on therapeutic progress in their areas. These include the National Heart, Lung, and Blood Institute[32]; the National Cancer Institute,[33-35] supported by the American Cancer Society; the Epilepsy Foundation of America; the National Commission for the Control of Epilepsy and Its Consequences; and the National Institute of Neurological and Communicative Disorders and Stroke.[36] Professional societies that have expressed concern include the American Society for Clinical Pharmacology and Therapeutics.[37] The American College of Cardiology sponsored an entire meeting on problems in the development and introduction of new cardiovascular drugs.[38] The problem has been acknowledged by all three of the most recent FDA Commissioners (Dr Herbert Ley,[39] Dr Charles Edwards, and Dr Alexander Schmidt).

Finally, prestigious national committees have arrived at similar conclusions. The President's Science Advisory Committee concluded (on a page adjacent to the one from which Dr Kennedy quoted) that it may:

be worth adapting U.S. regulations so that not even a single important new entity introduced into selected foreign countries during the previous year fails to become available in the U.S.[40]

More recently, the President's Biomedical Research Panel has concluded that the delays and costs that the FDA's protective systems impose on drug development constitute a *hazard to public health.*[41]

It is obvious that the medical, research, and professional communities, in addition to the FDA itself, are justifiably concerned about the extent to which therapeutic progress is being inhibited in the United States, both in an absolute sense and by comparison with other advanced countries. The concern is real; it is not a fiction created, as Dr Kennedy alleges, by the pharmaceutical industry.

Straw Men

Dr Kennedy goes on to charge, as he has in earlier speeches[5,8,9,42] (*The Washington Post*, Nov 24, 1977), that those who believe there is a drug lag are "soft on efficacy," that the "drug lag propagandists *really* seek a watering down or elimination of the 1962 efficacy amendment to our basic law."[8] This is a remarkable assertion, since not even the pharmaceutical industry has called for such action. It is true that on occasion the American Medical Association, out of a growing sense of frustration over the heavy hand of the FDA on the practice of medicine, has called for repeal of the efficacy provision and that some distinguished economists have pointed out that there are ways to achieve drug safety and efficacy other than by legislation (*Newsweek*, Jan 8, 1973, p 49). However, most scientists and academics take the view[43] that the efficacy law itself is desirable and what is really needed is better implementation by the FDA of its own regulations. While a few individuals and certain congressmen may favor repeal, it is doubtful whether Dr Kennedy could name any well-known academic clinical pharmacologists who have ever advocated repeal of the 1962 amendments. The main function of this straw-man ploy is to deflect attention from the FDA's demonstrated inability to use properly the extensive powers it already has.

THE ASYNCHRONY NUMBERS GAME

Dr Kennedy asserts that "the whole [drug lag] matter has been hopelessly mired in the statistics"[5] and that a qualitative assessment is needed to make sense of the numbers. That is what Dr Simmons[1] said in introducing the FDA's "value ratings" in 1973 in a serious attempt to go beyond the numbers, yet Dr Kennedy here blithely proceeds to use bare numbers for his entire argument. Not only does Dr Kennedy's article lack any qualitative assessment of the drugs denoted by his 1976 numbers, the drugs are nowhere named. The reader is thus unable to make any personal evaluations, and there is no evidence in the article that Dr Kennedy even knows the identity of these drugs, let alone their therapeutic value.

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Table 1.—Introductions of New Chemical Entities

	Exclusive to Country Shown Compared With All Five Others	Exclusive to Country Shown Compared With United States	Exclusive to United States Compared With Country Shown	Ratio, Exclusive to Country Shown: Exclusive to United States
DeHaen data for 1976*				
Great Britain	10	18	7	2.6†
France	14	27	11	2.5†
Germany	14	32	9	3.6†
Italy	9	18	11	1.6
Japan	2	10	13	0.8
United States	5	...	...	...
More extensive data for Great Britain-United States comparison‡				
Great Britain (1962-1971)	...	43	14	3.1
Great Britain (1972-1976)	...	72	21	3.4

*As cited by Dr Kennedy.[5]
†Average of three countries is 2.9.
‡Nine major therapeutic areas that cover most of the areas in deHaen data.

Dr Kennedy proclaims that new chemical entities (NCEs) are the item of interest, implying that others have been unaware of this. On the contrary, this measure has consistently been used as the focal point since the original drug lag studies in 1972.[17,44-47] Dr Kennedy compounds his strategem by erroneously claiming that *all* NCEs are therapeutically important: "Data provided by Paul deHaen are based on this fundamental distinction [ie, restricted to NCEs] *and involve only new and important chemical entities*"[5] [emphasis mine]. In fact, the deHaen data are not compiled on the basis of any therapeutic interpretation. Obviously, not all NCEs are important; this was recognized in the literature years ago, and deHaen's and Simmons' rejection of the simple "numbers game" in 1973 is still valid today.

Leaving aside the fundamental inadequacy of using bare numbers to address questions of therapeutic significance, does Dr Kennedy's analysis actually tell us how the United States measures up against other countries in the number of new drug introductions? One can condense Tables 1, 2, and 3 from Dr Kennedy's article into a single table that answers the question immediately. The essential data (shown here in Table 1) are the numbers of NCEs introduced into each country exclusively during 1976.

Column 2 of Table 1 shows the number of NCEs exclusively introduced into each of the countries listed in column 1 (NCEs that, by the end of 1976, were available in that country but in none of the five others). This number was five for the United States, ten for Great Britain, and 14 each for France and Germany. Column 3 shows the number of NCEs introduced into each country but not introduced into the United States, while column 4 gives the converse figures, the number of NCEs introduced into the United States but not into each of the other countries. The number of drugs exclusively available in each of the European countries was much greater than in the United States. The ratios in column 4 indicate that in 1976, 2.6 times as many drugs were introduced exclusively into Great Britain as were introduced into the United States; the corresponding figures for France and Germany were 2.5 times and 3.6 times as many as in the United States. The average for these three countries was 2.9 times that for the United States.

Analyzed in this way, Dr Kennedy's data show that numerically there is indeed a large lag between the United States and all the drug-developing countries of Western Europe, a fact hidden by Dr Kennedy's analysis. Moreover, one must guard against using this snapshot picture of a single year to infer overall trends, since trivial asynchronies in marketing could lead to large short-term apparent differences between countries that may not be representative of the general trend. Dr Kennedy's attempt to use the asynchrony argument to claim that there is a universal drug lag in all countries is like claiming that one can predict a person's age by the month in which his birthday falls.

NCEs in the United States and Great Britain

To avoid this trap, data are needed over a several-year period to allow useful comparisons. Such data are available specifically for the comparison of the United States with Great Britain, and these are shown in Table 1 for nine major therapeutic areas, including virtually all the categories specifically named in the deHaen analysis[44] (W. M. Wardell, MD, PhD, unpublished data, October 1977). Data are given for two periods: 1962 through 1971 (ie, the decade following the 1962 amendments) and 1972 through 1976. From these data (summarized in the bottom section of Table 1), it can be seen that the numbers Dr Kennedy uses for 1976 substantially *underestimate* the US lag behind Great Britain; over the five years through 1976 for the nine major therapeutic areas selected, 43 drugs were introduced exclusively in Great Britain and 14 in the United States, ie, 3.1 times as many in Great Britain as in the United States. The corresponding Great Britain-United States ratio for the decade 1962 through 1971 was 3.4. Comparing these figures with Dr Kennedy's ratio of 2.6 for 1976 shows that the differences for 1976 were atypically small compared with the preceding 15 years. (This would be consistent with the gradual improvement mentioned by Dr Crout. It will be recalled, however, that Dr Crout believes that more recently the backlog at the FDA is increasing.) The full data, including 18 tables listing specific drugs, nine figures, and 30 pages of interpretation of the therapeutic significance of individual drugs, were made available to Dr Kennedy at his request in the summer of 1977, but were not taken into account in his article. (Dr Kennedy actually sent two members of his Office of Planning and Evaluation to Rochester, NY, to obtain the manuscript describing the period 1972 through 1976; data for the previous decade were already published.)

A similar analysis should be done

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Table 2.—Cardiovascular and Respiratory Drugs, 1963-1976

	Date of Introduction*		Lead, mo	
	Great Britain	United States	Great Britain	United States
Cardiovascular drugs				
Antihypertensives				
Guanoclor sulfate	1964	...	...	...
Guanoxan sulfate	1964	...	...	...
Bethanidine sulfate	1964	...	...	...
Debrisoquin sulfate	1967	...	...	...
Diazoxide	1972†	1/73	(7)	...
Clonidine hydrochloride	3/71	9/74	42	...
Prazosin hydrochloride	9/74	6/76	21	...
β-Blockers				
Pronethalol hydrochloride	1964‡	...	...	...
Propranolol hydrochloride§	1965	11/67	(29)	...
Oxprenolol hydrochloride	11/70	...	...	...
Practolol‖	1970	...	...	...
Timolol maleate	6/74	...	...	...
Sotalol hydrochloride	6/74	...	...	...
Pindolol	10/74	...	...	
Acebutolol hydrochloride	4/75	...	...	...
Metoprolol tartrate	7/75	...	...	...
Atenolol	1976	...	...	...
Antiarrhythmics				
Verapamil hydrochloride	1967	...	...	...
Lidocaine¶	...	10/69	...	...
Disopyramide	6/72	...	...	...
Bretylium tosylate	11/72	...	...	...
Phenytoin#	8/73	...	...	...
Mexiletine hydrochloride	1976	...	...	...
Respiratory drugs				
Bronchodilators				
Metaproterenol sulfate	1962	7/73	(133)	...
Ethomoxane hydrochloride, clorprenaline hydrochloride, and methapyrilene hydrochloride	1963	1/60‡	...	...
Bamifylline hydrochloride	1965	...	...	...
Proxyphylline	1967	...	...	...
Acefylline piperazine	1968	...	...	...
Albuterol	1969	...	...	...
Terbutaline sulfate	6/71	3/74	33	...
Rimiterol hydrobromide	6/74	...	...	...
Antiallergics				
Cromolyn sodium	1968	6/73	(60)	...
Beclomethasone dipropionate	11/72	5/76	42	...
Betamethasone valerate**	9/73	...	...	...

*The dates of introduction represent the best information currently available. The date of New Drug Application (NDA) approval is given for US drugs, and generally, the date of marketing is given for British drugs. Where the month of British marketing is not known, the lead has been estimated on a June date and is shown in parentheses.

†This drug was available earlier than this in Great Britain for hospital use.

‡Subsequently withdrawn.

§The dates given are earliest approval dates. Propranolol was approved for use as an antihypertensive in Great Britain in February 1969 and in the United States in May 1976.

‖Practolol is now restricted to parenteral use in hospitals because of toxic reactions that developed during long-term oral administration.

¶Date of British marketing is not available. Date given for US approval is for antiarrhythmic indication.

#This date is for approval for antiarrhythmic indication.

**Not new chemical entity, but important new dose form (inhaler).

for mutually available drugs, ie, those that by the end of the observation period were available in both the United States and in each country under consideration. While Dr Kennedy does not present enough information to perform such an analysis, the United States–Great Britain comparison already referred to showed a similar disparity between the two countries: mutually available drugs accounted for less than half of the total number of NCEs introduced into either country during the years 1972 through 1976. Among these mutually available drugs, 2.5 times as many became available first in Great Britain as in the United States, with British leads of around ten years in some cases.

On examining the clinical implications of the comparison between Great Britain and the United States during the years 1972 through 1976, the therapeutic differences between the two countries were found to have narrowed considerably compared with the decade 1962 through 1971 (W. M. Wardell, MD, PhD, unpublished data, October 1977). The main therapeutic areas in which, by December 1976, the United States was still substantially behind Great Britain included the cardiovascular area, the treatment of peptic ulcer, and the therapy for CNS diseases, including depression, epilepsy, and migraine. In other areas the differences were scattered and, while generally in the direction of a British lead, did not form as strong and consistent a pattern as was observed in the previous decade. This evaluation, however, dealt only with the most obvious differences; a more detailed interpretation might increase the perceived clinical significance of these differences. Furthermore, because of the long duration of the drug development process, the effects of recent regulatory changes are not yet reflected in these data.

Since Dr Kennedy chose not to deal with any drugs by name, it is instructive to determine exactly how the United States compared with Great Britain in important therapeutic areas. Table 2 compares the United States with Great Britain for the years 1963 through 1976 in some illustrative areas of cardiovascular and respiratory therapeutics; these data document the delays and the absence of drugs from the United States. Furthermore, delays in the approval of labeling particular *uses* in the United States (eg, in the case of propranolol, a seven-year delay of approval for treatment of angina as well as for hypertension) make these differences even greater than they appear at first.

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narrowing, and one of the reasons for this was probably an improvement in the FDA's performance. This is consistent with what has been claimed by Dr Crout and reflects credit on the agency, but if someone denies the existence of the drug lag, it is difficult for him to claim credit for decreasing it.

OVERALL WORLD SLOWDOWN

It is true that there has been a world slowdown in pharmaceutical innovation during the past two decades. However, Dr Kennedy conveys the impression that the United States is but one of many countries sharing in the slowdown and is not exceptional. The preceding analysis of Dr Kennedy's own numbers shows that whatever the world picture, the United States lags considerably behind other Western nations in the introduction of new drugs.

THE KNOWLEDGE DEPLETION HYPOTHESIS

Having first obscured and then begged the question of the US drug lag, Dr Kennedy invokes what is known as the "knowledge depletion" hypothesis as the cause of our problem. This hypothesis proposes that the decline in pharmaceutical innovation is attributable to a depletion of our existing stock of biological knowledge during the fertile period of therapeutic innovation of the past two decades, and that before new progress can occur there need to be further fundamental advances in basic knowledge. At first sight this is a plausible hypothesis, and it has been casually advanced by several people in industry, government, and academia. Whenever the hypothesis has been used, however, it has been as an undocumented assertion.

On closer examination the hypothesis is not compelling. Basic knowledge about disease and therapeutics is increasing at an exponential rate, a fact apparent to any scientist who attends scientific meetings and reads the literature. The nation's vast investment in basic biomedical science during the past two decades has resulted in a huge body of basic knowledge that is available for therapeutic applications. It is impossible to reconcile this well-established "knowledge explosion" with the notion of "knowledge depletion."

The most up-to-date and detailed assessment of this situation is the Report of the President's Biomedical Research Panel (April 1976):

Human beings have within reach the capacity to control or prevent human disease. Although this may seem an overly optimistic forecast, it is, in fact, a realistic, practical appraisal of the long-term future.

There do not appear to be any impenetrable, incomprehensible diseases. This, in itself, represents the major advance for biomedical science, and it is a change which has occurred only within the past 25 years.[41]

The report identifies the transfer of information and technology, and in this context the FDA itself, as a special problem. It states:

Meanwhile, there is a different kind of hazard to public health, posed by the prolonged delays and great costs of developing new and potentially useful drugs which the FDA's own protective systems have imposed. In some respects, the agency has become a formidable roadblock. While it is clearly beyond our charge to propose ways for improvement of the FDA, the problem is there, and we are obliged to cite it in the context of this report.[41]

The report also identifies the areas of "greatest promise" and the "impasse areas." Under the heading "Pharmacological Sciences Overview," the areas of greatest promise include some of the major problems that we currently face, eg, cardiovascular disease, proliferative diseases, drug design, control of drug dosage and its delivery to specific targets, pharmacology of genetic engineering, quantification of risk-benefit assessments of important old and new drugs, and therapy for neuromuscular disease.

Conversely, under the heading of "impasse areas," the FDA's regulation of drug development and release is again singled out for particular attention:

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 assure ethical control in clinical evaluations, increase developmental costs. There is a real danger of bringing the development process and access to clinical resources to a halt.

Many feel that the American public is being denied new drugs currently available abroad because of excessive FDA requirements.[41]

Thus, the panel's conclusions emphasize that biological knowledge has never been acquired at a higher rate than at present, that the prospects have never been more promising for therapeutic advances, and that the FDA's regulation is a major roadblock to the therapeutic exploitation of this basic knowledge.

In any case, the knowledge depletion hypothesis is a separate issue from the drug lag and should not be allowed to obscure the question of whether the United States lags behind other countries in the availability of existing new therapeutic drugs.

'BENEFITS' OF THE DRUG LAG: FDA'S RISK-AVOIDANCE POLICIES

Dr Kennedy cites the field of β-blockers as an example of the benefits of strict regulation, specifically practolol (which, along with propranolol, is the only drug mentioned by name in his article). It is worth exploring the therapeutic consequences of the drug lag in β-blockers.

One clinical effect of particular interest is the ability of certain β-blockers to prevent myocardial infarction and coronary death. This has been best examined in secondary prevention studies in which patients who have had one myocardial infarction are followed up to observe their subsequent incidence of reinfarction and death.

The results from three clinical trials[48-50] have shown that two β-blockers (practolol and alprenolol—both unavailable even for investigation in the United States) can reduce by approximately 40% the mortality in patients during the first year or two after discharge from the hospital following a myocardial infarction; there was also a trend toward a reduction in nonfatal reinfarction. No comparable studies have yet been performed with any other β-blocker.

In the opinion of the editors of the *1977 Yearbook of Drug Therapy*, the practolol study[50] represents "probably one of the most important studies of the decade,"[51] and a leading cardiologist, Dr John Ross,[52] in an editorial in the *Annals of Internal Medicine*

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discussing the results of the practolol study, has concluded that "at the very least, the results of the multicenter trial seem sufficiently convincing to recommend that . . . [prophylactic therapy with propranolol for all patients after anterior myocardial infarction] be seriously considered." (This recommendation for propranolol, the only β-blocker available in the United States, is for a use that is not only "unapproved" in the United States, but for which no clinical studies have been completed. A $25 million propranolol study is currently being undertaken by the NIH, but the results will not be available before 1982—seven years after the practolol results were published—and the FDA has no plans to act on the matter before then [A. M. Schmidt, written communication, May 3, 1976]).

The proper use of practolol in postinfarction patients could now be saving 10,000 lives each year in the United States at a cost, in terms of side effects, that can now be made trivial by comparison (W. M. Wardell, MD, PhD, written communication, Feb 17, 1976). A similar argument—without the toxicity problem—applies to alprenolol. These important advances are what Dr Kennedy triumphantly takes credit for "protecting" us from; the concept of risk-avoidance has been turned pyrrhically on its head.

In addition to "saving" the United States from the only drugs that had, up to 1977, been definitely shown to reduce postinfarction mortality, the FDA's β-blocker policy[53] has set back cardiovascular therapy in this country by years. At a time when the frontiers of β-blocker research throughout the world had moved on to the question of preventing coronary death and reinfarction, economic, clinical, and intellectual resources of both the FDA and industry in the United States went into reexamining propranolol's efficacy and toxicity in angina and hypertension (about which the answers were already well known and long accepted among American cardiologists); this scientific wheel-spinning lasted for approximately seven years—the lag in approval dates for these two indications between the United States and Great Britain. Meanwhile, evidence has accumulated pointing to the probable efficacy of at least one other therapy (sulfinpyrazone) for prophylaxis against postinfarction death, and there is now real concern that the seven-year delay may have already ruled out forever further placebo-controlled evaluation of β-blockers for this indication in the United States.

Separate evidence pointing to a general protective effect of β-blockers comes from studies of mortality and myocardial infarction rates in patients with angina or hypertension. This evidence, which dates back to 1966, has been reviewed by Lambert.[54] While the designs of most of these studies are imperfect, the weight of the evidence now makes it hard to ignore the probability that treatment of angina or hypertension with certain β-blockers lowers the incidence of myocardial infarction and sudden death. The size of this reduction is not clear because of the design of the studies, but in some series it appears to be well over 50%. These data reinforce the conclusion that the long delays in the introduction and use of β-blocker drugs in the United States have had a substantial impact in terms of potentially preventable cardiovascular mortality in this country,[19-21] in addition to their effects on clinical research.

A CAUTIOUS ADMISSION OF FDA SLOWNESS

Dr Kennedy concedes that "certain FDA practices have in certain instances slowed the passage of drugs through the system" and points to improvements that he has made to deal with these. One claimed improvement is that the FDA can now identify new drugs of unusual potential and is willing to accord such drugs priority (fast-track) consideration in the Investigation New Drug-New Drug Application (IND-NDA) process.[55]

Let us examine one example of this, the case of valproate sodium. Although this drug was acted on with alacrity in the glare of unprecedented publicity in the final stages leading to its NDA approval in February 1978 (three weeks before a congressional hearing was scheduled if the FDA had failed to approve it), its early history is not one of speed at either the company or the FDA, and its fate under the FDA's classification system is revealing. The IND study on this drug was submitted in December 1974, by which time the drug had been marketed abroad for several years and was already recognized as a drug of choice for certain types of epilepsy. Nevertheless, the FDA's classification system assigned it to class B (ie, not meriting the fast-track treatment).[56] It was not until October 1977 that the drug was first referred to the FDA's Neurologic Drug Advisory Committee. The fact that the FDA's system failed to recognize the importance of an already-marketed drug of choice does not make one sanguine about the FDA's claimed ability to identify important new drugs even earlier, ie, at the investigational stage—before a drug's therapeutic potential can be predicted by anyone—when the research process is most susceptible to inhibitory regulation.

JUSTIFICATION OF THE PROPOSED NEW LAW

The deficiencies in the FDA's performance that Dr Kennedy concedes are used to introduce the need for a new law. It is not clear whether a new law is required to achieve the objectives that he specifies, since most of the problems cited could be addressed under the existing law and regulations. The one mandate the FDA really needs from Congress is that of assisting or encouraging the improvement of therapy for disease rather than of simply avoiding drug-induced harm. Although at least one previous FDA commissioner has averred that this could be accomplished under the existing law,[57] a positive mandate from Congress would be valuable in this respect.

CONCLUSIONS

During the past five years, the scientific and medical staff at the FDA have painstakingly built up a reputation for sober and credible analyses of reliable facts. Outside observers have come to respect the data supplied by the FDA's professional personnel, and the quality of debate rose enormously. The agency began to command the respect of the scientific, academic, and medical communities.

In recent months, there has been a

angina and hypertension (about which the answers were already well known and long accepted among American cardiologists); this scientific wheel-spinning lasted for approximately seven years—the lag in approval dates for these two indications between the United States and Great Britain. Meanwhile, evidence has accumulated pointing to the prob- the case of valproate sodium. Although this drug was acted on with alacrity in the glare of unprecedented publicity in the final stages leading to its NDA approval in February 1978 (three weeks before a congressional hearing was scheduled if the FDA had failed to approve it), its early history is not one of speed at either the company or the FDA, and its fate reputation for sober and credible analyses of reliable facts. Outside observers have come to respect the data supplied by the FDA's professional personnel, and the quality of debate rose enormously. The agency began to command the respect of the scientific, academic, and medical communities.

In recent months, there has been a

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disquieting increase in pseudoscience and sophistry. It would be difficult to regard the "calm look" article as a cogent argument from anyone; coming from a respected government agency with a staff of more than 7,600 and a budget of $245 million in 1977,[58,59] it seriously underestimates the intelligence of JOURNAL readers and other taxpayers.

The approach exemplified by that article can only embarrass and discourage the career scientists and physicians who have worked so hard to improve the agency. If permitted to continue, that approach will ultimately destroy the FDA's scientific and medical credibility.

Nonproprietary Names and Trademarks of Drugs

Beclomethasone dipropionate—*Vanceril, Viarex.*
Bretylium tosylate—*ASL-603, Darenthin.*
Clonidine hydrochloride—*Catapres.*
Cromolyn sodium—*Aarane, Intal.*
Debrisoquin sulfate—*Declinax.*
Diazoxide—*Hyperstat.*
Guanoclor sulfate—*Vatensol.*
Metaproterenol sulfate—*Alupent, Metaprel.*
Oxprenolol hydrochloride—*Trasicor.*
Pindolol—*Visken.*
Prazosin hydrochloride—*Minipres.*
Terbutaline sulfate—*Brethine, Bricanyl.*
Valproate sodium—*Depakene.*

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