
6. **Issues and Options**

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Current interest in prescription drug evaluation and monitoring is focused on the premarketing approval process, while postmarketing surveillance has waned as a policy issue. The recommendations of the Joint Commission on Prescription Drug Use, issued in January 1980, have not been implemented, and the linchpin of its recommendations, a national Center for Drug Surveillance, reached its zenith before the commission issued its report when the center concept (renamed as the "National Center for Drug Science") was included in the 1979 bill that passed the Senate but was not acted on by the House of Representatives. In contrast, in the first session of the 97th Congress, the Senate passed the Patent Term Restoration Act of 1981, in large part as a direct response to the length of the drug approval process. As mentioned earlier, the House of Representatives also voted on the bill, but under suspension of its rules. Although the bill received a majority of the votes, a two-thirds vote was required for passage under such conditions, and the bill fell just short of the two-thirds majority needed. Shortly prior to publication of this report, the report of the Commission on the Federal Drug Approval Process and the current Food and Drug Administration (FDA) review will both also be complete. Both focus on methods to hasten drug approval by FDA.

Thus, policy formulation and implementation for the premarketing approval process is being pursued without parallel efforts for the postmarketing period. As one person has remarked (43):

I don't really see that any significant shortening of approval time can be engaged in as a result of a tradeoff in regard to postmarketing surveillance, although this was originally thought to be a possibility when a former FDA commissioner suggested that such was the case.

Others do see a linkage between the approval *process* and postmarketing surveillance, although they agree that there are no direct tradeoffs in the kinds of information obtained (4):

Postmarketing evaluation studies can be conducted much more cheaply than clinical trials . . . As a motivator for industry, it is desirable to have the drug marketed sooner with a return on investment while studies are being conducted. At the same time, much larger observational studies can be done, at the same cost, [to] evaluate drugs in their customary use situation. It is important to recognize that phase III clinical trials and postmarketing drug evaluation studies are not alternatives. They address different issues and are complementary. The appropriate question is whether it would not be better to reduce the size and cost of phase III with limited likelihood of losing meaningful information and conduct much larger studies after marketing.

Hence, some relationship does exist between proposed changes in the premarketing approval process and the monitoring activities of the postmarketing period. This relationship can be clarified by the answers to two questions. Can the size and cost of phase III clinical trials be reduced with limited likelihood of losing meaningful information? And, should pharmaceutical manufacturers be required to maintain the level of their drug evaluation responsibilities by increasing postmarketing surveillance?

Issue 1:

Revising premarketing tests and shortening the drug approval process.

The efficacy and safety tests in animals and humans specified in FDA regulations for premarketing approval are based on broad statutory language (21 U. S. C., sec. 355 (d)). "Adequate tests by all methods reasonably applicable" are necessary to show that a drug is safe for use. There must also be "substantial evidence that the drug will have the effect it purports or is represented to have," where "substantial evidence" is defined as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific

training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could be fairly and responsibly concluded by such experts that the drug will have the effect it purports or is represented to have. ”

Efforts to shorten the drug approval process have focused not on the statutory language but on the regulations issued by FDA to implement the law. Thus, the focus here is on oversight issues, not on legislative changes.

Proposals to curtail or eliminate phase III premarketing tests, or shift them to the postmarketing period can be evaluated both theoretically and experientially.

Theoretically, phase III testing is significantly **more sensitive than phase II testing**. Adverse effects with an incidence of 1/100 or more are more likely than not to be detected in the 100 to 200 patients in phase II. But the theoretical sensitivity of detection rises in phase III to 1/500 with 500 patients, and 1/1,000 with 1,000 to 3,000 patients (see ch. 4, table s).

These observations are relevant to the detection of adverse reactions, but they are not so relevant to the detection of therapeutic effects. A drug that helps only 1 in 100 patients would not be very effective, so effectiveness should be established in phase II. Phase III is intended to gather additional evidence on a drug's effectiveness for specific indications.

If phase III testing were curtailed or eliminated, there is also the question of whether premarketing evaluations would test sufficient numbers of patients to reasonably ensure a drug's safety or give substantial evidence of its efficacy. Even under current regulations, the use of a drug on humans is very limited before the drug is released for market: 20 to 80 patients in phase I; 100 to 200 patients in phase II; and 500 to 3,000 patients in phase III—a range of only 620 to 3,280 patients per drug (excluding controls). Curtailing the larger phase III tests would lower the range of patients tested to 620 to 780, and eliminating phase III tests altogether would reduce that range further to 120 to 280 patients who would be tested with a drug before it is released for general use.

In addition to theoretical criteria, **experiential criteria could be applied in considering proposals to curtail or eliminate phase III tests**. The diminished power to observe adverse drug effects that such changes theoretically entail may not in fact be found, or if it is, it may concern only infrequent minor effects. As was mentioned previously, FDA is reviewing past phase III tests to see if the trials for chronic effects or those with large sample sizes have contributed useful information beyond that obtained in phase II and early phase III. This review should indicate whether or not actual experience reflects the theoretical differences discussed above between phase II and phase III tests involving 500 versus 1,500 to 3,000 patients. Agreement of the experiential data with the differences theoretically predicted would strengthen the hypothesis that curtailing phase III tests would lower the capacity of current premarketing tests to identify adverse reactions. If the experiential data fail to reflect the theoretical differences, then a better case can be made for curtailing phase III, with or without transfer of some of its testing to the postmarketing period.

Current interpretations of the statutory requirements for “adequate tests” of safety and “**substantial evidence**” of effectiveness emphasize **methodology**, as reflected in the requirement that each indication for which a drug is intended be supported by at least two well-controlled clinical trials. This is the reason for the preceding discussion of statistical guidelines and the complementarity of normative guidelines in evaluating how FDA revises its drug approval regulations and procedures. **But FDA can alter the criteria by which it approves drugs**. For example, propranolol, the first beta-blocking drug approved for use in the United States, was approved by an advisory committee on the basis of all the evidence presented to FDA, even though no one study was found to be adequate and well controlled (21). And in late 1981, timolol, another beta-blocker, was approved for use in preventing death and recurrent heart attacks in patients who have survived initial heart attacks. This approval was based on a foreign study—a 3-year Norwegian study showing that the risk of death or a second heart attack following a first heart attack was

reduced by about one-third when timolol therapy began within 28 days and continued for up to 33 months (26). Although the study was Norwegian, the results were accepted for publication by the most prestigious medical journal in the United States, the *New England Journal of Medicine* (57). (Approval for another indication, high blood pressure, was based on U.S. studies.)

Approval of timolol may also have been influenced by a similar study of propranolol in the United States by the National Heart, Lung, and Blood Institute (NHLBI). In the clinical trial of propranolol, NHLBI's Policy and Data Monitoring Board took the unusual step of curtailing the trial when data indicated that patients receiving propranolol experienced a 26 percent lower mortality from all causes than did a control group. According to the Beta-Blocker Heart Attack Study Group (2):

The results . . . strengthen and extend the conclusions of previous studies of beta-blockers in survivors of acute myocardial infarction. This large study of a noncardioselective agent is in accord with the results of the recent trial of timolol maleate.

The criteria for FDA's acceptance of timolol, therefore, closely approximated the requirement of two well-controlled clinical trials, notwithstanding the fact that one of these trials was performed in another country.

The approval of propranolol and timolol, however, do illustrate that FDA can grant exceptions to its usual requirement of two well-controlled U.S.-based clinical trials. In the case of timolol, the validity of the Norwegian study was confirmed by its acceptance for publication in a prestigious U.S. medical journal, and even though approval was based on this one study, the results of the NHLBI trial on propranolol, another beta-blocker, must surely have influenced the FDA decision to approve timolol for prevention of heart attacks. In the case of propranolol, the first beta-blocker drug to be approved by FDA, approval was based on the preponderance of the evidence as judged by an advisory committee.

In such a case, expert judgment relies on qualitative, not quantitative, criteria in approving a drug, and such an approach falls outside the theo-

retical and experiential guidelines outlined above. **If FDA is to rely increasingly on such qualitative criteria through the increased use of advisory committees, it will be necessary for FDA to develop general guidelines to aid the advisory committees in their deliberations.** Otherwise, in a case-by-case approach, evidence of the same quality may lead to approval for one drug and nonapproval for another.

Issue 2:

Improving postmarketing surveillance and its role in the drug approval process.

Controlled clinical trials, the most accepted scientific means of identifying and confirming a drug's effectiveness and safety, are used in drug testing in the premarketing stage, but the evidence they yield is necessarily limited because their sample sizes are small and the patients they test represent only a fraction of the kinds of patients who will eventually use the drug. Other shortcomings of small controlled clinical trials are that rare but serious adverse effects or effects with a long latency will not be observed, and that average conditions of use are not duplicated. These limitations of premarketing testing can only be addressed in the wider use that comes with marketing the drug. Thus, **even if phase III testing were not curtailed or eliminated, FDA's powers in the postmarketing period could be strengthened to enhance its surveillance role.**

Generally, postmarketing surveillance “systems” that have been advocated are not systems in the formal sense, but a series of related activities oriented toward several purposes, with the regulatory approval process being only one use. The activities most frequently mentioned include the following three.

First is the building of a resource base through training of additional experts and improving epidemiological tools such as methods for case-control and cohort studies. The concept of a national Center for Drug Surveillance, advocated in the report of the Joint Commission on Prescription Drug Use, was one such attempt. Others believe, in contrast, that the resources are already in hand. According to Jick (40):

Contrary to the views stated in the report [of the Joint Commission on Prescription Drug Use], I believe that methods to efficiently perform postmarketing surveillance are known and well tested, and that a vast amount of data has already been collected to evaluate drug toxicity.

Remington states (61):

IM]ethods for estimating characteristics of large populations, although available since the 1940's, have not been assimilated to any appreciable extent into the field of drug evaluation . . . I think we must begin to apply modern mass population methods to modern problems of drug evaluation, both at the pre- and post-marketing levels. Such methods, however, are particularly appropriate to the evaluation of marketed drugs.

Second is strengthening voluntary reporting to identify possible adverse drug reactions. Once such reactions are suspected, clinical trials, case-control, and cohort studies could be used to determine whether an association with drug use in fact exists. In this regard, FDA has come under criticism insofar as its adverse drug reaction reporting activities are concerned. For example, the activities listed in chapter 4 have been criticized as being little more than a catalog, with no assessment of the relative values of the various activities (80). Furthermore, in a recently released followup to a study conducted in 1974, the U.S. General Accounting Office concluded (29):

Many adverse reaction reports do not get to the Division maintaining the system and many others require a long time to get into the system. Some of the missing or late reports involved serious reactions which were not discussed in the drug labeling. Reporting by non-manufacturer sources, such as hospitals or physicians, could also be increased.

Third is developing an efficient method for monitoring selected drugs after their release into the market. The most frequently mentioned mechanism is formation of prospective cohorts of drug users, utilizing existing data bases such as those previously identified, i.e., Medicaid, Medicare, the military health systems, and some health maintenance organizations. In the opinion of one expert, appropriate large-scale systems are available, but only drug companies currently use them (41).

These components of a postmarketing surveillance "system," and FDA's role in supporting and using them, are oversight issues.

There are also several legislative options that could strengthen FDA's powers in the postmarketing period. The following legislative options are presented for congressional consideration.

Option 1: Give FDA the power to require postmarketing studies.

Currently, FDA has no express power to require a drug's sponsor to conduct postmarketing studies of the types summarized earlier under "phase IV" testing. Drug companies have agreed to such requests in the past, however, because refusal might mean nonapproval of the drug.

FDA is examining these studies to see if they provided the kinds of information identified in its objectives for "phase IV" testing. Additional questions are to determine when adverse reactions became specified on the package insert, and whether the source of the identification of adverse reactions was spontaneous reports, the postmarketing study, or both.

However, a broader analysis is needed, one that does not focus only on these specific studies. It would be helpful if FDA also assessed a sample of drugs that have been marketed for several years to see if significant additional adverse reactions were later discovered that were not uncovered during premarketing trials. Or a study could be conducted on the significant adverse events that were discovered during the postmarketing period. In either of these latter types of studies, the assessment focus should be on whether the adverse effects could have been discovered through studies of the kinds performed by the manufacturers at FDA's request. This assessment could provide additional information for deciding whether formal postmarketing monitoring would be valuable.

The larger postmarketing studies carried out by manufacturers at the request of FDA have cost \$1 million to \$3 million each (11), and the industry is certain to resist giving FDA explicit authority to require them. Industry might be more willing to conduct postmarketing studies if the drug approval process were shortened, however, since it

could obtain a quicker return on its investments. In the absence of such a tradeoff, Congress could consider increasing FDA's appropriations to finance selected postmarketing studies on a drug-by-drug basis.

A variation of this option is for FDA to use its existing regulatory powers over advertising and promotional practices to "certify" an industry-sponsored postmarketing study. Although initially reluctant to conduct postmarketing studies, the industry now sees them as part of its marketing strategy. Physicians may cease to cooperate, however, if they feel they have been used to promote a company's product. FDA certification could be used to distinguish between postmarketing monitoring and "product support studies" that are used to interest physicians in a manufacturer's products and to defend a drug's safety and therapeutic value (69).

Option 2: Give **FDA the power** to restrict the distribution, dispensing, and administration of a drug.

FDA has considerable power in withholding approval for a drug, but once a drug is approved, there is a significant shift in the burden of proof and in the amount of evidence required to rescind approval. If FDA had the authority to restrict drug marketing or less burden of proof in rescinding approval, it might give approval more freely in the first place. Restrictions on drug use and a lesser burden of proof for FDA to rescind approval would be particularly pertinent in the first several years of marketing, when adverse effects are still quite likely to be identified. The therapeutic-toxic ratio of some new drugs is so narrow that it seems reasonable to provide the means whereby FDA can restrict the use of certain prescription drugs to groups of specially trained or experienced physicians.

S. 1075, the bill introduced in 1979 and passed by the Senate, would have given restrictive powers to FDA, provided that: 1) the drug presented significant risks to patients or the public health; 2) a drug could not be determined to be safe unless restrictions on distribution and dispensing were imposed; 3) the restrictions could reasonably be expected to reduce the risks while permitting its use in appropriate patients; and 4) no other ad-

ministrative or educational actions permissible under the law could reasonably be expected to reduce the risks. The bill also would have allowed a drug to be restricted to practitioners with special training or experience in its use or to practitioners for use in certain facilities, but only if this were necessary to determine drug safety; and no practitioners could be excluded solely on the basis that they were not eligible for certification in a medical specialty. The 1979 Senate bill also would have required FDA to review any imposed restrictions every 2 years.

The Medical Device Amendments of 1976 (Public Law 94-295) contains somewhat similar language in its section on "restricted devices." According to this amendment, a device could be restricted in its sale, distribution, or use if, "because of its potentiality for harmful effect or the collateral measures necessary to its use, the Secretary determines that there cannot otherwise be reasonable assurance of its safety and effectiveness." The law also contains a prohibition against excluding practitioners solely because of their ineligibility for certification in a medical specialty (21 U. S. C., sec. 360j(e)).

In a limited or phased distribution, drugs could be introduced into different geographic regions rather than into the whole country at once. The regions could be chosen with attention to the fact that some drugs are used more in one part of the country than another. Introduction of drugs on a regional basis could also provide some insurance against unexpected adverse effects in that less of our population would be at risk, but different regions could be used for the first marketing of different drugs so that no one region would be the "guinea pig." By specifying the regions well, comparable regions could be compared for reported side effects (.5.5).

A variation of this option is to develop a parallel approval process for the use of a limited group of drugs during phase III testing. This special phase III testing would be considered only as a relatively exceptional procedure restricted to drugs of unusual need and promise. For drugs of apparent unusual therapeutic value compared with alternative therapies and with acceptable risk, a limited number of physicians could be permitted

to use a drug without the fully detailed record-keeping requirements of phase III (28).

Option 3: Change the standard for a drug's removal from the market from "imminent hazard to the public health" to "unreasonable risk of illness or injury to any segment of the population" or some other less stringent standard.

Such a change was contained in the 1979 Senate bill. However, under the present law, the "imminent hazard" standard is to be used only in cases where a drug's harmful effect would be so immediate and severe as to justify suspension of due process until after the drug has been removed from the market. The "imminent hazard" standard applies only to cases where FDA suspends approval of a drug first, then gives the drug sponsor prompt notice and an opportunity for an expedited hearing. FDA otherwise can remove a drug from the market on the basis of new evidence on safety or effectiveness or for other reasons such as discovering that approval of the drug was based on an untrue statement of a material fact. To take such action, however, FDA must give due notice and an opportunity for a hearing before it can proceed.

Substituting "unreasonable risk" for "imminent hazard" in the standard would blur the present distinction between those cases when due notice and opportunity for a hearing should be required before a drug could be taken off the market and those cases when it would be justified to remove a drug from the market prior to notice and an opportunity for a hearing. In other words, "unreasonable risk" is already the standard for those cases when, in order to protect the drug sponsor's economic interests, FDA must give due notice and an opportunity for a hearing before taking action.

If such a change in the standard were approved, FDA would be able to remove a drug for any of the currently accepted reasons to question safety without first giving notice and an opportunity for a hearing.

In the Medical Device Amendments of 1976, no such "imminent hazard" standard is specified. There is, however, a slight difference in the wording of the law. It states that, if a drug does not represent an "imminent hazard," withdrawal of the drug's approval can proceed "after due notice and opportunity for a hearing" (21 U. S. C., sec. 355(e)). For devices, withdrawal of approval can proceed "after due notice and opportunity for **informal** hearing" (emphasis added) (21 U. S. C., sec. 360(e)).

In sum, efforts to shorten the drug approval process in the premarketing period could take place through reinterpreting the guidelines for assessing safety and efficacy. This report has provided theoretical and experiential criteria for evaluating how such changes could affect the detection capabilities of the current guidelines. It has also discussed the desirability of guidelines for the kinds of qualitative changes FDA is implementing regarding the evidence required for drug approval. These changes include accepting foreign data and cumulative evidence (as opposed to the requirement of at least two well-controlled clinical trials). Finally, the report has identified options relating to FDA's postmarketing surveillance. These options could be pursued independently of any revisions in the premarketing drug approval process, but they could also be implemented to require drug sponsors to maintain their level of drug evaluation responsibilities if there is a change in current premarketing approval requirements.