

SOUNDING BOARD

A Proposal for Radical Changes in the Drug-Approval Process

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Drug development is the process by which new therapies are created and brought to market to treat diseases. It is hard to imagine that such an activity would not be universally admired and lauded, but recently the pharmaceutical companies that develop new drugs have been criticized by patients, legislators, and the press.¹ This criticism has been focused on the high cost of prescription drugs and the disparity between the costs of these drugs in the United States and in other developed countries such as Canada and the United Kingdom.¹ In addition to concern about cost, a more recent issue is the public's loss of faith in the integrity of the industry and its ability to deliver safe and effective drugs. This loss of faith has followed a series of revelations about drug toxicity, which some people have claimed has been hidden from the public and regulators. It has also been suggested that the Food and Drug Administration (FDA), which is responsible for the regulation of new drugs, is not sufficiently stringent.²⁻⁴ These are not happy times for pharmaceutical companies or the agency responsible for their regulation. Perhaps, however, this situation provides an opportunity to examine whether changes should be made to the drug-approval process to encourage the development of new drugs with high scientific risk and to provide incentives for studies of the long-term safety of drugs.

First, it is worth reviewing some of the variables of drug development. The creation of a new drug is risky⁵ and expensive.⁶ In 2004 dollars, the average cost of developing a drug is more than \$860 million.⁶ Although arguments have been made that this cost is inflated, this is a huge amount of money and in the long term is unlikely to be sustainable.

Most of the basic science that underpins drug development occurs in the public sector,⁷ and this has led to the suggestion that there are alternatives to commercial drug development.¹ I do not

believe these alternatives are desirable or realistic. New drugs are developed virtually exclusively by for-profit companies and always will be, because only these entities have access to the capital required and to investors with an appetite for the risks involved. In spite of the criticism directed toward them, pharmaceutical companies have produced a substantial public health benefit. In the United States, rates of death from heart disease and stroke⁸ (Fig. 1) have been cut in half in the past 30 years — largely by the use of drugs that reduce known risk factors such as hypertension and elevated lipid levels. The development of highly effective drugs to treat HIV infection has transformed the prognosis of that disease. In both cases, the discoveries in basic science were made through government-funded research, but effective drugs were developed in the private sector.

In spite of this success, there are worrisome signs for the future. It was confidently predicted that the revolution in genomic medicine would make drug development easier and more efficient; however, for the past several years, productivity has decreased for all phases of drug development, thus reducing the likelihood that a compound will reach the market⁹ (Fig. 2). In addition, the number of new drug applications submitted to the FDA has decreased during the past 10 years¹⁰ even though the genomic revolution should have led to an explosion in this number.

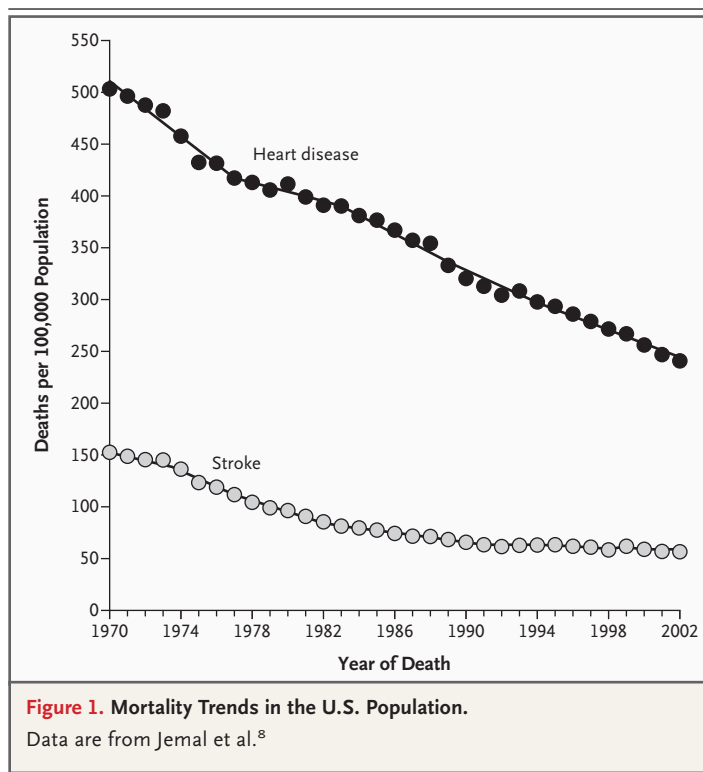
The high cost of drug development favors risk-averse drug-development strategies such as creating new formulations, combining already approved agents, and making subtle chemical changes that allow a drug that is about to face competition from a generic alternative to enjoy a new lease on life. These strategies have resulted in many statins, large numbers of beta-blockers and combinations of beta-blockers, angiotensin-converting-enzyme (ACE) inhibitors and

combinations of ACE inhibitors, and angiotensin-receptor blockers and combinations of angiotensin-receptor blockers.¹¹ However, not a single drug has been developed to prevent Alzheimer's disease or osteoarthritis despite predictions of a huge increase in the prevalence of these diseases in the coming years as the baby boomers age. Why is this? It is because our drug-approval system makes it hard, if not impossible, to devise a development plan that would demonstrate that a drug prevents rather than reduces the symptoms of Alzheimer's disease or osteoarthritis and allows such a drug to reach the market before its patent life runs out. In addition, despite considerable advances in our understanding of such diseases, there is no validated and tested path to successful FDA approval of a drug to prevent these conditions. This lack of a clear plan for drug approval adds high regulatory risk to the already high scientific risk of failure.

To encourage the development of drugs for the diseases faced by our aging population, I propose four radical changes to the drug-development and drug-approval process. These proposed changes are designed to provide incentives to demonstrate a drug's long-term safety, perform head-to-head drug-comparison studies, complete phase 4 commitments that had been agreed to, convert end points of surrogate markers or biologic markers to clinically meaningful end points, and encourage drug development with high commercial risk (Table 1).

The fundamental philosophy underlying my proposed changes is that as compared with other therapies, safer, more effective, or uniquely effective therapies are inherently more valuable to patients and increased clinical value should be reflected in increased commercial value through a longer period of exclusivity (the patent holder's exclusive right to sell a drug without competition from manufacturers of generic drugs).

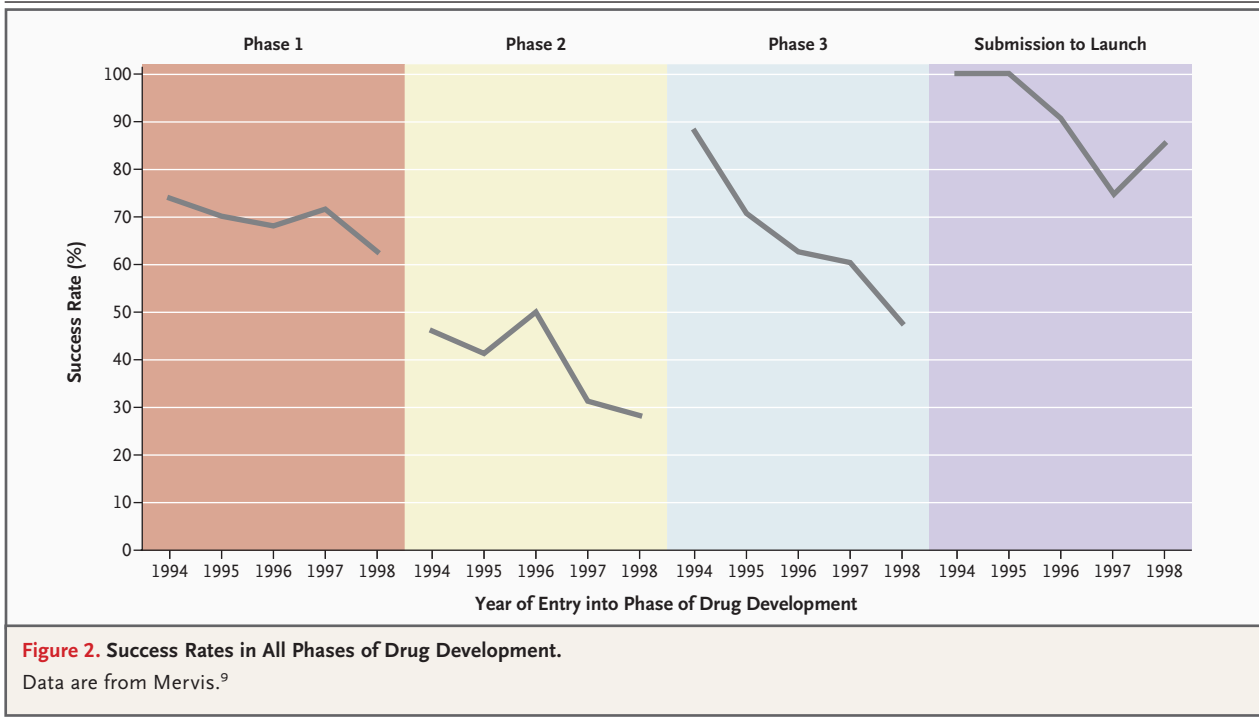
There is a distinction between patents and exclusivity. Patent holders have the right to a monopoly on their invention for a limited time, which according to the Uruguay Round Agreements Act is 20 years from the date of the application for the patent (with some provision to compensate for delays by the patent office). However, because a drug company cannot sell a drug until it has received FDA approval, the effective patent life of a drug is substantially shorter than the nominal patent life. Therefore, in the United



States, Congress extended, beyond the duration of the standard patent, the period during which the original patent holder has the exclusive right to sell a drug (i.e., extended exclusivity) and before competition by a generic alternative is permitted.¹² An additional six months' exclusivity has been granted for performing studies of drugs for children. An extended period of exclusivity can also be obtained through regulatory inertia. For example, because of lack of a path for FDA approval of generic biologic products ("biogenerics"), these products have an effectively unlimited period of exclusivity even when their patent life is exhausted.

LACK OF LONG-TERM SAFETY DATA

My first proposed change to the drug-approval process relates to the current lack of long-term safety data. The availability of data that have called into question the safety of cyclooxygenase-2 inhibitors years after they were first marketed and the uncovering of doubts about the safety of antidepressants for young people have highlighted the lack of a system to demonstrate the safety of drugs used on a long-term basis by millions of patients.



To encourage the generation of such data, an extended period of exclusivity should be offered to drug manufacturers after the completion of FDA-mandated studies that demonstrate a drug's long-term safety. This extended exclusivity will make drugs with demonstrated long-term safety data more valuable than those without such data. A drug for long-term use could be approved on the basis of studies similar to those currently in use. The FDA could then mandate or the manufacturer could elect to perform appropriately designed clinical trials to demonstrate the drug's long-term safety. The privilege of an extended period of exclusivity would depend on the FDA's having previously approved the study design, the standard therapy with which the drug was being compared, and the level of increased safety required. If an equivalence-study design was used, the study would have to be adequately powered to exclude a safety difference of a clinically meaningful size. Demonstration of the preferred and predefined safety outcome would lead to the extension of the period of exclusivity. Thus, drugs with demonstrated long-term safety would become more valuable than those for which no such data existed. Such long-term safety data could also be used in marketing. Failure to complete mandated safety studies on time would result in the loss of extended exclusivity.

Our reliance on regulation alone to demonstrate the long-term safety of drugs has been an unequivocal failure. In addition, we currently have virtually no data on the comparative efficacy or safety of different drugs, and the results of the limited comparison studies that we do have are not reassuring.^{13,14} My proposal for incentives encourages, under FDA supervision, the provision of such long-term safety and comparison data.

UNMET PHASE 4 COMMITMENTS

A drug can be approved with a commitment from the drug company to perform further studies after approval (phase 4). These so-called phase 4 commitments confirm either the drug's safety or efficacy. When there is an unmet need for a particular treatment of a serious or life-threatening disease, a drug can also be approved under a

Table 1. Goals of Proposed Changes to the Drug-Approval Process.

- Demonstration of a drug's long-term safety
- Performance of head-to-head drug-comparison studies
- Completion of phase 4 commitments
- Conversion of end points of surrogate markers or biologic markers to clinically meaningful end points
- Encouragement of drug development with high commercial risk

“fast-track” system; this approval is based on a surrogate measure such as tumor shrinkage in a single uncontrolled study of a cancer treatment.¹⁵ The approval is conditional on agreement by the sponsor to complete confirmatory studies after approval. In theory, the failure to complete such studies should result in the drug’s withdrawal. The progress in meeting phase 4 commitments is frankly disturbing and shows that the present system is not working.^{15,16} According to the FDA’s 2005 report on performance of these commitment studies,¹⁶ of 1191 open post-marketing commitments, only 114 (9.6 percent) had been met, yet none of the drugs with incomplete phase 4 commitments have been withdrawn from the market. This sanction is not credible and has not been carried out.

My second proposed change to the drug-approval process relates to these unmet phase 4 commitments. I propose that we provide incentives for the completion of these commitments by offering only a limited, shorter period of exclusivity with accelerated approvals. I also suggest that we allow the normal period of extended exclusivity to be restored when the mandated phase 4 studies are completed and yield data that confirm the drug’s efficacy and safety. If such mandated studies are not completed or if the drug’s efficacy or safety is not confirmed by such studies, exclusivity will be lost at the end of the shortened exclusivity period granted at the time of accelerated approval. Faced with the loss of exclusivity and competition from generic drugs in the marketplace, companies will meet their phase 4 commitments — the potential financial penalty of not doing so will simply be too great.

Promotion of a drug with unmet phase 4 commitments or mandated safety studies that are incomplete would be limited and would require a prominent acknowledgment of the immature state of knowledge of the drug. The same restrictions on promotion would apply to drugs approved under my third proposed change to the drug-approval process below.

LACK OF CLINICALLY MEANINGFUL END POINTS

To encourage the development of drugs with high commercial risk to prevent chronic diseases, we need to develop a strategy that will convert the approval of such drugs on the basis of apparently beneficial changes on a relevant surrogate, im-

Table 2. Characteristics of a High-Need, High-Risk Therapeutic Area.

Absence of effective or nontoxic therapies
Sufficient scientific or biologic uncertainty as to successful therapeutic strategies
Lack of a previously successful path to drug approval
Large potential effect of successful therapy on disease burden and public health

aging, or biologic marker to the demonstration of benefit on a clinically meaningful end point (e.g., prevention of cognitive deterioration in patients at risk for Alzheimer’s disease or avoidance of the need for hip replacement in patients with early osteoarthritis).

When too much time is required to demonstrate a clinically meaningful benefit in a pre-approval study, initial FDA approval could be given on the basis of a change in the end point of an imaging or biologic marker. However, that initial approval would provide only a limited period of exclusivity during which the sponsor would have to demonstrate that patients also benefited with respect to a clinically meaningful end point (i.e., meaningful improvement in function or a reduction in morbidity or mortality). The timely provision of such data would result in an extension of the period of exclusivity. The early loss of exclusivity because such data were not provided would result in a loss of commercial value. This change would create a huge incentive to convert the drug approval to a hard end point while accelerating the approval process and drug development and reducing risk and cost.

INADEQUATE INCENTIVES FOR DRUG DEVELOPMENT WITH HIGH COMMERCIAL RISK

Our current drug-approval system does not adequately reward the development of the most beneficial drugs. Manufacturers of drugs that are not demonstrably different from many others on the market are offered extended periods of exclusivity, although the risk involved in this drug development is relatively low. However, no incentives are offered to manufacturers for the development of drugs for which a path to drug approval has not been trodden previously. Although the risk of failure in these uncharted areas is inevitably higher, the benefits to patients may be great. Thus, my fourth proposed change to the drug-approval process is to encourage the devel-

opment of drugs for currently unserved therapeutic areas for which the risk of drug development is high. The characteristics of these unserved areas are listed in Table 2.

INCENTIVES FOR THE DEVELOPMENT OF DRUGS FOR HIGH-NEED, HIGH-RISK AREAS

The prevention of Alzheimer’s disease or osteoarthritis might be a good example of such high-need and high-risk therapeutic areas. These areas would be identified and agreed to in advance by an independent scientific group. Once an area was designated as being high need and high risk, an extended (i.e., longer than current) period of exclusivity would be available to manufacturers of successfully developed drugs in this area, and the extended exclusivity would increase the value of these drugs. Development plans for such high-need, high-risk areas could also be carried out on the basis of relevant imaging on biologic markers, as outlined in my third proposed change to the drug-approval process.

To ensure that this scientific consensus group remains focused on the areas of highest impact that merit the award of extended exclusivity in advance, the number of areas for which such exclusivity can be granted should be limited to 5 to 10, and these areas will change over time as successful therapies are developed. Of course, the trickiest problem will be for regulators to identify these areas of need and then to identify true advances in the amelioration or cure of these con-

ditions; this will require stable, credible, and science-based leadership at the FDA.

INCENTIVES FOR DRUGS THAT ARE “FIRST IN CLASS”

The present drug-approval system perversely rewards the 10th drug in a class with the same period of exclusivity as the drugs approved earliest in that class; this has contributed to the risk-averse development strategy described previously. The first few ACE inhibitors carried greater development risk than the 10th ACE inhibitor; thus, their manufacturers should have been granted a lengthened period of exclusivity to encourage their assumption of such higher risk. The identification of new “druggable” targets is desirable, but as compared with the development of drugs for well-understood targets, such development targets carry a greater risk of both clinical and commercial failure; therefore, success should be rewarded with longer periods of exclusivity.

Manufacturers of late drugs in a class, sometimes called “me too” drugs, would be given a shorter period of exclusivity unless or until they demonstrate that their drugs had some meaningful advantage (such as increased efficacy or improved safety) over other drugs in their class. This focus on an increased benefit in turn would encourage head-to-head comparisons among drugs — which currently are almost totally lacking.

The fundamental goal is to reward true, high-

Table 3. Improving the Drug-Approval Process through “Economic Darwinism.”

Problem	Proposed Solution	Comments
No long-term safety data No direct head-to-head comparative studies	Granting of extended period of exclusivity for drugs with data that demonstrate long-term safety	Study design requires preapproval by the FDA Will usually involve comparative studies
Phase 4 commitments not fulfilled	Granting of extended period of exclusivity only when phase 4 commitments are met	Present completion rate very low Currently no credible sanction
Inability to ensure timely conversion of surrogate and biologic marker end points to clinically meaningful end points	Approval based on biologic marker or surrogate marker — granting of limited period of exclusivity Granting of extended exclusivity only when converted to clinically meaningful end point	Some biologic markers and surrogate markers will not correlate to meaningful clinical benefit, and drugs approved on the basis of such end points will lose extended exclusivity
No incentives for drug development with high commercial risk No encouragement to make a paradigm shift rather than replicative strategies	Granting of additional (beyond current) extension of exclusivity for predefined high-need, high-risk areas Use of biologic markers and surrogate markers possible, but with limits described above	Achieving consensus independent of commercial and other pressures is key Use of an independent body such as NAS or IOM* to define high-need, high-risk areas Number of designated high-need, high-risk areas restricted to 5 to 10

* NAS denotes the National Academy of Sciences, and IOM the Institute of Medicine.

risk innovation that improves medical care — an “economic Darwinism” — in contrast to our current system, which rewards duplicative, relatively low-risk drug development and encourages the use of new, expensive, heavily marketed drugs at the expense of older, equally effective drugs of the same pharmacologic class.

CONCLUSIONS

The changes that I propose (summarized in Table 3) would use incentives to encourage the development of drugs to treat and prevent diseases for which we have no current therapeutic options and to develop new, more effective, and safer drugs for diseases for which current therapies do exist. Will such incentives work? I believe so. The six-month extension in the period of exclusivity offered for studies of drugs in children resulted in an increase in the number of such studies. The incentives in my proposals rely on the generation of data demonstrating improved efficacy or safety, or both, not just the completion of studies. The status quo is always more comfortable than radical change. However, the problems in our current drug-approval system and the costs of drug development to both pharmaceutical companies and patients make the attractions of change irresistible and the status quo untenable.

Dr. Wood reports having received consulting or lecture fees during the past two years from Scirex, Sapphire Therapeutics, Abbott Laboratories, Elan Pharmaceuticals, NicOx, Medco, Novartis, and Eli Lilly; having acted as an adviser to various reinsurance companies regarding pharmaceutical matters; and serving as a director of Antigenics, chairman of the clinical advisory council and an investor in Symphony Capital, and a director of Symphony Neurodevelopment and Symphony Evolution. On September 1, 2006, Dr. Wood will become managing director of Symphony Capital. No other potential conflict of interest relevant to this article was reported.

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CORRECTION

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In Figure 1, the label for the y axis should have read, "Deaths per 100,000 Population," not "Deaths per 100,00 Population," as printed. The figure has been corrected on the *Journal's* Web site at www.nejm.org.