MORE REGULATION OR BETTER THERAPIES?

William Wardell

THERAPEUTIC DRUGS are quite literally a life and death matter: declines in the development of these drugs and unreasonable barriers to their use mean that men and women will be sick who might be well and will die who might live. Doctors and (one hopes) patients know this, and so do the Congress and the Food and Drug Administration (FDA). But no one is quite sure what can be done to remedy the problems we face in this area today—ever-growing research time and costs, delays in new drug introduction, declines in the innovation that could produce better drugs.

This is not a new concern, nor one that has escaped the attention of policy-makers. Congress has been discussing comprehensive reform measures for several years, while over at the FDA a task force began to rewrite that agency's regulations on drug development and approval last February.[1] Then in June, the General Accounting Office issued a preliminary report on its two-year study of the FDA's new-drug approval process. As with most of the eleven past public inquiries into this subject, the GAO study points to bureaucratic holdups, communication problems, and, as a consequence, excessive delays. It notes, for example, that the average time from submission of a new drug application to approval of the drug for marketing is now thirty-four months, whereas the statutory requirement is six months.

From the excessive delays in the approval process come delayed new drug introductions —some of them so delayed that drugs that have been used safely abroad for years are not yet available here. This is the "drug lag." The GAO identifies several causes of the problem, some amenable to legislative or regulatory action but most requiring better operating practices within the FDA and also the pharmaceutical industry. It is my judgment that the drug lag and the unhealthy state of pharmaceutical innovation in the United States (a subject the GAO's report does not cover) stem largely from an underlying malaise in new drug regulation.

The Drug Lag

This is, as I say, not a new problem. It became obvious back in the late 1960s—in the wake of the 1962 amendments to the Food, Drug, and Cosmetics Act. And, in the intervening years, it has become even more acute.

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[1]These are the IND and NDA regulations, respectively. IND refers to the Investigational New Drug exemption. An IND application must be filed with the FDA before human studies on a new drug can begin. When sufficient data on the drug's safety and efficacy are available from clinical studies, an NDA (New Drug Application) is submitted to the agency. When this is approved—signifying that the FDA deems the safety and efficacy data to be adequate for specific therapeutic indications—the drug may be marketed in this country for those uses.

The drug lag is most dramatically revealed in comparisons of this country and the drug-developing countries of continental Europe. But it is most thoroughly documented in studies comparing the United States with Britain—a country with comparable standards of medical practice and the only other English-speaking country that develops drugs in significant numbers. Our research team at the University of Rochester recently completed a new update study of this problem. In nine therapeutic areas examined in detail for the period from January 1962 through March 1979, three to four times as many new drugs became exclusively available in Britain as here. Of that minority of new drugs introduced into both countries, about twice as many were introduced earlier in Britain—often by many years.

But drug availability is not the only way regulation affects therapy. Another important factor is the range of therapeutic indications—that is, the disease conditions—for which a drug is approved by the FDA. Since the United States imposes the most specific (restrictive) labeling approvals of all major drug-developing countries, simple numerical summaries that reveal the smaller number and later availability of drugs here substantially *underestimate* the therapeutic constraints on U.S. doctors and patients.

Many of the drugs that have been delayed in reaching the U.S. market are therapeutically important. For example, the United States was the fifteenth country in which the anti-inflammatory drug indomethacin was marketed, also the fifteenth for the diuretic ethacrynic acid, the thirty-ninth for cephalexin (the first oral cephalosporin), and the fortieth for the anti-tubercular antibiotic capreomycin. Yet all of these drugs were developed by U.S. firms. When the advance originated with a foreign-owned firm or institution, the United States has usually been even further down the list. It was the thirty-second country to approve the important anticancer drug adriamycin, the forty-first to approve the antimania drug lithium carbonate, the fifty-first to approve the anti-tubercular drug rifampin, the sixty-fifth to approve the anti-asthma drug cromolyn sodium, and the one-hundred-and-sixth to approve the antibacterial drug co-trimoxazole.

We can gain added perspective on the drug lag by looking at specific therapeutic areas.

• *Cardiovascular drugs.* Although cardiovascular disease—including heart attack and stroke—has been the main cause of death in the United States for many years, this is an area in which the differences in the therapies available in the United States and Britain have been particularly large. To all intents and purposes, the FDA's doors were essentially closed to cardiovascular drugs for an entire decade.

Thus, in the years 1963–73 when new antihypertensive drugs were continuing to appear in Britain, none was approved for use here. Since 1973, U.S. mortality from stroke has declined in part because of the National High Blood Pressure Education Program. But new management at FDA's Cardio-Renal Division has also helped by overcoming that division's logjam in antihypertensive drug approvals. As a result, the availability of antihypertensive drugs in this country is now more in line with world trends, although certain lags persist.

Cardiac arrhythmias are a common cause of coronary death. Yet only two antiarrhythmic drugs were approved in the United States from 1962 to 1975, both after substantial lags, while another important antiarrhythmic has been in regulatory limbo since 1968, at least in part because of the powerful inhibitory influence of a single FDA reviewing officer.

In the area of heart attack prevention, another FDA reviewing officer blocked even research on the problem. In 1969, this employee prevented E.R. Squibb and Sons, Inc., from conducting a controlled study to determine whether aspirin in normal doses would prevent heart attack and death in patients who had already had a heart attack (and were hence at high risk of having another). The FDA made repeated demands for additional data and animal studies, requested the submission of all the world's literature on aspirin, and even wanted to close down Squibb's entire clinical research program on *all* drugs if the firm went ahead with its aspirin project. Squibb finally dropped the project. In 1974—five years later—the National Institute of Health initiated a $16 million investigation (paid by tax money) of precisely the same effects of aspirin. If, when the NIH study is completed a year from now, it confirms what has long been suspected about the beneficial impact of aspirin on heart attacks and coronary death, then the health costs of having had that knowledge frivolously delayed for sev-

eral years—costs of illness, lost days of work, burdens on families, and death—will have been extremely high. The popular allegation that aspirin "couldn't be approved for marketing if it came along as a new drug" is no joke: in 1969 aspirin could not even get to the starting line.

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The fact that even a well-known drug like aspirin could be subjected to ridiculous research barriers of this kind suggests the height of the hurdles confronting really new and important investigational drugs at the FDA during that bleak period—and also illustrates the extreme vulnerability of the industrial firm that argues with the FDA. Moreover, the fact that the situation improved after the agency made management changes illustrates the powerful influence that individual personalities and management practices can have on drug development in the United States. Examples like this (and there are many others) should be borne in mind in discussions of overregulation of pharmaceutical innovation.

- *Respiratory drugs.* Years of delay in the availability of at least four respiratory drugs (metaproterenol, terbutaline, cromolyn sodium, and beclomethasone inhaler) represented severe disadvantages to many asthma sufferers in this country, who had to settle for older therapies that were less effective and more dangerous than the newer drugs available abroad. By now the most glaring therapeutic gaps in this area have been eliminated.
- *Central nervous system drugs.* Many new antidepressants are available in Britain but not in the United States. While it is not clear that these British drugs offer any great advantages in efficacy, some of them are much safer than their U.S. equivalents. This is a particularly important characteristic for drugs designed to combat a condition in which attempts at suicide are common. All antidepressants on the U.S. market are particularly lethal when taken in sufficient overdose.

There are also significant U.S.-British differences in the drugs available for epilepsy. Of the eleven anti-epileptics approved in Britain or the United States from 1960 through March 1979, none was introduced here only, and just one became available earlier here. The six-year lag in the availability of valproate, in particular, and the continued absence of nitrazepam substantially reduced the treatment options for epileptic patients in this country.

Finally, patients who suffer from migraine could benefit from drugs either available exclusively or approved earlier in Great Britain for that indication—for example, clonidine, propranolol, and pizotifen.

- *Gastrointestinal drugs.* The absence of carbenoxolone (for peptic ulcers) and chenodeoxycholic acid (which dissolves gallstones) and the delays in the availability of metoclopramide, lactulose, pentagastrin, and (despite its claimed "fast-track" treatment) cimetidine have had important effects on the health of U.S. patients who suffer from gastrointestinal diseases. The chenodeoxycholic acid case is particularly interesting. From studies performed abroad, we already know that this drug is effective. Yet it appears that even before the required U.S. studies are completed, the drug will have been superseded abroad by a related drug (ursodeoxycholic acid) that is more effective and less toxic.

Counterarguments

The first line of defense of successive FDA commissioners has been to deny—at least when in office—that a drug lag existed, while avowing, nevertheless, that they would abolish it. (The defendant claims his dog could not have bitten the plaintiff because he did not own a dog and he kept it chained up.)

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The FDA's second line of defense has been to claim that the lag is beneficial or, at the least,

unimportant. The claim that the lag is beneficial is, in essence, an argument that the United States has avoided substantial new-drug toxicity by avoiding new drugs. Ironically, the drug chosen to illustrate this (the beta-blocker practolol) has, despite its known toxicity, an extremely high benefit/risk ratio when used to prevent heart attacks and coronary death. If practolol were available and used optimally in heart attack patients here, I estimate that it would save at least 10,000 lives a year, with a degree of toxicity that would be small, controllable, and highly acceptable to those patients at risk, given the drug's life-saving benefit.

The claim that the drug lag, while not beneficial, is unimportant necessarily assumes that there are adequate substitutes here for the drugs that are unavailable. But this discounts the fact that substitutes are usually not exact substitutes. Patients can benefit from the expanded range of efficacy or toxicity provided by having a wider variety of drugs—even when, on "average," the drugs may look similar in clinical trials. Two drugs that each benefit 50 percent of the population might together cover 100 percent of the population if their spectrum of efficacy does not overlap. Furthermore, certain drugs that may not benefit the "average" patient often have great advantages for certain individuals. Having more drugs available enables physicians to tailor therapy to individual patients, thereby providing maximal efficacy, safety, comfort, and convenience.

Declining Drug Innovation

The drug lag is a visible symptom of even more fundamental problems in the process of U.S. pharmaceutical innovation. A more sensitive quantitative measure of innovation is the flow of new chemical entities (NCEs, meaning new molecular structures) from the laboratory to the testing-in-humans stage—one of the earliest points at which the drug development process comes under regulatory control.

Very recently my research group at the University of Rochester obtained data from the whole U.S. pharmaceutical industry on all NCEs first tested in humans from 1963 through 1976. Among our major findings are these:

(1) Only a small portion of the U.S. industry creates and does research on truly new molecules: as few as seven of the thirty-six companies making up the research-based part of the industry account for half of all new NCEs tested in humans.

(2) Increasingly, the first testing of U.S.-originated NCEs in humans is done abroad: up through 1969, the fraction was 10 percent, but the most recent data indicate this could now be as high as 45 percent. The trend is even steeper for the large multinational companies because they already have foreign research capabilities.

(3) The number of NCEs studied in humans each year by the entire U.S. industry has generally declined since 1964, falling particularly sharply (possibly by as much as 40 percent) between 1974 and 1976.

(4) The average time required from filing an investigational new drug application to gaining approval for marketing (for the one out of ten that is eventually approved) rose from six years in 1974 to nearly nine years in 1976. Of this time, six years are required for the IND (clinical investigation) phase, and two-and-a-half years for the NDA (application for marketing) phase.

(5) Preliminary data on all NCE IND filings by U.S.-owned firms indicate that the proportion that is self-originated (rather than, say, licensed from foreign firms) fell sharply, from about 80 percent (or more) over the period 1967–75 to 63 percent in 1976.

There is thus a substantial decline in U.S.-originated drug candidates now in the pipeline and potentially available for marketing nine years hence, a continuing rise in the duration and thus the costs of development, an increasing movement of U.S. compounds abroad for early clinical testing, and an increasing reliance by U.S. firms on outside sources of innovation.

Other data support the picture emerging from these observations. The high cost for a U.S. firm to bring an NCE to the U.S. market, estimated at $54 million by Ronald Hansen, represents a substantial barrier, especially to smaller firms. An additional disincentive is the dwindling patent life that remains as development time increases. Since the seventeen-year patent clock runs during the whole development and approval phase, the average effective patent life for NCEs that received NDA approval fell from 13.8 years for those approved in 1966 to 8.9 years for those approved in 1977. This decline was fairly closely accounted for by the rise in development and approval time.

We can thus expect the incipient downward trends in U.S. innovation to continue unless something unusual happens in the environment for innovation. Despite the tinge of euphoria engendered by an increase in NCE NDA approvals in the past year or two, that environment has not improved. This is the most important—and most depressing—finding from the most recent data. It means that, beginning about 1984, there will be a substantial decline in U.S.-originated NCEs reaching the U.S. market.

Similar influences affecting at least two related areas could foreshadow the fate of drug research. In vaccine research and production, because of decreasing financial returns and increasing risks, the role of the private sector has declined markedly while that of government has increased—a situation that concerned the government-sponsored task force that examined the problem recently. Second, in the area of medical devices, which was subjected to tighter regulation under the Medical Device Amendments of 1976, the fate of small, highly innovative firms is of particular concern.

Why the Decline?

Clearly, no single factor is solely responsible for the decline in innovation and the attendant drug lag. Nevertheless, regulation stands out as a dominant cause, partly because its influence on innovation is so direct and powerful. For example, the four sets of regulations recently issued or proposed under the FDA's Bioresearch Monitoring Program (which seeks to improve the quality and reliability of clinical and preclinical data) will raise new barriers to research by an amount and at a cost that cannot possibly be justified (even leaving aside the FDA's direct costs—$16.4 million for the program in the first year, with an additional 600 inspectors to enforce it).

Even beyond the high cost of developing new drugs, firms are concerned about the return on their investment once the drugs are developed. Except for the occasional and elusive big winner, there is an increasing likelihood that drug firms may not be able to earn a profit adequate to justify new investments in research, in part because government agencies are increasing the number and scope of costly drug utilization controls. These controls include HEW's Maximum Allowable Cost Program (which restricts the amounts that government can pay for multiple-source medicines) and third-party fiscal reimbursement regulations (which determine the diseases for which drugs can be prescribed). Moreover—and this compounds the problem—increasing fractions of the funds previously devoted to innovative research are now being diverted into defensive or wheel-spinning work to satisfy rising regulatory requirements.

There is, however, one factor that does *not* contribute to the decline in innovation, and that is our scientific knowledge base in pharmacology. The exciting increase in our scientific understanding is one of the few bright parts of the picture. Nevertheless, in a curiously bold move, the FDA has touted a transparently specious "knowledge exhaustion" hypothesis to explain the decline in innovation. At first, the FDA asserted that pharmaceutical innovation was slowing down worldwide because the supply of basic biomedical knowledge had been somehow "outrun." More recently it has claimed that the acquisition of exploitable biomedical knowledge is cyclical and that the world has been at the bottom of the cycle since the early 1960s. Both ideas are so preposterous —so reminiscent of Lysenkoism—that they should embarrass their sponsors. Their attraction to FDA personnel appears to lie in their ability to deflect attention from the inhibiting influence of regulation rather than in intrinsic truth.

Efficacy: Subtleties and Idiosyncrasies

While the overt effects of drug regulation are obvious, it is not generally recognized that the problem lies more in a subtle conflict over scientific nuances than in gross statutory and regulatory dicta. The proof-of-efficacy requirement in the 1962 amendments to the drug law is in itself reasonable, and so are the 1970 regulations by which the FDA officially interprets the law. The problems stem in the first place from the FDA's reading of its regulations and from the judgment calls of its reviewing officers and advisers, who make necessarily subjective decisions on whether specific data meet what they believe to be the FDA's constructions (written or unwritten) of its own regulations. Yet, in a sense, what the FDA and its officers do is itself

part of a larger problem—the constant pressure on the FDA to be excessively strict.

When Is a Study Not a Study? The definition of the 1962 requirement for "substantial evidence" was worded in the plural: there must be "well-controlled investigations." The FDA has consistently interpreted this to mean at least two significantly positive well-controlled clinical studies of efficacy before a drug can be approved. But this turns out to cause problems.

Results from one recent multi-center study showed that the drug arabinoside-A reduced the mortality from one kind of encephalitis (herpes simplex) from 70 percent to less than 30 percent. The single study was the joint product of fourteen separate clinics following a common protocol. But it was only one study—or was it? In other words, did the FDA still need an *additional* placebo-controlled study (in which a precisely calculable number of Americans would have to be sacrificed to prove the efficacy of a drug everyone already knew was efficacious), or could the agency somehow avoid the constraints of its two-study interpretation?

By a clever metaphysical end run, the FDA succeeded in doing just that—first, by saying that a multi-center trial would qualify if *three* separate investigators within the study demonstrated significant results within their own sets of patients and, then, by ignoring the three-investigator requirement when it proved obviously inapplicable to a study involving only fifty patients in all. As far as one can tell, this represented a sensible course for the FDA. But from "two studies" to "three investigators" to neither of these seems a little tortuous. It would have been better to have avoided the original rigidity of the "two-study" interpretation.

It must be conceded, however, that there is a climate of opinion giving the FDA good reason to try to stick to the most conservative interpretation of any law or regulation. In 1974, for example, the agency approved the beta-blocker drug propranolol for use in angina pectoris—a gesture at least six years overdue. Thirteen published studies were correctly deemed by the FDA to be "well-controlled" and thus to satisfy the law's "substantial evidence" requirement. Later, however, the agency was unfairly harassed at oversight hearings of the House Intergovernmental Relations and Human Resources Subcommittee when a stunningly ignorant and biased consultant alleged (erroneously) that every one of the thirteen studies had unacceptable defects. The committee then asserted that the FDA had broken the law in approving propranolol for angina without the requisite two well-controlled studies. This bizarre case shows why the FDA tends to seek protection in the letter of the law—or of its own regulations.

Is Foreign Evidence "Evidence"? Other times, as noted, the FDA shows no inclination to avoid unnecessary arbitrariness. Thus, one cause of delay in drug availability (and of ethical concern as well) has been the FDA's longstanding demand that, in general, two controlled trials be conducted *in the United States*, regardless of data already available from abroad. Although the agency published new regulations in April 1975 that would allow it to accept foreign clinical results under certain conditions, it is not clear that it is now following these regulations. Consider this excerpt from a proposal by FDA to its Cardiovascular Advisory Committee in May 1977 on the regulatory handling of beta-blocker drugs:

> How much U.S. data will be required *when adequate well-controlled clinical studies have been conducted abroad?*
>
> *If foreign studies are adequate* to evaluate safety and effectiveness for both short and long-term use, then *two adequate and well-controlled short-term studies will be required in the U.S. to corroborate* the findings.... If only short-term studies are available, then two long-term U.S. studies would be necessary [emphasis added].

The requirement for two U.S. studies when foreign studies *are* adequate is at best questionable. It also raises serious ethical issues of the same type as were raised by the example of the encephalitis drug discussed earlier: if a drug has already been shown to be effective (in this case, abroad), how many U.S. subjects must be tested to re-prove efficacy? If a drug reduces mortality (as certain beta-blockers do), how many Americans have to be sacrificed here? In cases where foreign data are not suspect, such chauvinism is indefensible.

When Is an Efficacious Drug Not Efficacious? Here, too, there has been no attempt at an end run. According to one FDA official, a drug considered by the agency to have substantial poten-

tial uses *other than* those for which its safety and efficacy have been established should not be approved for any use until these other potential uses have been adequately studied. An example of this policy is seen in the FDA's ruling that drugs belonging to a class known as nonsteroidal anti-inflammatory analgesics could not be approved as analgesics for any indication—no matter how potent they were as analgesics—unless at least a short-term study was performed to ascertain their anti-inflammatory potential for treating rheumatoid arthritis. The mind boggles at what this philosophy would do to the age-long search for the elusive, strong, but nonaddicting painkiller that the world needs so much. Fortunately, this particular construction was repealed in February 1979, but the philosophy underlying it pervades other therapeutic areas.

In this regard, the regulatory handling of beta-blockers is similar but even more complicated. It was suggested in the FDA's 1977 beta-blocker status report (and the view has apparently been adopted) that at least initial studies on *three* indications (angina, hypertension, and arrhythmia) should be carried out before a beta-blocker could be approved—even if the evidence were adequate—for any *one* of these uses. While reasons can be adduced to support this position, it is difficult to reconcile it with the straightforward intent of Congress that drugs should be shown to be effective for their labeled use.

This interpretation—like much of the FDA's body of operating practices—is neither in the law, nor—as far as I can determine—in the written regulations. It is an ad hoc ruling that nevertheless has the effect of law. It is these rulings and interpretations, some of them apparently unwritten, that one questions when asking whether the FDA's practices reflect the intent of Congress, or indeed the intent of the FDA's own written regulations.

How Should the System Be Improved?

Dr. Jere Goyan, who succeeds Donald Kennedy as FDA commissioner in October, will be trying to improve regulatory performance. What steps might he take?

The Research Process. There is general agreement on the need to unburden the early stages of clinical drug investigation (Phases I and II). Since the safety record for these stages is excellent, the FDA could be permitted to delegate responsibility for monitoring and reporting to the clinical investigators and the sponsors, with supervision by local ethical review committees and with the final results reported to the FDA.

But even while Congress has been considering such a change, a considerable burden of additional regulation has been proposed or actually put in place. Among those being proposed are the sponsor/monitor, clinical investigator, and Institutional Review Board regulations emanating from under the FDA's Bioresearch Monitoring Program; among those already in place are the Good Laboratory Practice regulations. Such ponderous rules will dampen and dissipate research effort—especially clinical research—while increasing the costs enormously. It is doubtful whether they will improve data quality since, by the FDA's own assessment, the room for improvement is not great.

In addition, the FDA is currently rewriting its entire set of IND/NDA regulations, a complex and important task that offers opportunities for facilitating or inhibiting new drug development. The wrong choices here could bog down therapeutic progress for the rest of this century. To optimize the welfare of present and future patients, it is essential that needless duplication of clinical research should be minimized. Requirements for the repetition of experiments where the outcome is already known (from either foreign or domestic studies) are ethically unsound for the patient, the investigator, and the sponsor, and could even put the regulatory agency itself at legal risk.

The Review and Decision-Making Process. One obvious improvement—attractive and eminently feasible because it would only involve changing the sequence of the review process—would be to start the NDA review as soon as the data generated under the IND studies started to come in. It is nearly incomprehensible that the NDA review should take almost three years (GAO's findings for 1978) following upon the six years already taken to generate the data. If this review were begun at the time the first results came in and were kept current, only the last study results and the sponsor's and FDA's summaries would have to be reviewed from

scratch at the time of NDA submission. This could easily be done in six weeks, thus cutting at least two years from the total NDA review time currently required without altering any of the current data requirements. FDA has been talking of such a "developing NDA" approach for at least two years, and should be encouraged to proceed with it. If resource constraints are hindering this, it would make sense to address that need at once.

Other problems in the review process could also be taken care of without any fundamental changes. It would surely help if the FDA were fully staffed with all the experts it needs to review new drugs and if arrangements for enabling FDA staff to have the benefit of expert outside advice were improved. The GAO report commented on the uneven distribution of work among FDA personnel, and it is my own impression that individual workloads are so high in some areas that the review of new drugs may be substantially delayed. I believe society would have gained more from 100 additional highly skilled reviewing officers and $5 million than from the 600 new biomonitoring policemen recently authorized at a first-year cost of $16 million. And if in-house experts are overburdened, the FDA should use more outside experts (for example, on contract) and more advisory committees. To this end, the extremely strict conflict-of-interest interpretations that now make it virtually impossible for some of the nation's best experts to serve on advisory committees should be relaxed at once. Attention should also be given to putting patients or members of the relevant nonprofit disease-oriented organizations on these committees. It is they who have a particular stake in the prudent consideration of the issues surrounding therapies in their specific areas—especially the high-risk therapies that regulators shy away from but that some patients so desperately need.

But a lot more could be done if we critically examined the current development and approval process. As things now stand, the embattled regulator has to make an all-or-nothing decision on a drug, and is therefore naturally cautious, inclined to ask for ever more data and to defer a decision until all conceivable doubts are resolved. Asking for more data is an easy way out. What is needed is to make the decision less apocalyptic and hence easier to make—perhaps by having it shared with advisory committees and by using enhanced postmarketing surveillance to catch any problems that might arise after marketing has begun.

Improved postmarketing surveillance makes good sense in any case, but it also offers a way out of the ever-increasing spiral of premarketing demands. While taking some of the pressure off the regulators, it could also, if used appropriately, facilitate drug development and increase the patient's protection at the same time. But while everyone agrees that more postmarketing surveillance is desirable, the question is whether it would actually be used to end (or even slow down) the spiraling demand for premarketing studies. The idea of a tradeoff has become obscured. Back in 1970, the anti-parkinsonian drug L-Dopa was approved for marketing at the end of Phase II trials, in return for a commitment by the sponsors to what ultimately proved to be a five-year program of intensive postmarketing surveillance of over 1,000 patients using the drug. (It is widely acknowledged that this early-release procedure was urged upon the FDA by congressmen suffering from Parkinson's disease who were anxious to obtain the drug's benefits themselves.) The tradeoff worked well. But recently, in the case of the drug azaribine, the FDA was accused of breaking the law when it permitted the sponsor to market the drug while conducting specified postmarketing surveillance in place of continued Phase III studies, which the sponsor claimed it could not afford. (The drug was withdrawn from the market a year later because of its toxicity, but the wisdom of that withdrawal can be sharply questioned.)

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The danger is that, given society's current attitudes, enhanced postmarketing requirements will simply be added on to existing premarketing requirements, raising even higher barriers to new drug development and leaving the patient no better off than before. But something must be done. Despite sincere attempts

at improvement by both the FDA and the industry, the present system for discovering, developing, and regulating new drugs is, by its burgeoning weight, inexorably crushing innovation to death.

I propose that, in all but very unusual circumstances, an adequate postmarketing surveillance protocol be substituted for the whole of the current Phase III portion of clinical investigation. That is, a drug should normally receive NDA approval if satisfactory efficacy and safety results have been obtained in the Phase II studies, subject to a commitment by the sponsor to perform postmarketing studies in accordance with a study design fully adequate for that particular drug. It is possible that "fully adequate" postmarketing surveillance could involve limitations on a drug's distribution or use in its earliest period of marketing—a highly controversial idea contained in most of the recent drug reform bills (for example, S. 1075) as well as in the GAO's report. I believe, however, that this additional step should only be required with occasional drugs and for special reasons. The crucial advance would be the development of truly effective postmarketing surveillance and the use of this form of "insurance" instead of Phase III testing.

This is not so radical a suggestion as it seems. Current Phase III trials, although the most costly and time-consuming part of the clinical development process, add very little to what has already been learned about a drug's efficacy and toxicity by the end of Phase II—and not nearly as much as is routinely learned through a few months' worth of high-grade postmarketing surveillance. Approval of drugs after good results from Phase II studies, coupled with much better designed and more intensive postmarketing surveillance carried out with the same high scientific standards that now govern Phase II and III trials, would provide better medical information and safeguards for the patient than currently exist. As seen from the L-Dopa example, neither new legislation nor new regulation is necessary to use this approach for other drugs.

A Process for Evaluating the Regulations Themselves. Both of the main drug regulation reform proposals currently before the Congress, S. 1045 (the Carter administration's omnibus bill) and S. 1075 (more limited amendments of the existing statute), contain provisions for subsequent studies of the bill's effects. This is an excellent idea, but it does not go far enough. There should be a continuing process for evaluating the impact of laws and regulations on the search for new medicines, and thus on public health. This would include research impact statements, cost/benefit analyses of new regulatory programs, and the monitoring of therapeutic progress under different regulatory regimes. Regulatory conservatism will obviously prevent new drug toxicity, but at the equally obvious cost of denying sick people the benefits of new drugs. It does not take a genius to see the high costs of forgoing the prevention of 10,000 preventable U.S. coronary deaths a year for, say, three years—the time for which the beta-blocker alprenolol has been approved for this use by Sweden's stringent regulatory system. Costs of this kind and magnitude must be taken into account in reforming drug regulation here.

THERE IS a real risk that the entire system for developing new drugs in the United States may even now be grinding to a halt. It could soon be too late to make the sorely needed changes, if it is not too late already. Reform of drug regulation is indeed becoming ever more a life and death matter. ■

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