

How the US Drug Safety System Should Be Changed

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If the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind, and all the worse for the fishes.

Oliver Wendell Holmes, Sr.¹

READING A RECENT NEWSPAPER MIGHT REMIND ONE of the above quote. One of the questions the nation is currently confronted with is what should be done to address the safety of drugs. In this Commentary, the current system of drug safety monitoring will be described and the limitations of the current system will be highlighted. A potential solution will then be proposed that will require legislation to implement.

Current System of Drug Safety Monitoring

The current system of drug safety monitoring includes pre-clinical testing followed by 3 phases of clinical studies (FIGURE). Drug approval is sometimes followed by post-marketing studies. Usually, only 500 to 3000 patients are studied before marketing. Therefore, by definition, adverse events that occur in 1 of 100 patients will be reliably detected, but adverse reactions that occur in 1 in 1000 patients or less commonly may not be detected, even if these reactions are very severe.²

The most commonly used systems for postmarketing safety assessment are spontaneous case reports of adverse reactions, computerized claims or medical record databases, and data collected specifically for the study. The system of collecting spontaneous case reports of adverse reactions is essentially a system developed in the 1950s, although it has since been computerized. This system consists of a collection of case reports of adverse reactions recognized by clinicians, most of which are submitted via the pharmaceutical manufacturer. However, the old adage that the plural of anecdotes is not data holds true. These assessments remain a loose collection of case reports, subject to enormous underreporting, as well as underascertainment or overascertainment, and thereby are greatly susceptible to artifacts. This system cannot be used to test hypotheses but simply to generate them.³

Newer approaches for data collection for postmarketing pharmacoepidemiology studies include computerized claims or medical record systems.⁴⁻⁶ First used in the late 1970s and early 1980s, these systems have been used commonly in recent years to test hypotheses and have become the state of

the art in pharmacoepidemiology. Pharmacoepidemiology studies also can be conducted with data collected specifically for the study, either with ad hoc data collection for non-experimental studies or postmarketing randomized clinical trials.

In recent years, there has been increasing use of "risk management" to optimize the use of newly approved drugs,⁷ improving the risk-benefit balance of drugs that otherwise might be marginal. In these situations, the US Food and Drug Administration (FDA) asks the manufacturer to intervene to channel the use of the drug. The severity of the intervention can be very variable. Perhaps the earliest example is isotretinoin, which has had increasingly stringent restrictions applied to prevent use in pregnancy.⁸ More recent examples include thalidomide and alosetron.⁷ The efficacy of most of these interventions remains to be established.

It is well recognized that adverse drug events are the most common iatrogenic causes of patient injury.⁹ It is also well recognized that most adverse reactions are the result of an exaggerated but otherwise usual pharmacologic effect of the drug.¹⁰ Yet, historically, these reactions have been ignored in pharmacoepidemiology, as they do not represent the focus of commercial and regulatory concerns. Indeed, pharmacoepidemiology has focused its efforts on rare adverse effects from newly marketed drugs instead of the common adverse effects from older drugs that are often used incorrectly. In an attempt to address this, the Agency for Healthcare Research and Quality has funded the development of 7 (soon to be 11) Centers for Education and Research in Therapeutics (CERTs); the charge of these centers includes improvement of how drugs are used.¹¹ The CERTs program had a total annual budget of \$5.9 million, temporarily increased by \$1 million in fiscal year 2006. It is useful to place this funding in perspective. For example, the \$70 billion expended on drugs as part of Medicare Part D will dramatically dwarf the \$5.9 million spent on ensuring that they are used correctly, as will the amount spent by the pharmaceutical industry on research and development (>\$30 billion¹²) and even promotion (>\$15 billion¹³).

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Limitations to the Current System

In the current drug development and monitoring system, carefully selected individuals who participate in premarketing studies may not reflect real-life patients in whom the drugs will be used. In fact, study participants may receive better care than “real-life” patients. Furthermore, premarketing studies are necessarily limited in duration. In addition, there is usually no information on the comparative effectiveness of the products. This inevitably yields many questions to be answered after marketing.

The current system also produces very high development costs, which in turn lead to a great need for immediate huge sales; ie, seeking “blockbuster drugs” and the aggressive marketing practices associated with such a pursuit. Yet, as noted above, less common adverse reactions will remain unknown at the time of early exposures to these drugs.

As a result, 51% of drugs have label changes because of major safety issues discovered after marketing¹⁴; 20% of drugs get new black box warnings after marketing¹⁵; and 3% to 4% of drugs are ultimately withdrawn for safety reasons.¹⁶ Of note, these are major adverse effects that were missed in premarketing studies and then later detected. Yet, when such safety problems have an incidence of less than 1 in 1000, they do not reflect a failure of the premarketing testing system, but are predictable. Indeed, previously unknown serious but rare

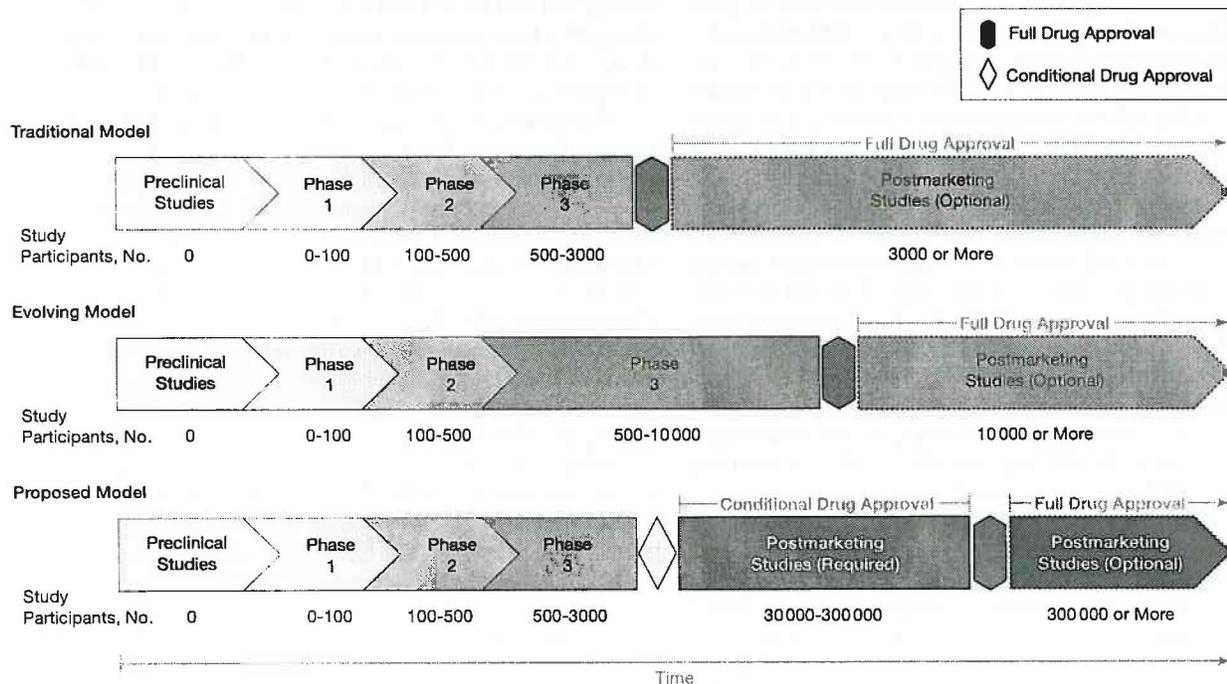
adverse events from drugs continue to be identified long after they are marketed (eg, aspirin and Reye syndrome¹⁷).

Another characteristic of the current system is the absence of an incentive for the sponsor to complete promised postmarketing safety studies. Such studies can be expensive and, once completed, can either bring bad news to the sponsor or no new findings, and they are very unlikely to result in a change in drug labeling that will help increase sales. Furthermore, the FDA does not have the power to require such studies, so it cannot punish companies that do not complete them.

Furthermore, direct-to-consumer advertising leads to overuse of the drug by patients for whom use of the drug is not compelling.¹⁸ With such advertising, the sponsor is seeking to increase use by patients who were not prescribed the drug by their physician on their own. Presumably, these patients may not need the drug as critically. Yet when these drugs are used early after marketing, data on drug safety remain incomplete.

The net effect is that the public misunderstands drug safety, believing that a drug is safe at the time of marketing, while events occurring as frequently as 1 in 1000 are predictably undetected. As a result, when there is a postmarketing discovery of a previously undetected adverse effect, the public's misperception is that someone did something wrong. This has also led to increasing concern about the safety of mar-

Figure. Alternative Models for Studying Drug Safety



Top row, historical approach; middle row, where the current system is evolving toward now; and bottom row, proposed approach. Phase 1 indicates dose escalation, usually in healthy study participants; phase 2, dose ranging (usually first time in patients); phase 3, pivotal trials for registration; phase 4, postmarketing (not always required).

keted drugs, and overreaction to this is leading to increasing premarketing requirements that delay access to drugs and result in some drugs being dropped from development.

Proposal for Studying Drug Safety

A proposed alternative approach includes 3 elements: conditional approval, an empowered FDA, and a complementary nongovernmental organization or organizations.

When a drug is initially approved, it should ideally enter a period of conditional approval. During this time, marketing (especially direct-to-consumer marketing) would be restricted. Drug labels would offer a clear caveat; eg, "Drug approval is conditional—this drug has only been studied in limited numbers of patients." This condition would be removed only when (1) the number of exposed individuals included in the studies of the drug increases from 3000 to 30 000 or even 300 000, to detect progressively rarer adverse effects, with this judgment made on a case-by-case basis, based on the expected use of the drug, potential risk of the drug, and comparative novelty of the drug; and (2) all answerable premarketing safety questions that have been raised based on the premarketing clinical trial experience have been addressed.

There are several pharmacoepidemiology approaches by which such information could be gathered, including registered release systems, monitored release systems, studies using existing databases of claims or medical records, population-based ad hoc case-control studies, large simple randomized trials, or, undoubtedly, other methods yet to be developed. Most if not all of this work would be expected to be performed by the drug's sponsor or by contractors supported by the sponsor. Any data collected from experiences with the drug in other countries should be included as well. In the Figure, the existing model for drug approval is in the top row. Unfortunately, the current system is moving toward the second row of the Figure, with a delay of drug approval, still followed by optional postmarketing studies. Instead, the proposed approach is shown in the third row, with conditional approval followed by postmarketing studies required before the condition is removed.

The second component of the proposal is an empowered FDA. The FDA needs an increased ability to regulate drugs after marketing so that it can, for example, require postmarketing studies and labeling changes, rather than these studies and labeling changes being subject to negotiation. The FDA also needs markedly increased resources to conduct and fund more postmarketing safety studies.

The third part of the proposal is the complementary, nongovernmental organization or organizations. An independent organization is needed for nonregulatory tasks that are not now, nor should be, the mission of the FDA. Included among other possibilities are attempts to change prescribers' use of drugs, including old drugs, performing postmortem examinations in the event of drug "disasters," developing new pharmacoepidemiology methods, training new scientists, and other such nonregulatory tasks. This body

probably should be a nongovernmental organization, since many of these tasks are academic in nature. This is a possible role for the CERTs, the Institute of Medicine, or other existing or future organizations.

Implications

A key benefit of this approach for the public would be that drug use immediately after marketing would be reduced to those who truly need the drug, in whom the risk-benefit balance in the face of uncertainty is more favorable. In addition, the sponsor would have an incentive to gather safety information quickly, instead of delaying such an effort. The net benefit for the sponsor would be the ability to obtain revenue during prolonged large safety studies; the public would recognize that an adverse reaction is not a failure of the system; and possible protection for the sponsor would be conferred against liability from early safety problems because of disclosure of such a possibility.

A previous multidisciplinary commission led by academics and funded by industry concluded the following:

1. A systematic and comprehensive system of post-marketing drug surveillance should be developed in the United States.
2. . . . should be able to detect important adverse drug reactions that occur more frequently than once per thousand uses of a drug . . .
3. An integral function of the postmarketing surveillance system should be to report the uses and effects of new and old prescription drugs.
4. . . . FDA should continue to strengthen its program in this area.
5. A private, non-profit Center for Drug Surveillance (CDS) should be established to further the development of a postmarketing surveillance system in the United States. . . .¹⁴

This was the Joint Commission on Prescription Drug Use, and the recommendations were made in 1980.¹⁹ It is long since time to act on these recommendations.

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EDITORIALS

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Evidence-Based Treatments for Alcohol Dependence

New Results and New Questions

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AN ESTIMATED 8 MILLION ADULTS IN THE UNITED States have alcohol dependence.¹ Of this number, only a minority ever receive treatment for the disorder, even when treatment is defined broadly to include participation in Alcoholics Anonymous. Of the alcohol-dependent individuals who receive treatment, only a small fraction ever receive a medication specifically approved by the US Food and Drug Administration (FDA) to treat the disorder.

In 1994, the FDA approved naltrexone for the treatment of alcohol dependence.^{2,3} This followed by nearly 50 years the approval of disulfiram, which was approved prior to the modern era of efficacy review. Meta-analytic studies of naltrexone have shown that the drug reduces the risk of relapse to heavy drinking and, to a lesser extent, the frequency of drinking.^{4,5} In 2004, following use of acamprosate in Europe for more than a decade, the FDA approved this drug for treatment of alcohol dependence. Meta-analysis of the European acamprosate studies indicated that the drug helped alcohol-dependent individuals maintain abstinence once they had stopped drinking.⁴ In contrast to disulfiram, which produces an aversive reaction when combined with alcohol, both naltrexone and acamprosate appear to exert their effects directly on the individual's motivation to drink alcohol.

See also p 2003.

In this issue of *JAMA*, the report by Anton and colleagues⁶ of the results of the COMBINE Study provides evidence that an FDA-approved medication can be of benefit when used to treat alcohol dependence in routine medical practice. These authors describe the results of a randomized, placebo-controlled trial of naltrexone, acamprosate, and the 2 drugs combined, conducted at 11 sites in the United States. To accomplish the aims of the study, a complex study design was required. In addition to study medication, 8 of the 9 study groups received low-intensity medical management and 4 of these groups also received combined behavioral intervention, a high-intensity psychosocial treatment. In a design feature unique among trials of medications to treat alcohol dependence, the study also included a group that received only the behavioral intervention with no active or placebo medication, making it possible to analyze the comparative effect of a placebo on drinking outcomes.

This study of nearly 1400 abstinent participants was well designed and well executed. Nearly complete data on participant drinking behavior during the 4-month treatment period lends confidence to the findings. Overall, alcohol consumption decreased by 80% during the treatment period, and all treatments were well tolerated. Compared with placebo, naltrexone significantly decreased the likelihood of heavy drink-

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