Ensuring Drug Safety: Where Do We Go From Here?
Bill Number:
Hearing Date: March 3, 2005, 10:00 am
Location: SD106
Witness:
Dr. Raymond Woosley
Critical Path Institute, University of Arizona, Tucson, AZ
Testimony

Senator Enzi and members of the Committee:

I am Dr. Raymond Woosley, President of The Critical Path Institute, a non-profit organization created to facilitate innovations in drug development. Our goal is to create a forum for drug development scientists from the FDA, academia and the pharmaceutical industry to evaluate innovations in drug development; innovations that will give patients the earliest possible access to the safest possible medications. We believe that such a forum, i.e. a neutral territory, is essential to bring about needed changes in the ways drugs are developed. The Institute is working closely with the FDA Commissioner's office and other scientists at the FDA, The University of Arizona and SRI International (formerly Stanford Research Institute) to develop a formal arrangement for this collaboration. I am also the Director of the Center for Education and Research on Therapeutics (CERT), a Center at the University of Arizona funded by the Agency for Healthcare Research and Quality. CERT is one of seven centers in the nation authorized by Congress to improve the medical outcomes from therapeutics. After thirty years of research and teaching in medical schools at Vanderbilt University, Georgetown University and most recently the University of Arizona, I will leave my academic position in July to lead the CERT and The Critical Path Institute. This will enable me to focus my efforts on what I believe is a crisis in pharmaceutical development.

A Crisis in Drug Development

This crisis can best be appreciated by looking at recent events and the following data:

1. The pharmaceutical industry spends 12- 15 years and almost a billion dollars for each drug that is successfully developed. Yet, in spite of such an investment in time and dollars, this process still fails to detect serious adverse effects of products until they are on the market, often for years, and millions of Americans have been exposed to potential harm.
2. Pharmaceuticals have been one of our nation's most successful industries. However, over the last ten years, the industry increased its investment in research and development by 250% but the number of new products submitted for FDA review has fallen by 50%.
3. The proportion of drugs that fail during development has doubled in the last ten years.
4. In the last eight years, over half of the fifteen drugs removed from the market because of safety concerns were, in fact, safe when used as directed in the labeling. Warning labels did not prevent drugs from being used in ways that resulted in harm to patients. Tens of billions of research and development dollars were wasted and many patients suffered serious injury.

5. Personalized medicines, the promise of human genome research, are only rarely being developed because of the high cost of drug development relative to the potential market size.
6. The protracted and costly development of drugs, combined with the limited time in the market before generic competition begins, results in unacceptably high drug costs and drug re-importation from countries that employ price controls.
7. Skyrocketing estimates for the cost of a Medicare prescription drug benefit have prompted consideration of policies and pricing negotiations that would limit access to new medicines and threaten future research and development of medicines that are needed by patients with chronic and debilitating diseases.
8. In addition to concern for the patients harmed by drugs, there is another societal concern. The removal of drugs from the market has resulted in hundreds of class action law suits that threaten the very existence of some of our nation's most successful companies.

So, while the issue of drug safety must be addressed, we must do so in the context of a broader crisis in which the wrong action(s) could further threaten the future viability of the pharmaceutical industry and the availability of vital new medicines. For example, adding a requirement for phase IV monitoring to our broken system without other changes would be catastrophic. At the same time, the absence of an effective drug safety program is one of the major contributors to the delays in drug development that adds to high costs and delayed access to important new medicines. Two-thirds of the FDA medical reviewers recently surveyed expressed concern that the post-marketing surveillance system at the FDA was inadequate. I have no doubt that this concern must have a negative influence the reviewers' willingness to assist the industry in accelerated development of even the most important new medicines. Therefore, it is essential and timely that we discuss how to improve the development of drugs and assure their safe use.

Basic "Facts of Life" for Pharmaceuticals

A critical first principle is that there is no such thing as a "safe drug". Even the title of these hearings, "Ensuring drug safety" is an impossible goal. No one can ensure drug safety; we can only expect the FDA to identify drugs with an acceptable risk/benefit ratio, inform the public, and develop methods to maximize benefit and minimize harm. FDA approval will never mean that a drug is "safe." Instead it signifies that the available evidence indicates that a drug should be "relatively safe when used as directed." All medicines that have pharmacologic effects must be assumed to have the potential for harm. This is a message that must be better appreciated by the public so that they are not surprised when newly marketed drugs are found to have adverse effects.

The FDA must be given adequate numbers of people and resources

Over the last twenty years I have served as a frequent advisor to the FDA, usually on issues of drug safety. In this capacity, I learned first hand the limitations that exist in the FDA's legal authority as well as the FDA's limited resources. It doesn't appear in their

budgets but information technology and computer allocations have been slashed in recent years. The agency that handles some of the most complex and vital data in the world relies upon information handling systems that were discarded decades ago in most corporations. Only 109 scientists monitor the safety data from over 3000 prescription drugs. Where a complete system of drug safety surveillance is needed, the FDA is forced to rely on its voluntary reporting system for adverse events.

The FDA lacks adequate legal authority to effectively regulate drugs

Once a drug is marketed, the FDA has no control over the way it is used in clinical practice. Relatively safe drugs are often used in unsafe ways (e.g. in combination with other interacting drugs or in excessive dosage or duration). As is the case in Canada and other countries, the FDA should be given the authority to restrict or suspend access to drugs when serious questions arise about their safety.

The FDA also lacks any authority to demand further research on marketed drugs. Warning labels, though commonly required by the FDA, are known to be ineffective. The only effective tools that the FDA has to protect the public are, 1) to keep a drug off the market or, 2) once on the market, try to take it off. Because of its limited resources, the FDA rarely attempts legal action to remove drugs from the market. In almost every case, drugs are voluntarily removed by the manufacturer because of pressure from the FDA and not deliberate legal action by the FDA.

A Better Tool Box

The FDA needs more options for action. The FDA could better perform its responsibility if it had a broader range of options with which it can respond to the ever broadening spectrum of drug information that is generated over the pharmaceutical life of a drug.

A proposal for staged approval of new drugs

Because more information than ever before is being generated about the value and risks of new drugs and because time is required for this information to be assimilated into the practice of medicine, there is a need for earlier approval followed by tightly controlled and more gradually increasing usage of new medications. Figure 1 demonstrates an alternative path for new drugs that I believe should be considered, debated and evaluated. It proposes an earlier approval but more gradual growth in use of a prescription drug combined with a comprehensive safety assessment in the marketplace. As can be seen, there is an earlier and more gradual rise in the number of patients treated in this model. This allows time for more complete safety testing and assimilation of the drug into the practice of medicine before millions are exposed to the drugs.

The first change suggested is in phase II, which would be expanded to include more complete characterization of the drug=s dose-response relationship in the intended population and sub-populations (e.g. the very elderly, those with renal insufficiency, co-morbid conditions, etc) and for completion of any necessary targeted drug interaction

studies. These latter studies should be those based on in vitro predictions, e.g. cytochrome P450 or drug transporter interaction studies. Phase II should include modern computing techniques such as in silico simulation of trials, enrichment using biomarkers, adaptive trial design and others suggested in the FDA's Critical Path Initiative.

Market-I: At the end of a more comprehensive and informative phase II requiring approximately four years, the drug could be approved for marketing to a carefully defined population of patients (Market-I in figure 1). This is very similar to the way AIDS drugs were developed in 2-4 years without taking dangerous shortcuts.

A Safety System: To make the early release of a drug feasible and rationale, it will be essential to have an intensive plan for post-marketing safety assessment and risk management. Academic programs such as the Centers for Education and Research on Therapeutics (competitively funded by the Agency for Healthcare Research and Quality to improve outcomes from medical therapies) can help develop risk management programs and conduct outcomes research on large databases and registries to confirm the efficacy and safety predicted from phase II. As they evaluate the safety of the drug, they can also use similar methods to confirm efficacy for initial indications and evaluate the potential efficacy of the drug in new indications. In most cases, the new drug should initially be given under observed conditions, using a system like the yellow card system in the U.K. in which physicians report the outcome of therapy in each patient receiving a specific drug on a "yellow card." Modern electronic medical record systems make it possible to have a system like the U.K.'s General Practitioner=s Network which tracks the outcome of every patient they treat with a new drug. Also, modern electronic registries can detect adverse event signals earlier and compare the safety of new and older drugs in a class. The CERTs could play a role similar to the pharmacovigilance centers in France and monitor drug outcomes in the community. The FDA and the pharmaceutical sponsor would have to agree to the use of measures to assure that the drug is used as directed in labeling. Sponsors could be encouraged to follow the lead of at least one innovative company that paid commissions to sales representatives based upon how well doctors in their region used the company's drug instead of how often the drug was prescribed. Effective risk management programs have been successfully developed in the past for drugs with the potential for serious toxicity, e.g. clozapine. Because this antipsychotic drug can cause fatal bone marrow toxicity in 1% patients per year of treatment, proof of monitoring of white blood count is required before the drug can be dispensed. This has reduced the incidence of fatal toxicity by 60%.

A Novel System: In Arizona, The Critical Path Institute and the CERT are exploring the feasibility of developing an innovative community based safety surveillance system. This system would resemble programs in the UK and France in that it would prospectively gather data on the outcomes of new medicines and submit it directly to the FDA. I believe that such a system must be developed de novo because the information needed to address drug safety cannot be gleaned from currently available databases. Data mining only works when the information you need is somewhere in the system. For the same reason, linking databases will never give adequate information. The system must be relatively inexpensive, should not interfere with the practice of medicine or pharmacy

and should be flexible enough to detect suspected and unsuspected adverse events of any newly marketed drug. It should be able to quantify the rate of adverse event occurrences and even answer questions of relative safety by comparing the outcomes with selected comparator drugs. It should provide positive feedback to physicians in order to prevent future adverse events and improve drug outcomes. If the system were effective, even drugs with the potential for serious adverse events might be able to remain on the market. For this or any program to be successful, the FDA must be given the staff and resources to participate in the design and implementation of this system and then to monitor the data that are gathered from this system.

The staged approval model would allow a pharmaceutical company to begin marketing its product earlier with a lower total capital investment and at a time when much more of the patent life is still in effect. It should also make it possible to detect any serious life-threatening problems earlier before millions have been exposed, reducing the frequency of litigation and class action law suits. Also, for companies using this track, serious consideration should be given to offering indemnification from law suits filed for adverse events in return for the sponsor paying for any medical expenses resulting from such adverse reactions. This would provide patients and the drug sponsor some protection from the potential harm from a new drug.

Market II: If after a period of careful observation on the market, the drug appears safe and effective, it could be given approval for an expanded market with fewer or no restrictions to its use (Market II on the diagram). Market II is effectively the same as the current market in which any licensed physician can prescribe a marketed drug for any indication, as long as the physician has evidence that such use has a scientific basis.

Pharmacist Assisted Care (PAC) and OTC: If a marketed prescription drug is found to be relatively safe and used for a condition that can be self-diagnosed by the patient, it has been customary for it to be given non-prescription status, often called Aover-the-counter@ or OTC. This may or may not be attractive to the pharmaceutical sponsor depending upon many economic and market factors. In some cases the sponsor would like to expand the market by having the drug available OTC. However in many cases such as the statin drugs for lowering cholesterol, some aspect of a drug's use requires medical supervision and the FDA is reluctant to approve its use without medical supervision. In these cases, there is no alternative now available but to deny approval of OTC status. However, in Canada and many other countries there is another option. The drug can be given Abehind the counter@ status. "Behind the counter" means that the drug is available in pharmacies for patients who ask for the medication but only after consultation with a pharmacist. The pharmacist can perform any pre-screening or counseling that could make it more likely that the drug will be used safely. This additional step, "Pharmacist Assisted Care" (PAC), could widen the therapeutic benefit to patients, better utilize the important role of pharmacists and minimize the risk of therapy. After a period of safe use in the PAC category, a drug may be recommended for full OTC status when justified.

The need for innovations in the process of drug development

To address the increasing delays and failures in drug development, the leadership of the FDA has proposed the “Critical Path Initiative”. This proposal includes efforts to optimize drug development and identify new ways to test medicines that will give greater assurance of safety and effectiveness than we have now. However, this plan will require new partners and new resources for the FDA. A recent report from former Secretary of Health and Human Services (HHS), Tommy Thompson, pointed out the need for partnering between FDA and the NIH, CMS and CDC. But to do this collaborative work, it must have resources that are not provided in the current budget. Also, the fact that the FDA budget is under the Department of Agriculture and not under the full control of the Secretary of HHS is an impediment to forming these partnerships.

The FDA’s Critical Path Initiative calls for academic partnerships to develop innovations that improve drug development. Forming these will also require that the Agency have the staff and resources to participate. Just as the Moffet Center in Illinois was established by the FDA to address food safety, academic sites can be “neutral ground” where scientists can share their knowledge and expertise in drug development and drug safety without commercial conflicts of interest. These public/private partnerships can enable scientists from the FDA, academia and industry to develop methods to increase the efficiency and informativeness of the drug development process.

The Critical Path Institute that I lead was created for this purpose. Out of serious concern over the relative safety and availability of new medicines, the citizens of Tucson and Southern Arizona have committed over $9 million to seed the initial work of the Institute.

We believe that an investment that enables the FDA to facilitate the development of safe drugs is a good investment, especially at this time. Medicare estimates that its prescription drug benefit will cost over $720 billion in its first ten years. That estimate surely assumes that new drug costs will continue to rise at its current rapid rate. If we are ever going to have less expensive new drugs, we must shorten the development time, increase the number of drugs successfully developed in order to stimulate competition in the marketplace and improve the safety information about these drugs. Increased numbers of drugs for a specific disease enable competition to yield lower drug prices. Larger numbers of drugs with different actions will better meet the needs of our biologically diverse population. “One size” does not “fit all.” Furthermore, adequately studied drugs and the safe use of drugs can result in lower healthcare costs and improved health.

Lowering drugs costs by accelerating the development of safer medications is a far better alternative than "re-importation" of drugs which is just an indirect means to use foreign price controls to lower our consumers’ drug costs. It would be preferable to give the FDA the resources it needs to help improve the process of developing drugs.

Summary of Recommendations:

1. Permanent experienced leadership for the FDA is essential. Acting Commissioner Lester Crawford, Acting Deputy Commissioner Janet Woodcock and many others

working with them are experienced leaders who can, with the proper resources, lead positive change at the FDA.
2. The FDA should be adequately funded to carry out its mission. This support should include funds for the Critical Path Initiative and an effective safety surveillance system.
3. The “user fee” system should be replaced with a system in which industry support is not directly linked to the FDA’s work and performance.
4. Determination of drug safety requires an assessment of both risk and benefit and should remain the purview and responsibility of the FDA, and not of a separate agency as I and others have previously suggested. However, the on-going safety evaluations of marketed drugs should be made by FDA scientists who were not responsible for the original approval recommendation.
5. The FDA should develop a comprehensive post-marketing assessment program for drugs using inter-agency collaborative programs and public-private partnerships.
6. Just as the National Transportation Safety Board is responsible for investigating all accidents and then makes recommendations for safety, there should be an analogous independent body to conduct in-depth review of the process used to detect serious issues/events in drug development and the response to those events by the FDA and industry. This body could assess the roles played by consumers, healthcare providers, health professions educators, the FDA, the pharmaceutical industry, the press and even Congress.
7. The FDA should be given the authority to release drugs in stages that are appropriate for the drugs’ level of development and the information that is known at the time.

I am extremely grateful for the opportunity to provide testimony is these hearing. I hope you find my perspective of value as you review the FDA’s drug safety system.

Raymond L. Woosley, MD, PhD
President, The Critical Path Institute