THE UNIVERSITY OF ROCHESTER
SCHOOL OF MEDICINE AND DENTISTRY
601 ELMWOOD AVENUE
ROCHESTER, NEW YORK 14642

CENTER FOR THE STUDY OF
DRUG DEVELOPMENT
(716) 275-2466

DEPARTMENT OF
PHARMACOLOGY AND TOXICOLOGY

May 8, 1979

Mr. Norman Latker, Esq.
3515 Woodbine Street
Chevy Chase, Maryland 20015

Dear Norman:

I enclose copies of any papers we have published or have manuscripts on, on the subject "regulation of medical devices." As you will see, most of our stuff is by analogy with the impact of regulation on drug development--you have our latest papers on drug development--so the main function of our device papers will be to give you some sort of framework for making the comparison.

It sounds as thought the story you got from GAO was different from the one Martin got. We don't know what is going on there.

I hope you will find Bill Dobelle a source of help--he is a very nice person and a real live wire.

Martin is going to put you in touch with Mr. Charles Fry of Pfizer's Public Affairs Department (New York office). Of the people we can think of immediately, Pfizer may be your best contacts in the area of publicizing the need for technology transfer. They have medical devices as well as drugs.

Yours sincerely,

William M. Wardell, M.D., Ph.D.

WMW/pr

P.S. I am also including a copy of a paper we published in Clinical Engineering which has a tangential relationship to medical device legislation.

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William M. Wardell, M.D., Ph.D.

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1977 U.S. MARKETED

NSWER THE FOLLOWING QUESTIONS WITH RESPECT TO THIS DRUG.

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COMPANY FROM WHICH DRUG WAS LICENSED, OR INDIVIDUAL, OR OTHER _____ AND COUNTRY _____ AND COUNTRY _____

LEASE FILL IN THE COUNTRY AND DATE WHERE THE FOLLOWING STAGES OF
HIS DRUG'S DEVELOPMENT TOOK PLACE.

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| . START OF PHASE 2 TESTING UNDER U.S. IND . . . . . | _____ | __/__ | __ | __/__ |
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LEASE FILL IN DETAILS FOR ALL NDA-APPROVED INDICATIONS, WITH THEIR CORRESPONDING IND'S, IN CHRONOLOGICAL OR D'S, IN CHRONOLOGICAL OR
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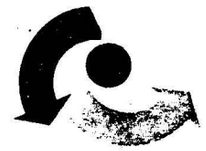

# PROCEEDINGS: THE CLINICAL EVALUATION OF MEDICAL DEVICES

## PROFESSIONAL AND REGULATORY RESPONSIBILITIES

Washington, D.C.
April 28, 1976

Association for the Advancement of Medical Instrumentation

# HOW WILL LEGISLATION AFFECT INNOVATION IN DEVICES?

**William M. Wardell, M.D., Ph.D.**

*Legislation has had some negative effects on innovation in the field of drugs. This past experience with the effects of drug regulation may be useful for understanding the possible effects of similar legislation on the device field. Dr. Wardell recommends that the research-based device industry start accumulating data to aid in future evaluation of the impact of current device regulations.*

What might happen to innovation in the device field based on what has happened to drugs in the past? What might be done to make the outcome of device regulation more favorable for the patient than drug regulation has been? My main field of expertise is drugs and their regulation;[1,2] so when I talk about devices, it will be by analogy with and extrapolation from drugs.

Drug legislation was prompted by disasters at several stages. By contrast, the pending device legislation is one of the few major pieces of new legislation in the

[1]Wardell, W. M., and L. Lasagna. Regulation and drug development. The American Enterprise Institute for Public Policy Research, 1975.
[2]Wardell, W. M. Drug development, regulation, and the practice of medicine. *J. Amer. Med. Assn.* 229: 1457-1461, 1974.

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health field that has not been prompted by a major disaster. Because there has been no need for undue haste, one hopes that the consequences of the new legislation will be thoroughly explored prior to its enactment.

The effects of legislation on drug development and therapeutic practice have been mixed. On one hand, the legislation has had a number of very good effects. Since the original Pure Food and Drugs Act was passed in 1906, quack patent remedies, together with untested remedies, have been eliminated. There is now a requirement for proof of a certain degree of safety, which was strengthened by the Food, Drug, and Cosmetics Act of 1938, and for evidence of efficacy, which dates from the Kefauver-Harris Amendments of 1962. In addition, drug claims and promotion are controlled to a greater extent in the United States than in most other Western countries.

Many of these achievements were greatly needed and were obtained only after hard fighting on the part of legislators and administrators, because the drug field in the past had been the scene of many abuses. One must acknowledge that the drug legislation and regulation passed in this century, in which the United States has led the world, has had many salutary effects.

On the other hand, it is becoming increasingly clear that the laws and, more importantly, the way in which they are implemented by regulations, have had some effects that are unwelcome and undesirable. The real questions are: Where does the point of balance between the desired and the undesired effects of regulation lie for the public interest? And, how can one maximize the public benefit? We sometimes still hear the ancient therapeutic adage, "First, do no harm," raised as if to justify strong regulation. But, it is important to realize that this adage comes from an era when there were no therapies capable of doing any good. Today the adage should read, "First, maximize benefit," because otherwise the patient risks being denied the fruits of several thousand years of therapeutic progress.

What are the negative impacts that drug legislation and regulation have had? An obvious example is the set of phenomena known as the "drug lag." The term drug lag is being used today in different senses by different people. I use this term to mean that in general, new drugs take longer to get from the research stage where they may show promise, to the point where this promise can be realized for helping patients, and that this is a trend happening both in an absolute sense (within the United States) and also in a relative sense, in that in this respect, the United States lags behind other Western countries.[3,4,5,6]

Of all the numerous aspects of the drug lag phenomenon, the one that is the most important but least studied to date is the impact of legislation and regulation on the

[3]Wardell, W.M. The "drug lag" and Americar
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[4]Wardell, W. M. Introduction of new therapeu
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[6]Wardell, W.M. Therapeutic implications of th
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[3]Wardell, W.M. The "drug lag" and American therapeutics: An international comparison. (Abstract) Fifth International Congress on Pharmacology, July 1972.
[4]Wardell, W. M. Introduction of new therapeutic drugs in the United States and Great Britain: An international comparison. *Clin. Pharm. Therap.* 14: 773-790, 1973.
[5]Wardell, W.M. British usage and American awareness of some new therapeutic drugs. *Clin. Pharm. Therap.* 14: 1022-1034, 1973.
[6]Wardell, W.M. Therapeutic implications of the drug lag. *Clin. Pharm.Therap.* 15: 73-96, 1974.

process of discovery and innovation. It is in this area that th pact can exert its most fundamental effect; it is also the point that is the most difficult to study, and so has received the least attention so far. That is why, to students of innovation, it is so interesting to be present at this particular place and time, on the threshold of the appearance of new device legislation. We have a unique opportunity to study the initial impact of this legislation on innovation in a way that was not thought necessary, and so not done, in 1938.

How would one set about beginning to measure the impact of this new legislation on research and development? The first things that one ought to examine, in a highly R&D-intensive industry, are what is happening to research costs and whether the rate of basic innovation is changing. In the case of drugs, R&D costs have certainly risen very fast in the past decade or so, and there are indications that the rate of innovation is declining. For example, there is evidence that the world ranking of the U.S. pharmaceutical industry in terms of innovation is declining, and U.S. firms are moving their R&D operations abroad at a greatly accelerated rate compared with their expansion of domestic operations.

It is relatively easy to document the declining state of pharmaceutical innovation within the United States. The facts are not seriously in dispute, although the magnitude is debated. The real points at issue are, how much of these effects is directly attributable to more stringent legislation and regulation, and how much is due to the numerous other factors that we know are operating?

There are severe problems in designing an experiment to measure the impact of drug regulation, because of numerous confounding variables, which include the effects of inflation and the effects of generally rising scientific standards (so that simply to demonstrate a given pharmacologic or therapeutic effect today is much more expensive than it was yesterday). Furthermore, there is an increasingly unfavorable climate for research in general and for human research in particular. These confounding factors all act in the same direction, as would increasing regulation, and they make it—at this rather late stage in the history of drug regulation—very hard to untangle the effects of the legislation and regulation alone. While there is no simple answer to this question, it is difficult to escape the conclusion that legislation and regulation play a major role.[7]

These difficulties of experimental design are complicated by the fact that in 1938, and even in 1962 when the Kefauver-Harris Amendments were passed, nobody had even thought of beginning to study this question. Thus, there were no baseline data collected at the time and no proper studies designed from which the impact of regulation could have been accurately measured by now.

Therefore, I hope that device manufacturers are already collecting the necessary baseline data and setting up good studies from which, by the year 2014 (when the

[7]Wardell, W. M. Regulation and pharmaceutical innovation: A review of the relationship between government regulation aimed at protecting health and human safety, and innovation leading to medically useful drugs. Presented at the National Science Foundation, June 1976.

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[9]Wardell, Introduction of new therapeutic dru
[10]Crout, J. R. *Hearings on Regulation of New D*
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[11]Schmidt, A. M. *The Commissioner's Report.*
[12]Schmidt, A. M. *The Commissioner's Report.*



device amendments of 1976 are as old as the 1938 drug law is today) there will
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There have been changes in drug innovation in which regulation played a role. Let
us look first at the numbers involved in the drug lag phenomenon, and compare
the United States with Britain—which is the other major English-speaking, drug-
developing country. In the decade following the Kefauver-Harris amendments of
1962, 180 new drugs (new molecular entities) became available.[8,9] They did not all
become available in both countries. Approximately half became exclusively avail-
able in one country and not the other. Of these, four times as many became
exclusively available in Britain as in the United States. This is a marked departure
from the pre-1962 situation, when the United States was well established as a
leader in drug innovation and introductions.

It is instructive to find that there are differences between therapeutic areas. Some
areas in which progress was slowest in the United States were the cardiovascular,
gastrointestinal, and respiratory areas. However, in the cancer area, for example,
there was very little difference between the two countries. This phenomenon of
differences between therapeutic areas is, in itself, evidence supporting the idea of
a regulatory impact, because we now know (e.g., from FDA's own testimony
before the Senate Health Subcommittee,[10] and from the FDA commissioner's
report[11] of his investigation into charges raised at those hearings), that the cardio-
renal division was one of FDA's problem areas from the management's point of
view. In a whole decade after the 1962 amendments, no more than one or two
drugs were approved at all in that division, and nothing from 1968 to 1972—an
experience that (in the words of the director of the Bureau of Drugs) "contrasted
with the experience of every other medically modern nation and with the experi-
ence of other divisions of the FDA."[12]

On the other hand, in the cancer area, the record has been quite good. It should be
noted, however, that in the field of cancer chemotherapy, another agency of
government—the National Cancer Institute—has as one of its functions the ad-
vancement of cancer chemotherapy. Indeed, according to the testimony of Dr.
Gordon Zubrod, director of NCI's Division of Cancer Treatment, the NCI actu-
ally uses its network of investigational centers around the country to overcome
the restrictions in FDA's investigational new drugs (IND) procedure, in order to
make investigational drugs available for therapeutic purposes. So at least part of
the reason for this progress in the cancer therapy area is that there exists an
agency of government whose job it is to promote drug therapy for cancer even to
the point of circumventing FDA's roadblocks. It is extremely interesting to note

[8]Wardell, The "drug lag" and American therapeutics.
[9]Wardell, Introduction of new therapeutic drugs.
[10]Crout, J. R. *Hearings on Regulation of New Drug R&D.* Senate Subcommittee on Health. September 1974, pp. 616-619.
[11]Schmidt, A. M. *The Commissioner's Report.* October 1975.
[12]Schmidt, A. M. *The Commissioner's Report.* October 1975, p. 599.



that the National Cancer Institute occasionally has violent cl s with FDA,[13] showing that even government departments may disagree with FDA's approach to the problems.

These interdivisional differences, and the above related data, are evidence supporting the case that regulation has a major impact on drug development, because the observed differences between therapeutic areas correlate well with the known regulatory differences.

What is the therapeutic significance of these international differences in drug introductions? An instructive example is seen in what happened to the whole area of nondiuretic antihypertensive drugs from 1962 to the present.[14] No drugs at all were approved in the whole nondiuretic antihypertensive area in the U.S. from methyldopa in 1963 until diazoxide in 1973. Over the same time period, at least 6 drugs were introduced in this area exclusively in the United Kingdom. Thus, there was a whole decade where there was no antihypertensive drug introduced here, despite the fact that useful agents were appearing continuously abroad. (Note, incidentally, that another division of HEW, the Public Health Service, mounted its national hypertension treatment year in 1974[15] with considerably fewer drugs to work with than other countries.)

A particular example of antihypertensive drugs is seen in the field of beta blockers, which for many years have apparently been regarded with particular disfavor by the cardiovascular division of FDA. Only one beta blocker (propranolol) has been approved in the United States; its initial approval was in 1965, but that was only for rather trivial indications. Over a period of several years, its major use came to be for angina pectoris (for which it is the most important advance in the last 100 years); most of the drug sold was for this purpose. For finally rationalizing propranolol's angina indication by FDA in 1973, Dr. Richard Crout, director of FDA's Bureau of Drugs, was subjected to extensive harassment, especially by congressional committees.[16] It was claimed by his critics that the evidence did not technically satisfy the law's requirements for proof of efficacy. (Such a view is greatly at variance with expert medical opinion and even with American textbooks of medicine of the time—which themselves are notoriously out-of-date.)

Meanwhile, propranolol—along with nearly all other beta blockers—had been found to be of value in a further indication, namely, for hypertension. These drugs became, in all Western countries except the United States, a major new class of compounds for the management of hypertension. Although they were recommended as major backup drugs for hypertension by the American College of

[13]*The Blue Sheet* 18: 4, November 1975.
[14]Wardell, W. M., and L. Lasagna. Regulation and drug development. Chap. X., pp. 109-123.
[15]Stokes, John B., III. The national high blood pressure education program. *J. Amer. Pharm. Assn.* 172-176, April 1974.
[16]Crout interrogation, Footnote 9, p. 171 in *Drug Development and Marketing*, edited by Robert B. Helms, The American Enterprise Institute for Public Policy Research, Washington, D.C., July 1974.

Cardiology, it took until 1976, 10 years after the discovery that these drugs are of value in hypertension, before they were approved for that purpose in the United States. This episode illustrates several of the difficulties that are encountered when one wishes to elucidate the cause of delays. FDA has said that the reason for the delay in approval of propranolol for hypertension was that the company had failed to submit a new drug application for that indication;[17] on the other hand, a company spokesman has replied that, in view of the trouble the company was experiencing with FDA approval for the relatively simple indication of angina, an application for the hypertension indication at that time would have been pointless.[18]

One often unrecognized feature of therapeutic discovery and drug development is that many important clinical findings are made empirically, after the drug has been introduced for another purpose. The beta blockers have been a classic example of this, and continue to be. This is becoming very clear in the case of two other beta blockers (alprenolol and practolol), which were once available as INDs in the United States but are now no longer available. It has been shown that these two drugs can reduce by approximately 40 percent the mortality in patients after discharge from the hospital following a myocardial infarction.[19,20,21] Although, as in any scientific study, one can find technical points to quibble with in the design and analysis of these studies, the data already available make it most unlikely that these drugs are devoid of activity in this respect. Using the figures available from these three studies, I estimate, very conservatively, that the potential mortality savings in the United States, if these types of drugs were approved for this purpose, would be approximately 10,000 lives a year. There are some indications that in the uses for angina and hypertension, beta blockers are also beginning to exert this mortality savings effect in the prevention of myocardial infarction and sudden death.[22] These latter findings are not yet confirmed or well proven, but if they are confirmed in the future, this will multiply the above estimates of mortality savings several times. The approval of propranolol for this indication in the United States is at least 6 years away, since no studies have yet been begun on it. Nevertheless, the FDA has no plans to take any steps to encourage the owners of alprenolol or practolol to study their drugs here for the prevention of sudden death in cardiac patients.

While we are considering drugs used in the treatment of sudden death, it is relevant to examine the evidence that currently exists on aspirin. Aspirin is known to prevent the aggregation of platelets, one of the steps in the production of

[17] Crout, J. R. New drugs for hypertension: An FDA reply (Letter to the Editor). *J. Amer. Med. Assn.* 14: 480-481, 1975.
[18] Cavallito, C. J. (Letter to the Editor) *J. Amer. Med. Assn.* 235: 475, 1976.
[19] Wilhelmsson, C., et al. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. *Lancet* 1157-1160, 11/16/74.
[20] Ahlmark, G., H. Saetre, and M. Kosgren. Reduction of sudden deaths after myocardial infarction (Letter to the Editor). *Lancet* 1563, 12/28/74.
[21] A multicentre international study. Improvement in prognosis of myocardial infarction by long-term beta-adrenoreceptor blockade using practolol. *Br. Med. J.* 735-40, 9/27/75.
[22] Stewart, I. McG. A prospective study of the comparative incidence of myocardial infarction in essential uncomplicated hypertensives under treatment containing or excluding a beta adrenergic blocking agent (Abstract). International Society of Hypertension in Sydney, 1976.



myocardial infarction and sudden death. In 1969, when the implications of this use were being looked at with some interest in the medical community, a United States drug company submitted an IND for the use of aspirin in the prophylaxis of myocardial infarction.[23] The company eventually had to withdraw it after a vigorous struggle with the FDA which required better evidence of the safety of aspirin in long-term administration, together with all the world's literature on aspirin. Five years after the company was forced by FDA to give up, the National Institutes of Health mounted a $14 million study to examine the effect of aspirin in myocardial infarction. Studies around the world have now begun to show that aspirin's effect may be positive. The definitive picture of aspirin's effects in preventing myocardial infarction is not yet available, but I think you can see the implications of these FDA actions. We are not talking about just one or two drugs, we are not talking about simply the numbers of drugs involved; we are talking about real therapeutic effects—and anyone who tries to argue against that is on losing ground.

When these arguments began to be brought up, particularly by the Dripps committee in 1972,[24] they were greeted with vicious rebuttals of dubious scientific quality from the FDA. Former FDA Commissioner C. C. Edwards was one of the most vigorous rebutters,[25] but he has since recanted.[26] Dr. H. E. Simmons was another rebutter.[27] Commissioner A. M. Schmidt has both acknowledged and denied the existence of a drug lag. Dr. J. R. Crout, director of the Bureau of Drugs, acknowledges the existence of a drug lag,[29] and I agree with Dr. Crout.

Now that we have considered both the question of drug lag numbers and the question of therapeutic impact, let us consider in more detail the fundamental question referred to earlier: What has happened to the discovery process, from which tomorrow's drugs and devices will have to come? An important task for economists is to define the costs of R&D for getting a single new molecule into the market, bearing in mind the low success rate at the earliest stages. According to some of the recent economics literature, in the decade from 1962 to 1972 there was a rise (of possibly tenfold) in R&D costs needed to get a new drug (new molecular entity) to the market.[30] Whatever the exact figure, costs have gone up. On simple

[23] *The Blue Sheet* 19: RN-4, September 1976.
[24] *Hearings on Regulation of New Drug R&D.* Senate Subcommittee on Health. September 1974, p. 608. Reprinted in U.S. Congress.
[25] *Competitive Problems in the Drug Industry.* Senate Subcommittee on Monopoly. March 1973, p. 9382.
[26] Edwards, C. Speech before the Pharmaceutical Advertising Club, New York City, September 18, 1975.
[27] *Competitive Problems in the Drug Industry.* Senate Subcommittee on Monopoly. March 1973, p. 9382.
[28] Reforming Federal Drug Regulation, Jules Bergman, Moderator. A Round Table sponsored by the Center for Health Policy Research of the American Enterprise Institute for Public Policy Research, Washington, D.C., February 23, 1976.
[29] Schmidt, A. M. *The Commissioner's Report.* October 1975, p. 599.
[30] Schwartzman, D. Pharmaceutical R&D expenditures and rates of return. *Drug Development and Marketing*, edited by Robert B. Helms. The American Enterprise Institute for Public Policy Research, Washington, D.C., July 1974, pp. 63-80.

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The next question of interest is the flow rate
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1975, nearly 50 percent of all U.S.-originate
abroad. This represents a fourfold to fivefo

Finally, what has been the fate of those new
have been filed since the IND requirement

[31] Wardell, W. M., M. Hassar, and L. Lasagna. Th
flow, and regulatory disposition of new chemic
maceutical industry since 1962. (*To be publishe*



economic grounds it would be very surprising if there had not been a negative
impact on the ar )t of research being done.

With this as a general background, I would like to show you the results of a survey we are currently undertaking at the University of Rochester on the flow and fate of new chemical entities as they emerge from the pharmaceutical industry and begin human testing, thus entering the regulatory pathway.[31] The results to date are from 27 companies (which make up nearly all of the U.S.-owned, research-based pharmaceutical industry), yielding 667 new chemical entities, which represents about 90 percent of the entire output of new molecules from the U.S. industry that have been administered to man since 1962.

The first point to consider is the time it takes for a new chemical entity (NCE) to obtain approval (i.e., to flow through the regulatory pathway). There were 33 such successes out of these 667 NCEs tested in man. For those drugs approved in 1974 (the most recent year for which complete data are available), the duration of the IND phase was 51 months, and of the new drug application (NDA) phase, 33 months. Thus, the total time required for clinical investigation and FDA approval of the successful drugs was 84 months. There were differences between therapeutic classes; for anti-infectives the mean time over the whole period has been 4.5 years, while for nonsteroidal anti-inflammatories it has been 8 years.

Next, if we look at the duration of the IND phase for all drugs that reached the stage of NDA *submission* (that is, for the ones that have not yet had NDA approval, as well as the ones that have been approved) the mean duration of the IND phase for those with NDA submissions in 1974 was 83 months. This means that ~~even if the NDA phase remains the same, those drugs presently in the system will~~ have a mean investigation and approval time of 10 years by the time their NDAs are approved.

These times required for investigation and approval have a direct bearing on the important question of patent lives. As the time taken in development increases, the effective patent life (i.e., the time from NDA approval to expiration of the patent) will decrease. The data we have compiled, which cover the period since 1965, show that the effective patent life has gone down from about 14 years for those NCEs with NDAs approved in 1966 to 1967, to 10 years in 1975. This agrees well with the 7-year development time shown above, the two figures together equaling the 17-year validity of the patent.

The next question of interest is the flow rate, in terms of numbers, of NCEs from U.S. companies into man. The rate has dropped about 60 percent since 1965, and at the same time there has been a large shift of early human study abroad. By 1975, nearly 50 percent of all U.S.-originated compounds were studied first abroad. This represents a fourfold to fivefold rise since the mid-1960s.

Finally, what has been the fate of those new chemicals for which IND applications have been filed since the IND requirement was begun in 1963? What we are

[31] Wardell, W. M., M. Hassar, and L. Lasagna. The rate of new drug discovery: The output, flow, and regulatory disposition of new chemical entities produced by the U.S. pharmaceutical industry since 1962. (*To be published*)



finding is that 90 percent of the INDs are dropped by the compa ies *before* NDA submission. Conversely, there is a high rate of approval of a dru ce it gets to an NDA submission (about 90 percent approval after 5 years). Thus, the companies delete 90 percent of their candidates during the IND phase, while the FDA in approximately the same additional time period holds back 10 percent of what is submitted to it, or about 1 percent of the original cohort of NCEs tested in man.

What this suggests is that if the proposed "developing NDA" concept, which Dr. Walters described, were introduced, it would probably increase the duration of the IND phase somewhat, but that, if used properly, it could well shorten the duration of the NDA phase. The latter phase is the main point at which the savings in time could be made.

In the light of what has happened to drugs under increasingly strict regulation, I would like to make some observations and some recommendations. There are certain obvious problems common to both device and drug regulation. One is that the device bill as currently written, like all the drug laws that have been passed or are currently proposed, has no positive mandate. By that I mean there is no discernible intent in the bill to optimize public health. The intent is solely to protect against hazard, which is a very different and more limited aim. This is a very real problem, because it will determine what FDA will come to perceive as its basic role in regulation. The consequences of this omission are already clearly apparent in the case of drug regulation, as I have shown.

In the Committee Report on the Device Amendments,[32] there are intimations of a positive mandate, and I understand that in some of the earlier drafts of the bill a positive mandate was included, which was later deleted. As it stands now, the device bill shares with all the drug legislation the real problem that the object and mandate given to FDA is to avoid harm rather than to maximize benefit. FDA often does try to interpret this to maximize benefit. There are many sophisticated people addressing the difficult decisions that indicate that FDA does use a risk-benefit approach in some areas. However, without a positive mandate from Congress, it is very likely that the new legislation will be administered in such a way as to depress innovation in devices as the older legislation has done to drugs.

My final point is that nowhere in the device bill, nor in any of the drug bills, is there any provision for finding out exactly what the impact of the bill will be in the years ahead. Until 3 or 4 years ago, nobody in the drug field outside the pharmaceutical industry had even begun to address the question of whether the regulation was doing good or harm. It is now very difficult to try to get data from those early years—particularly the preregulation era—that would tell us exactly what impact the laws have had on innovation.

Just as drug and device bills and laws impose safety and efficacy requirements on the drugs and devices they regulate, there should also be safety and efficacy

[32] Medical Device Amendments of 1976. Report by the Committee on Interstate Foreign Commerce (H.R. Rep. 94-853, 94th Cong., 2nd Sess., 1976).

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requirements on the bills themselves. I would recommend that some group—FDA, or AAMI, or an independent body—should now be gathering the scientific and economic data that are needed to document the present state of the research-based device industry. This documentation would need to include, for example, the present details of research costs, broken down by therapeutic area, so that the impact of this law on public health can be measured. It will be a very difficult task, in terms of experimental design, data gathering, and analysis. But if it is not started now and done properly, then I believe that 13 years from now the U.S. research-based device industry will look back as the drug industry now looks back on the Kefauver-Harris Amendments, and will find itself in the same rather leaky boat that the research-based drug industry is in now.

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# PROBLEM-SOLVING TECHNOLOGY: APPROACHES TO EVALUATING THE IMPACT OF REGULATION--THE EXAMPLE OF PHARMACEUTICAL INNOVATION

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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

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

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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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.

Further details about the history of these NCEs back to 1963, and corresponding data on NCEs that have been licensed, are

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Further details about the history of these NCEs back to 1963, and corresponding data on NCEs that have been licensed, are

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

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

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

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

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.

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

obtained.

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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