

**Fundamental Improvements in Drug Safety for the 21<sup>st</sup> Century:  
Time for a Systematic, Electronic Infrastructure**

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## **Introduction**

Mr. Chairman, Senator Enzi, and members of the Committee, thank you for the opportunity to testify today, as the Committee takes steps to improve our current system for monitoring the safety of drugs. This year is a critical year for strengthening the ability of the Food and Drug Administration (FDA) to help Americans live longer and better lives through access to safe and effective medicines that keep getting better.

As you and others have noted, there are opportunities to improve the pre-market process for evaluating the safety of drugs, particularly through new resources that would enable FDA to develop better information tools for evaluating the safety data it receives as well as better scientific tools for evaluating preclinical and clinical safety. But the greatest opportunities for improvement are in the post-market process. Consequently, I will spend the bulk of my time outlining steps I believe we can to improve the post-market process for evaluating drugs after they are approved for marketing.

With the highly-publicized drug safety incidents involving Vioxx (a selective anti-inflammatory drug) and newer antidepressants (selective serotonin reuptake inhibitors, or SSRIs) in 2004, followed by the Institute of Medicine's recommendations for a range of changes to enhance postmarket drug safety at FDA in 2006, it is clear that our current system of monitoring the safety of marketed drugs can be significantly improved. I want to thank the Chairman and Senator Enzi, and the other members of this Committee and the Congress, for your leadership to address this challenge as effectively as possible. Your leadership, in conjunction with hard work by the FDA and new ideas from patient advocacy groups, product developers, and other stakeholders, has created a unique and unprecedented bipartisan opportunity to achieve a fundamentally more effective system for monitoring drug use and aggressively addressing the questions about safety that inevitably arise in the post-market setting.

Legislation to improve post-market drug safety involves a combination of better information on drug risks, new regulatory authorities, organizational reforms, and additional resources to carry out these new steps effectively. Significant new resources for FDA to support drug safety programs are absolutely essential to this strategy. Now is also the best opportunity we have ever had to move to a 21<sup>st</sup> century, electronic approach to monitoring and acting on potential drug safety problems, one based on much more complete and timely information than is available to FDA today. In particular, building on the elements to improve safety information in the legislation proposed by Senators Kennedy and Enzi, it is feasible to implement much more active, complete population-based monitoring of adverse events associated with prescription drugs, to identify and follow up on drug safety problems much faster and more effectively than in the past. This system, which would draw on public and private electronic prescription and health information which has not yet been put together in a comprehensive strategy for drug safety, would directly address the delays in developing and addressing safety "signals" that have resulted in delays in resolving drug safety problems like Vioxx. While this public-private collaborative system would require limited additional resources, it would significantly reduce the duplicative and rising costs of case-by-case efforts by drug

manufacturers and health plans to address safety issues – efforts that are also incomplete and inconsistent. It could also achieve safety improvements that are not possible through imposing more regulatory requirements on drug manufacturers or making organizational changes at the FDA.

### **Key Questions and Objectives for Improving the Drug Safety System**

With this unique opportunity to make fundamental enhancements in drug safety, it's important to keep asking some key questions as we consider possible solutions.

#### **First, will the proposed steps have the greatest impact on reducing the likelihood of another Vioxx or SSRI-type event?**

In evaluating approaches to enhance drug safety, there are at least three main areas to consider. None of these alone are sufficient to achieve success, but if all are addressed together, the result can be fundamental improvements in our postmarket monitoring system:

- **Regulatory authority:** Pending legislation and the IOM recommendations appropriately recognize the need to review and consider updating FDA's regulatory authority to require drug manufacturers to take appropriate and effective steps to mitigate risks associated with marketed drugs. FDA's current selective application of RiskMAP tools is a necessary component of post-market monitoring, for drugs that present special issues that cannot be addressed through standard labeling and communication. Given the limited resources available to the agency to oversee these authorities, and the already high costs of our health care system, a key principle at FDA is efficient regulation: achieving the regulatory goal of addressing safety risks without imposing excess costs or unnecessary burdens. In addition, the elements described below – sufficient resources and better information – can help achieve the intended goal of a new authority more effectively and with less burden.
- **Resources and technical capabilities:** FDA needs the manpower, technical skills, and technical support to carry out their increasingly complex oversight requirements effectively. Inadequate resources even for existing FDA activities, let alone enhanced drug safety activities, is now widely regarded as a significant problem. As I will discuss, in addition to providing more resources to FDA – and a relatively small amount of additional funding, properly spent, can go a long way – there are significant opportunities for public-private collaborations with expert academic groups to augment FDA's capabilities on drug safety.
- **Good Information:** Regulatory decisions, like other policy decisions, can only be as good as the information on which they are based. Too often, we have faced important questions about drug safety that have major consequences – whether a drug should be on the market, and which patients should use it – without information that is nearly as good as it could be and should be. Today, as prescription drug information is increasingly electronic, there are growing opportunities to use more data more effectively for post-market safety.

Second, **will the proposed steps achieve the maximum improvement in safety at the lowest cost?** Of course, no one wants to put a price on health. But we have consistently imposed very tight budgets on the FDA, and many people are also concerned about the impact of regulatory burdens that may increase the time and cost of making lifesaving drugs available to the patients who need them. Consequently, in making policy decisions about drug safety, it's important to ask whether a particular safety goal is being achieved at the lowest feasible cost to taxpayers, and to the consumers and patients who will ultimately be using the drugs. By considering all the tools available to improve safety – new regulatory authority for the FDA, as well as new resources and better information – we can achieve major improvements in post-market safety while minimizing additional costs and difficulties in access to valuable medications.

I want to be clear that additional resources will be required to provide adequate support for post-market monitoring. But if designed carefully, an enhanced post-market safety system can make tight budget dollars go much further toward achieving the goal of maximizing benefits from medications and avoiding inappropriate drug use, and may lead to significant cost savings from addressing safety questions more completely and efficiently.

To be maximally effective, the improved drug safety system would:

- Recognize, based on pre-market testing and other biomedical knowledge, potential areas of risk for drugs, particularly new drugs coming on the market, to help avoid safety problems in the first place and focus postmarket monitoring on identifying true safety signals rather than random associations
- Identify safety “signals” – whether potential risks are actually observed – much more quickly and reliably
- Permit significantly better and more timely monitoring of how drugs are used in practice
- Enable postmarket clinical trials and other costly, sophisticated clinical studies to be focused more quickly and effectively on instances where a safety signal is real, but whether a drug has caused the signal cannot be determined from monitoring drug use and patient outcomes alone

Finally, because the 21<sup>st</sup> century should be an era of electronic health care to improve quality and avoid excess health care costs, an ideal safety system should be based on and should foster effective health information technology (IT). We are past the time when our core strategy for postmarket safety should be relying on the hope that overly busy health professionals will file individual reports on adverse events involving drugs. “Health IT for drug safety,” and catalyzing the movement to electronic data systems more broadly, is an idea whose time has come.

It is possible, by building on the steps in pending legislation, to make major progress toward this fundamentally enhanced drug safety system this year. In the next sections, I describe how both the current system and proposed administrative and legislative

changes can help get there, and some specific, feasible ways to build on these steps to make sure we get the most out of the unique opportunity we face today.

### **Current Drug Safety System and Proposed Improvements**

While most of my testimony addresses post-market issues, I would like to commend the Committee for seeking to make some important enhancements in the pre-market setting to avoid drug safety problems later. In particular, while there isn't and won't be any completely safe drug, improving the science of pre-market evaluation of drugs can help reduce the risk that patients will have serious adverse events without delaying or reducing access to needed cures. Improving the science of drug safety includes such steps as supporting the development better preclinical and clinical techniques for predicting whether a drug will cause serious risks such as liver and cardiac toxicity. These drug side effects often complicate and add to the costs of drug development programs. It also includes the development of new clinical trial designs such as adaptive approaches that can surface more information more efficiently about the safety and effectiveness of drugs. New technologies such as pharmacogenomics can also help target drugs more effectively to patients, so that they will be more likely to realize benefits and avoid side effects of new drugs. Building on its "Critical Path" initiative, FDA has recently reported on plans outlining these and other scientific improvements, and these steps are reinforced by the proposed legislation. However, I also want to emphasize that these improvements will only be realized if sufficient additional resources accompany the new emphasis on better science for developing drugs. These investments will be well worth it: a more robust scientific base for pre-market drug evaluation will provide a better understanding of potential areas of risk for drugs, and which patients may actually face those risks, particularly for new drugs coming on the market. It will help focus our post-market monitoring on identifying true safety signals rather than random associations.

Even with these and other proposed pre-market reforms, there will inevitably be unresolved questions related to the safety of every drug that comes on the market. This is because no feasible amount of premarket testing in clinical studies can evaluate all real-world conditions of use – patients with multiple comorbidities, varying practice settings, possible use in off-label clinical indications, and the like. These real-world circumstances may affect both the benefits and risks of treatment, and with the growing potential of genomics and other steps toward personalized medicine, there will likely be more and more to learn in the post-market setting about how drugs can be used most effectively in particular patients. Because it is not possible to replicate all of these settings and surface all of these real-world issues in pre-market testing, it is very important to have reliable and effective ways of learning more about the safety and effectiveness after drugs start to be used in clinical practice. Creating a true "life cycle" strategy for maximizing drug benefits and minimizing risks is a key challenge for the nation's public health, and deserves the careful and deliberate consideration of this Committee.

Right now, our post-market surveillance is largely dependent on FDA's Adverse Event Reporting System (AERS) as well as limited use of existing electronic health databases.

While these tools are important, it is feasible to achieve fundamentally better post-market safety monitoring, by building on some recent developments in electronic records of prescriptions, medical services, and patient outcomes.

FDA is currently working on an improved AERS system, AERS II, which will make it easier to collect reports from clinicians and enable better tools for evaluating this information once it is received by FDA, so that the most important safety signals can be surfaced more quickly. Pending legislation could also strengthen FDA's authorities to compel drug manufacturers to take potentially costly further steps to support the collection of such data on their drugs. However, even with these enhancements, the potential to detect safety problems much earlier and more reliably will continue to be missed. AERS, with the required event reports from manufacturers that make up most of its data, is not routine and automatic. Rather, it depends on busy health care providers filing reports on a case by case basis, and then often requires further followup to obtain reasonably complete medical histories and utilization details. Only a small fraction of adverse events are captured with such a system, and they are not captured consistently.

Consequently, with regard to preventing future incidents like Vioxx and the SSRIs, if we remain unable to identify most adverse events in a consistent and timely way, it may still take years longer than necessary to confirm whether potential safety "signals" are real. Further, important issues such as whether the safety concerns are specific to an individual drug, versus broader drug class effects (e.g., is the enhanced cardiovascular risk with prolonged use also present in other cox-2 inhibitors, or perhaps in an even broader range of nonsteroidal anti-inflammatory drugs?) cannot be reliably studied using "one-off" event reporting on particular drugs. To solve these problems, we need a more comprehensive and routine system for identifying adverse events, not a system primarily dependent on case-by-case reporting requirements for individual drug manufacturers.

FDA has long recognized these limitations, and has taken steps to build a more active system for drug safety surveillance, similar to the systems that are in place when it comes to medical devices through FDA's MedSun initiative or for vaccines through the Vaccine Adverse Event Reporting System. In fact, FDA has purchased or obtained electronic data on prescription use, medical utilization, and complications for certain populations – health plan data, or Medicare Part B data linked to hospital use and other complications – to help evaluate certain individual drug safety questions. The recent PDUFA IV draft agreement provides some additional funding and staff to support this analysis, and pending legislation also supports the use of such electronic databases. Further, in its recent administrative actions, FDA has proposed some additional enhancements to its ability to obtain and analyze electronic population databases. Recently, FDA has also sought broad public comment and expert input to design a "Sentinel Network" that would begin to link each of these individual databases and authorities together – the makings of a true, systematic approach to identifying safety signals in a broad part of the U.S. patient population. However, current legislative authority and budget authority does not provide as much momentum as it could for achieving this system. Without such steps, it is unlikely that our drug safety system will have the data, resources, and analytic capabilities to minimize the risk of future post-market safety problems. At the same time,

proposed legislation holds the potential to achieve fundamental improvements in post-market drug safety.

### **Establishing a Routine Electronic System for Reliable Post-Market Drug Safety**

In 2007, it is feasible to achieve fundamentally better post-market safety monitoring, by building on existing initiatives and proposals combined with recent developments in electronic tracking of medication use and patient results. This updated system would have:

#### *1. Faster, More Reliable Detection of Potential Safety Problems (“Signal Detection”) Using Better Data and Technical Support*

The core feature of this approach is the creation of a public-private infrastructure to draw together relevant population-based, electronic data on prescriptions linked to information related to patient complications, such as hospitalizations for particular diagnoses or death. The data sources include insurance claims databases maintained by large private health insurers and by Medicare, some state Medicaid programs, and potentially other government programs including the VA. Virtually all of these data, with full patient privacy protections (e.g., full compliance with HIPAA requirements and other steps to assure confidentiality), are already being used for particular safety studies. But there is not yet an established system for reliably putting the power of these data sources together to answer drug safety questions as quickly and completely as possible. This infrastructure could potentially be augmented by additional clinical data sources as they become available, such as electronic medical records and computerized data from research networks such as NIH’s emerging consortium of academic medical centers that have received Clinical Translational Science Awards (CTSAs).

While public and private stakeholders have already taken many steps to make this network a reality, recognition of the central value of this approach and limited new resource support through legislation would create the momentum to bring this surveillance or sentinel network for drug safety together now. For example, legislation could note that safety questions could be addressed through such a network, where it could provide more complete and efficient answers than RiskMAP requirements for a drug manufacturer, who would not have the capacity to develop this kind of comprehensive data.

To assure that the network’s efforts focus on the most pressing safety questions from a public health standpoint, it could be guided by the FDA with reliance on the FDA’s expert advisory groups. For example, in conjunction with a process for public input such as an advisory committee meeting or a public posting for comment, the FDA could identify the top safety questions to be answered using the data in the network, and outline the methods that would be used in the data analysis. These top questions would include adverse events that are suspected (but not proven) for new drugs as well as for existing drugs and drug classes, and severe, idiosyncratic adverse events (e.g., aplastic anemia, liver failure). FDA oversight of this process is appropriate and necessary, because FDA

is charged with using all available information to reach appropriate conclusions about drug safety and effectiveness for purposes of labeling and marketing in the United States.

While FDA oversight of this process is necessary, carrying out the analyses of these data will require the ongoing participation of additional academic experts, even if additional resources enable the FDA to make needed enhancements in its statistical and epidemiologic capabilities. Interpreting observational data to identify safety “signals” – whether there is a significant and meaningful association between use of a drug and an important adverse event – is generally not straightforward. Fortunately, many groups with relevant expertise are available and are already working on these kinds of safety questions. These include: the Centers for Education and Research on Therapeutics (CERTs) which, with funding from the Agency for Healthcare Research and Quality (AHRQ), already conduct analyses using these data to address key issues on the effects of treatments, including questions of interest to FDA; academic programs that focus on drug safety and effectiveness issues, such as MIT’s Center for Biomedical Innovation, and on learning more about treatment effects in routine clinical practice, such as Duke Medical Center’s community-based clinical networks; and many other experts in the public and private sectors. Expert groups like these can form the backbone of an ongoing infrastructure for routinely answering priority safety questions using electronic population data quickly and effectively.

The reports from these analyses, using much larger population-based electronic data, have the potential to identify much more quickly whether there is a significant association between use of a drug and an adverse event. For example, according to calculations by Richard Platt (Principal Investigator of the HMO Research Network CERT), electronic and other data actually used to determine a significant association between Vioxx use and serious cardiovascular events took almost three years to detect a statistically significant association, based on the limited population data available for analysis at the time. If data from large health plans could have been pooled to provide more definitive evidence on this potential safety risk, as envisioned in this strategy, the significant association could potentially have been detected within just several months, enabling much faster action to address the safety problem. Moreover, if the safety monitoring infrastructure enables needed data to be put together for analysis more quickly when needed for priority safety questions, the “lag time” in obtaining the data needed could also be reduced compared to the situation today, when such data must be assembled on a “one-off” basis. This would provide additional speed in resolving possible safety questions, as well as lower costs compared to “one-off” studies by particular drug manufacturers or health plans that are less complete and consistent.

It is important to note that a significant association between use of a drug and an adverse event does not necessarily mean that the drug has caused the adverse event. Such associations may occur by chance, or because the patients actually taking a drug differ in ways that are important but hard to measure, compared to other patients who are not taking the drug. For example, patients in poorer health may be more likely to be treated with a drug, and also be more likely to have subsequent cardiovascular problems because of their health status not because of the drug. Consequently, until statistical methods can



be enhanced, the more complete data developed as part of this drug safety infrastructure are generally not suitable for simply “fishing” for statistically significant associations between drugs and adverse events. Rather, as noted above, this system will be most useful for monitoring rare, serious adverse events that generally should not occur, and following up on questions where a suspicion of a safety problem has already been raised but has not been resolved. Other sources of evidence, such as suspected signals based on pre-market clinical and biological data, can provide the needed guidance for this system. For example, pre-market and peri-market clinical evidence of a potential elevated risk of cardiovascular events with prolonged use of Vioxx suggested the possibility of a safety signal; with that clinical foundation, determining quickly whether a significant association does exist is important supportive evidence. In many cases, however, further clinical evaluation will be necessary to understand the implications of a clear “safety signal,” as described below.

## *2. More Complete Monitoring of Patterns of Drug Use*

In addition to providing much faster and more reliable evidence on the association between drug use and important adverse events, this drug surveillance network would also provide much better insights into how drugs are being used and how use is changing over time. For example, many new drugs over time may be used in indications other than those for which they were initially approved by the FDA. These “off-label” uses can provide important clinical benefits for many patients; at the same time, the quality of the evidence on their safety and effectiveness may be more limited than for approved indications. The same data used to provide much better evidence on potential safety problems can also provide a more complete picture on which types of patients are being treated, subject to the limitations on clinical detail in existing electronic databases. For example, even when new drugs are clearly beneficial for their approved indications, patients who are elderly, have multiple comorbid diseases, are taking other prescription medications, or are from racial or ethnic minority groups are often underrepresented or cannot be represented in sample sizes large enough in pre-market clinical studies to determine if significant differences in risks or benefits exist for them.

The large populations incorporated in this surveillance network would permit more insights into how drugs are being used in different types of patients, and may highlight areas where risks or benefits may be greater, or where significant use is occurring and risks and benefits are unclear. This tracking of actual prescription drug use is, once again, likely to involve much more population data than are generally available to a drug manufacturer about which patients are actually using the drug, and so can provide insights about how drugs are being used that are not possible through a manufacturer RiskMAP.

## *3. Determination of Causal Relationships through Better-Targeted Followup Studies*

In many cases, establishing a statistically significant relationship between drug use and an adverse event may not be sufficient to determine that the drug caused the adverse event, even in light of prior evidence. Clinical trials in which patients are randomized to

different treatments, or other sophisticated clinical studies, may be needed to provide definitive evidence. For example, a drug may have a significant association with an adverse event, but it may be due to the characteristics of the patients using the drug not the drug itself. In these cases, the enhanced drug surveillance described here will not settle the safety issue, but it can be very useful in identifying the most important questions for further clinical study and the most effective research methods for resolving the questions. Quickly identifying significant rates of adverse events, and better characterizing which patients are actually using the drug and experiencing the events, can guide the further clinical-epidemiologic studies and post-market clinical trials needed to reach a definitive conclusion. Because these clinical studies will be guided by much better evidence on drug use and adverse events, they can be designed and implemented more quickly and efficiently. Such trials can be very costly and time-consuming, and so targeting them effectively is an important public health goal.

Further, establishing the surveillance network to bring together FDA staff, academic investigators and other clinical experts, and much better post-market data will itself lead to better post-market clinical studies. For example, the network could facilitate working with health plans to set up such studies, and could reduce the scope and cost of further data collection and analysis as part of the studies. It will also facilitate the development and validation of improved statistical methods for reaching conclusions using these improved data.

Because the building blocks for all three of these key steps toward an ideal post-market safety system are already in place, it is feasible to implement this health IT-based system now. Private health plan data are already being used plan by plan for these purposes; some Medicaid programs already participate in safety studies; Medicare Part A and B data have also been used; and Medicare proposed using Part D data for such purposes last fall. Moreover, the resources required would also be relatively limited, and in any case it is less costly to build a post-market safety infrastructure that can be used routinely and quickly than to try to re-create it (less comprehensively) on a “one-off” basis through drug by drug RiskMAPs.

This approach is not intended to replace current adverse event reporting systems or planned improvements in those systems. But the key question is where the new post-market requirements and efforts in the pending drug safety legislation should be focused. A relatively modest investment in an infrastructure including available electronic population data related to drug use and adverse events, plus a capacity for routine and transparent analysis of these data, would lead to a much more comprehensive capacity for identifying safety signals and acting on them effectively than we have today. It’s time to move from a drug by drug approach to a systematic, routine, population approach to promoting drug safety in the United States.

This is also the best path for the future – a future that should include much more extensive use of electronic, interoperable, real-time clinical data systems for active safety surveillance. Indeed, not only is this approach a big step forward based on using

electronic data today, but it provides a much stronger foundation into which more sophisticated data from electronic medical record systems can be added. Over time, the speed, clinical sophistication, and analytic sophistication of the post-market network will continue to increase, with continuing benefits for the safety and effectiveness of drugs.

## **Conclusion**

Chairman Kennedy, Senator Enzi, and members of the Committee, your leadership has created the opportunity to make fundamental progress on enhancing drug safety and the effective use of drugs in the United States. As part of this effort, it is possible to learn more about the risks and benefits of drugs before they come to market, and to do a fundamentally better job of addressing the safety issues that will inevitably arise when drugs are on the market. This will require some new investments in drug safety, but most of all, it will involve a shared commitment between the public and private sector to build systems and collaborations that can surface and resolve drug safety questions as quickly as possible. With all of the advances that we are making in the more effective use of IT in healthcare, we should aim for nothing less than world class data for evaluating drugs through their life cycle. And we should not wait, so that better information on drug risks and benefits can enable the FDA, health care providers, and patients can get the most out of prescription drugs, and so that we make the most of this unique opportunity to prevent or mitigate future drug safety problems.