

Testimony

of

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The Adequacy of FDA to Assure the Safety of the Drug Supply - part II

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Committee on Energy and Commerce  
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Mr. Chairman, members. Thank you for the opportunity to provide testimony before the Subcommittee on this very important topic. I am Raymond L. Woosley, MD, PhD, President and CEO of The Critical Path Institute (C-Path) which is based in Tucson, Arizona and Rockville, MD. I am a physician and pharmacologist with over 40 years of experience in the study of medications. C-Path is a non-profit, publicly funded organization that operates under a Memorandum of Understanding with the FDA to create and facilitate collaborations that advance the FDA's Critical Path Initiative. The Critical Path Initiative began in 2004 because of a near doubling of the failure rates of drugs in clinical development and a development process that has evolved to the point that it now takes an investment of 15 years and \$1.3 billion to bring a single innovative product to market. The critical path initiative is all about "process improvement," that is, improvements that will enable **innovative** medical products to be **safely**, quickly, efficiently and reliably brought to market for patients and the public.

Why is the consideration of innovation so important to this discussion drug safety? Quoting a colleague, Dr. Hugh Tilson, "**without innovation, all we will have are the products of yesterday.**" Truly innovative new products have much greater potential for benefit compared to those products that are simply incremental improvements over those already on the market. However, innovative products also present special challenges for safety evaluation and surveillance because they may have new forms of unanticipated toxicity. All agree that we need to improve our ability to develop safe medical products. However, it is essential that we do so without threatening the opportunity for innovation or interfering with our ability to translate our nation's \$90 billion annual investment in biomedical research and development into better health. **A Basic Principle:** Essential to our understanding of drug safety is recognition that: Neither drug risk nor benefit can ever be fully defined before drugs reach the market. The enormous

variability between people means that any reasonable premarket safety evaluation must be confirmed by an ongoing evaluation after products reach the marketplace where they will be used in many more people and in different ways than before. Drugs must be carefully evaluated throughout their life cycle. This is best shown in a recent example. As a result of a new clinical use for the old drug, methadone, we just recently detected a life-threatening adverse effect on heart rhythm that had been undetected for over 50 years. Thus, careful surveillance should be continuous and not confined to just the newest drugs. A corollary to this rule is that, when a drug has to be removed from the market due to toxicity, it is not necessarily the result of any mistakes made by anyone, including the developer or the FDA.

**Premarket Evaluation of Safety:** For decades we have needed better ways to evaluate drugs before they enter human testing. The methods that are recommended today are the same ones developed over fifty years ago. One of C-Path's first projects under the Critical Path Initiative, the Predictive Safety Testing Consortium (PSTC), was conceived by scientists at the FDA. PSTC is a collaboration that includes 160 scientists from the sixteen largest global biopharmaceutical companies in which they share and cross validate their safety testing methods. Regulatory scientists from the FDA and, their European counterpart, EMEA, are participating. Based upon the outcome of the work, the FDA will make recommendations for new standards for improved safety testing methods. I strongly encourage Congress to support the Critical Path Initiative and foster this kind of "precompetitive" collaboration. Congress has helped solve this type of issue before when it created Sematech in the 80's to preserve the competitiveness of the computer chip industry. Unfortunately, today the FDA has a limited numbers of scientists and few resources to participate in evaluation and setting of standards. In order to have greater safety, efficiency and predictability in new drug development, we must expand this type of work

in public-private collaborations. Furthermore, the improved testing methods will result in safer drugs reaching the market and identification of biomarkers that can predict which patients are at risk for harm before they receive the drug.

**Post-marketing Safety Assessment:** Prior to the U.S. adoption of user fees and efforts to reach international harmonization on methods, the FDA's high approval standards and prolonged review times resulted in more new drugs being first marketed in Europe. In response, European countries developed post-marketing active surveillance systems to quickly detect adverse events. The UK's yellow card system and the General Practitioner Research Database are valuable and proven tools. The French developed a pharmacovigilance system that includes sixteen regional specialized centers that employ scientists trained to detect and accurately characterize adverse events that occur with newly marketed drugs. Unlike Europe, the U.S. does not have an effective active surveillance system capable of rapid and accurate detection of safety problems with new drugs. This is therefore a serious deterrent to the timely approval of important new therapies. Because the agency's budget requests for active surveillance have been denied in the past, the FDA is forced to rely solely on its voluntary Adverse Event Reporting System (AERS). It is not by choice that the FDA has placed so much reliance on the AERS system.

Even when the FDA is given adequate resources, we should not expect that the FDA will be able to singly address all aspects of post-market safety assessment of new drugs. Over half of the drugs removed from the market in the last 15 years were safe when used as directed. In 1997, Congress authorized the Agency for Healthcare Research and Quality to create Centers for Education and Research on Therapeutics (CERTs) with the mission of conducting programs to improve the health outcomes from drugs, biologicals and devices. There are now eleven CERTs that have established a network of health plans that serve approximately 100 million Americans.

With relatively modest additional funding, this network of health plans could serve as a sentinel network and conduct the active surveillance that is needed to assure the early and accurate detection of adverse effects of new drugs.

**Calls for Change at the FDA:** It is my firm belief that many of the current problems at the FDA can best be addressed by giving the agency the resources it needs to execute its mission and to gain access to the "science" that will better inform decision making. Most disagreements among agency scientists and subsequent criticisms of agency actions can be better addressed if the FDA has more staff and scientists with the time and resources necessary to make decisions that are based on better data and a fuller appreciation of the science. Today, the limited resources at the FDA means that there is no travel budget for attending scientific conferences or participating in meetings that would enable agency employees to keep current on the rapidly evolving technical advances for the products they regulate. I do not believe that FDA scientists must continue to be actively conducting research in order to stay abreast of scientific advances in their chosen field. However, they do need opportunities outside of their review work in which they gain a critical appreciation of the newest relevant scientific advances.

The Institute of Medicine, the Government Accountability Office and many others have called for a change in the "culture" and organizational structure at the FDA. In my interactions with the FDA, which span four decades and address issues important to drugs, devices, diagnostics and even dietary supplements, I have seen, first hand, the enormous scope of the scientific questions that the agency scientists must face in regulating the many products that consumers rely on. This broad mission will never be served well by a single or rigid organizational structure. Likewise, the culture will never be ideal, unless the FDA regulators, who began their careers as scientists, are given access to the scientific methods and the data they

need to make their decisions. How can anyone expect an organization to have a healthy culture when it has interim leadership more than half of the time? How can anyone expect an organization to maintain a high level of productivity or take on more authority when it has only a small fraction of the people and resources required to accomplish its current mission? With stable leadership and adequate resources, positive changes in the culture will follow.

Some have called for post market safety assessment to be separate from the Office of New Drugs. I believe that post-market assessment of drugs must include an ongoing assessment of benefit and risk simultaneously. I would not recommend creating a system in which the "drug approvers" and the "drug removers" are pitted against one another. Drug approval decisions and subsequent evaluations are very difficult questions that require a consensus be reached by an interdisciplinary team based on the best possible scientific information. We should accept that there will often be dissent in this process. In an effective organizational structure, the dissenters should feel that they have been given a fair chance to express their opinions but at some point a single consensus and decision is required. Ties and minority opinions are not options.

**In summary**, the Food and Drug Administration is expected to protect the public health by regulating the industries that produce foods, drugs, biologicals, diagnostics, devices, veterinary products, etc but it has never been given adequate resources. If adequately funded, the FDA can also create a system to conduct active post-market surveillance of new medical products. I have no doubt that the FDA is protecting the public health as well as anyone could expect considering its often temporary leadership, complex and ever increasing mission and the severely constrained resources that it has been given. It is possible to have a world class safety surveillance system and, at the same time, pave the way for more innovative new therapies to reach patients.

## Major Points

1. The future of the pharmaceutical industry is threatened by its inefficiency and an unacceptably high failure rate of drugs during development and after marketing.
2. Greater drug safety must be achieved without threatening the opportunities for innovation.
3. Biological differences between people will result in rare drug toxicities that could not have been predicted and must be detected early after marketing.
4. The FDA's Critical Path Initiative (CPI) includes important "precompetitive" work to develop better and more predictive safety testing during development. New biomarkers from this work will further enable therapies that are targeted for those who can benefit with lower risk of harm.
5. The FDA's Office of Drug Safety (ODS) needs an independent source of reliable, timely information from an active, electronic surveillance system like the one available in AHRQ's CERTs that includes a network of health plans serving 100 million Americans.
6. To be successful in its mission, the FDA requires:
  - Stable leadership
  - Increased funding for adequate numbers of scientists and staff for CPI and ODS
  - Access to the science and technologies that enable optimal decision making
  - Retain the single system to make benefit/risk assessment over each drug's life cycle