The Development and Regulation of New Medications

The development of new medicines urgently needed by the public is excessively long and costly.

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Summary. The unmet needs of many patients make the successful search for new and better drugs an urgent goal. Increasing regulatory demands have generated delays in the availability of new drugs and concerns about the long-term profitability of the innovative pharmaceutical industry. A rational and flexible approach to drug regulation could ease some of the most worrisome constraints without jeopardizing the public welfare. Changes in our national drug regulatory policy and in the performance of the Food and Drug Administration will serve our society better than drastic legislative mandates intended either to emasculate the FDA or to grant the agency broad new powers.

Public discussion about medicines has tended, in recent years, to center about the toxic effects of chemicals, or allegations that we are an overmedicated society, that doctors prescribe drugs badly, and that the drug industry spends an excessive amount of money brainwashing the country's physicians, the result being an unholy alliance that extracts money from our citizens in return for poisoning their bodies with dangerous chemicals.

This article does not address these propositions, although there is abundant reason for believing that they are off the mark in many respects (*1*). My main theme is that we desperately need better medicines, and that the current state of drug development and regulation is sick and getting sicker.

Why Do We Need New Drugs?

Any doctor's office or hospital can readily provide the answer. There is no area of medicine that does not suffer by reason of inadequate drugs. Many cancer patients can expect little from our present therapies. Schizophrenics would welcome long-term treatment that does not carry with it the risk of irreversible neurologic damage. Severely afflicted arthritics find present remedies far less effective and more toxic than desired. Microorganisms can be expected to spawn strains that are resistant to widely used antibiotics. The muscular dystrophies do not respond significantly to available drugs. The list goes on and on, to the frustration of the sick, their relatives, and physicians, who want to help but often cannot.

There should be little disagreement, therefore, about society's need for new and better drugs. How are we to find them? Discovery is related to available knowledge, to the adequacy of current methodology, to support of both basic and applied research, and to the ease with which discoveries can be turned into approved new remedies. The history of scientific progress (*2*) testifies to the "usefulness of useless knowledge" (*3*) and to the unpredictable course of discovery. The scientific literature also bears eloquent witness to the rate at which new information is being recorded. Integrating and applying new data may pose problems, but the "knowledge depletion" hypothesis as an explanation for the decline in new drug development scarcely deserves credence. (It must be admitted, however, that the decrease in monies allocated to basic research by recent federal administrations warrants serious concern about the future. In times of economic depression, governments irresistibly cut back on such "luxuries" as the arts, education, and research, heedless of the fact that such ill-considered economies mortgage society's future.)

Most applied research is performed by industry. Hence the economic health, scientific wisdom, and social commitment of industry are of crucial importance to the process of drug development. New drugs will continue to come primarily from the larger innovative drug firms, not small "generic" houses. The industry allocates a high percentage of its profits to research and development (R & D), but the payoff from such investment depends on the costs of drug development and the likelihood of adequate return.

Is Drug Development Becoming Too Expensive?

The best available data on the productivity and expenditures of the U.S. drug industry in the last few years (*4*) suggest that it now takes a U.S. firm about 8 years and $54 million to bring one of its new drugs to the U.S. market, if one considers (as one must) the total costs of research programs, that is, the costs of working up the failures as well as the successes.

Such estimates are depressing, despite the fact that our pharmaceutical industry is obviously not teetering on the brink of disaster. If the current trends persist, the situation will deteriorate still further. Furthermore, there are worldwide pressures to constrain the profits of industry without concern for the long-term impact of putative short-term economic gains for consumers or third-party payers. The "MAC" (maximum allowable cost) program (*5*) and the generic substitution laws (*6*) in many states are examples in point. Moves by foreign governments to reduce the price of drugs covered under national health schemes are another example. (In most countries it is far more important today for a manufacturer to get his drugs approved for reimbursement than simply to have them approved for marketing.) It seems perverse to take private industry to task, as many have in recent years, for failure to develop drugs for the Third World countries while at the same time reducing economic incentives to industry.

The simplest way to increase the funds available for drug development is to shorten the time and cost of drug development. Such moves not only extend the

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0036-8075/78/0526-0871/$01.00/0

effective life of the patent (which, because of development time, now runs about 11 years or so instead of 17) but also allows income to be earned from sales. But is this speedup possible without jeopardizing the safety of the public? I believe it is.

Old Drugs

Let us start with old drugs, both "over-the-counter" (OTC) and prescription drugs. Some of the expenditures now forced on drug houses pay for so-called "defensive" research to support claims for old drugs whose documentation has been deemed faulty by the Food and Drug Administration (FDA) or its advisory groups. There are a good many drugs or drug combinations which almost certainly are effective but which, because of the period when they were discovered, were not subjected to modern, double-blind, controlled trials. Several FDA commissioners have asserted that all drugs must be judged by "the same standards," and that we cannot possibly apply different standards to drugs simply because some are old and some are new, or because some are dispensed on prescription only and others are available for purchase without a doctor's prescription.

At first blush, such a consistency might seem admirable, but on closer scrutiny this position smacks of pathological evenhandedness. To begin with, there are important differences between OTC and prescription drugs—else why have a distinction? OTC drugs are generally intended for use in situations where self-diagnosis and self-treatment make sense. To achieve "safety," it is common for OTC preparations to contain doses (of unquestionably active drugs) that err on the side of conservatism; that is, it is clearer that they are safe than that they will be effective in such dosage for most patients. Such a policy has long been held to be socially sound, but it necessarily makes it harder to demonstrate efficacy in controlled trials.

Furthermore, old drugs, be they OTC or prescription, have one advantage over new drugs—a track record. A drug that has been taken by many thousands or millions of patients and prescribed by doctors for years is hardly in the same position as one that has not. It is common for critics of the use of the marketplace as a criterion of efficacy to point to the misplaced confidences of the past—in bleeding, leeches, puking, and purging. But such practices long ago fell into disrepute, not because of double-blind, controlled trials, but because obviously better treatments came along.

Would it really make sense to demand (as for new drugs) two controlled trials on digitalis? Rolaids? Tums? One can sympathize with the plight of the FDA staff—if they are flexible, will they be at the risk of criticism or lawsuits if they demand new evidence for some drugs but not for others? Can our society devise ways of allowing such judgments without jeopardizing the public, the FDA, or the research-based drug industry? A rigid compulsiveness may have appeal for barnacled bureaucrats or legal lemmings, but is it preferable to a reasoned flexibility? Would not the funds and manpower spent in defensive research (and in reviewing it!) be put to better use in expediting the search for new drugs? Is it desirable to have time-tested remedies taken off the market because the manufacturer is unwilling or unable to perform new trials?

New Drugs

What about new drugs? How can their discovery and development be facilitated? First, let us consider "the drug lag" (*7*). While it is possible to argue about the significance of the drug lag, its occurrence can only be denied by a cavalier disregard for the facts. Indeed, both academicians and FDA officials have acknowledged the fact that other countries often market drugs before we do. The most detailed comparisons are by Wardell (*7*) and contrast the situations in the United Kingdom and the United States, two countries whose medical systems and regulatory sophistication are on a similar plane. While the lag between us and the United Kingdom has decreased in the last few years, it remains significant.

There are, to be sure, both advantages and disadvantages in a society's having early access to medicinals for its people. No drug has ever been completely understood at the time of its introduction; the surprises are not necessarily important, but sometimes they are. The longer one waits for other populations to get experience with a drug, the more chance there will be for revised judgments about it.

When a country is deprived for years of a safe hypnotic drug or a more effective antiasthmatic or antiepileptic drug, the cost in terms of morbidity or mortality can be substantial. But there is the thalidomide story, which demonstrated that occasionally an unanticipated side effect (in this case phocomelia, the absence of one or more limbs in babies born to women who took the drug at a crucial time in pregnancy) will be so distressing that the chemical is withdrawn from medical use.

The cost-benefit calculation is not a simple one, especially since it must be a cumulative one that takes into account the total impact of a policy on the society over a period of years. One cannot take cognizance only of the examples that suit one's argument. Also, we are poor at quantifying benefit from, and therapeutic outcome achieved with, drugs, so that it is often difficult, if not impossible, to come up with even ballpark figures for the benefit that a drug confers on the sick.

Reasons for the Delays

Granted that there are delays in introducing drugs into the United States, what are the reasons? One can quickly eliminate any notion that there is dilution of effort by the pointless submission of worthless drugs. The data indicate that almost every new chemical entity for which an NDA (new drug application) is filled with the FDA ultimately makes it to the market (*8*). So—what is gained by the delay?

One unfortunate source of delay has been the FDA's demand that two controlled trials be conducted in the United States, regardless of the number and quality of foreign trials already available. Where foreign data are not suspect, such chauvinism is indefensible, and it is gratifying to see that the FDA has acknowledged its past errors in this regard (primarily on paper, but to some extent in fact).

Usually, the FDA seems primarily concerned about "safety." The agency is rarely asked by hostile congressmen or consumerists why a drug has *not* been approved, but they are often chided because of a marketed drug's toxicity. Little wonder that the FDA should move at a snail's pace in granting approval.

There is a forlorn hope that asking for data from a few hundred (or even a few thousand) more cases will somehow clarify all the toxic problems to be anticipated with a drug. Would that this were so! One can readily calculate the likelihood of a toxic effect after failing to find it in a sample of given size. For instance, if one has studied 3000 patients without a given side effect occurring, one can be 95 percent sure that the side effect will oc-

cur no more often than once in 1000 times (provided the patients are "typical"). To be 99 percent sure, it would take 5000 cases. The numbers thus quickly become unrealistic if one is interested in truly rare effects.

Long-delayed side effects (like the vaginal adenocarcinoma in young women born to mothers who had taken diethylstilbestrol in pregnancy two decades earlier) pose insuperable problems prior to marketing. So does drug abuse, or the risk of massive overdose, or the interaction of the new drug with all conceivable drugs and disease states.

There is, therefore, a lot that one wants to know about a drug that is only discoverable after marketing (*9*). The answer seems simple: study the drug after marketing in the "naturalistic" setting that obtains in the real world (*10*) and stop delaying a drug's marketing for bad reasons.

Another problem lies in FDA personnel and attitudes. There has been a recurrent criticism, in a series of in-depth reviews of the FDA by different committees (*11*), of the quality and organization of the agency. FDA commissioners have usually lauded their personnel while in office, only to describe them with more candor on leaving government. There have always been dedicated and talented men and women in the FDA, and there seem to be a few more of them now than in the past, but the agency has long been peopled by public servants, many of whom combine a lack of scientific sophistication with a paranoid hatred of the drug industry and an abiding distrust of clinical investigators.

Donald Kennedy, the present FDA commissioner, is the first nonphysician to hold the post since George Larrick. A respected basic scientist, he has indicated his intention to hold a series of hearings in various cities to "demythologize" the medical profession—a strange assignment for the director of a regulatory agency, unless a denigration of the physician's role is intended to suggest that the FDA must protect the public from their doctors. It is not a campaign calculated to win for Kennedy the respect of the profession at large.

Proposals for Reform

There has been a flood of legislative proposals intended to revise the Food, Drug, and Cosmetic Act. Some wish to repeal parts of it so as to take power away from the FDA; others wish to grant the agency even more powers than it now has by law and by its ability to promulgate regulations.

No doubt some amendments could improve the Act, but it seems to me that since the current laws allow the FDA to demand evidence for both safety and efficacy of new drugs, and the means to take any drug that is an "imminent hazard" off the market forthwith, the fault seems less with the law than with the way it has been implemented.

The FDA, whose last commissioner complained that Congress and the public were constantly thrusting new responsibilities on the agency without the means to discharge such responsibilities, now says that it needs all sorts of new investigative powers, plus the right to impose civil and criminal penalties on physicians it deems miscreant.

I see no evidence that Washington has a monopoly on wisdom or probity, or indeed that there is more of such qualities within the FDA than in the medical profession or the drug industry. And in one respect the FDA is more vulnerable to unfair pressures than is the private sector. It is constantly badgered by everyone—the media, the drug industry, the medical profession, the consumerists, and the academicians. The top FDA brass spend so much time testifying before Congress or giving speeches that one wonders how anything ever gets done, and it is difficult to see how this kind of behavior can change in the foreseeable future, given our national penchant for trial by public ordeal.

The stakes are too high for us to continue along the present road. Drug development is too important to let it fall prey to unbridled political passions or internecine warfare. Fourteen years ago, in this periodical (*12*), I pleaded that the government, academia, physicians, and the public join in a partnership to achieve solutions to the drug problems facing us all. Instead of that, the intervening years have seen a series of pitched battles between the affected parties.

Extremist points of view are to be heard from all quarters. Commissioner Kennedy has recently stated that "there is a crisis of confidence in testing procedures and in regulation as well" (*13*). The public is beginning to show signs of disaffection with everyone—the experts, the FDA, Congress, physicians, the lot. Saccharin and Laetrile show what can happen if the public is sufficiently aroused as to wish to take matters into its own hands. This is appropriate for a democracy, but one cannot but feel that things would proceed more smoothly and more wisely if matters of drug development and regulation received the attention and guidance they deserve from the most knowledgeable members of our society.

There are so many problems to which men of goodwill could address themselves: How much preclinical toxicity data may reasonably be demanded? Are the endlessly proliferating GLP (good laboratory practice) or GMP (good manufacturing practice) requirements cost-effective? How are we to encourage the search for "orphan drugs"—drugs for rare illnesses or which for other reasons are never going to repay the money required to bring them to market? How is the small entrepreneur with a new drug or medical device to carry on in the face of escalating costs? How do we optimize drug usage? Is it possible to diminish the rate at which American R & D monies are moving abroad? Can investment in the search for new drugs be made attractive enough to attract capital in the future?

There is so much to do (*14*). Can we get on with it?

References and Notes

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