SUMMARY OF TESTIMONY OF CAROLINE J LOEW, Ph.D., PhRMA
"ASSESSING THE SAFETY OF OUR NATION'S DRUG SUPPLY"

May 9, 2007

- Drug safety is a top priority for PhRMA and its member companies, and PhRMA wants to work with FDA and all stakeholders to improve the already robust drug safety system in a meaningful way the preserves innovation and patient access.
- Drug safety is a balance between benefit and risk. Assessments that focus solely on risk will lead to decisions that will have an adverse impact on patients and the public health.
- Drug safety is an extensive, ongoing process that starts long before a medicine enters the marketplace, and continues long after it has been made available to patients. Drug safety does not begin or end at approval.
- The assessment of drug safety today is more robust than ever before thanks to new science, tools and technologies. Improvements to the drug safety system should focus on the further development and evolution of these tools.
- FDA's drug safety system is robust and effective. However, it could be further improved with additional resources and a more modernized approach to drug safety that takes full advantage of the latest scientific tools and resources.
- FDA's proposal to reauthorize the Prescription Drug User Fee Act (PDUFA-IV) includes significant funds for such enhancements and modernization – approximately $150 million over 5 years to hire 82 additional staff for drug safety activities, to increase use of modernized techniques and reduce reliance on spontaneous adverse event reports. PhRMA supports this proposal.
- The FDA's PDUFA-IV proposal also addresses the IOM's most important recommendations relating to additional resources and improvements in the science of drug safety.
- PhRMA has undertaken a number of major programs in recent years to improve drug safety and transparency. Examples include a publicly available database of clinical study results, disclosure of information on ongoing clinical trials, establishment of a public-private partnership for biomarker research, development of training programs for adverse event detection and reporting, and research studies on new tools and methodologies associated with drug safety.
- Any drug safety reforms should strengthen FDA's oversight capabilities without impeding innovation or patient access. PhRMA would support targeted legislative revisions to clarify FDA's authority as it relates to clinical trial registries and databases, postmarket study authority, labeling authority and distribution restrictions.
- PhRMA urges Congress to reauthorize PDUFA as quickly as possible.

TESTIMONY OF CAROLINE J. LOEW, Ph.D.

SENIOR VICE PRESIDENT

SCIENTIFIC AND REGULATORY AFFAIRS

PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

BEFORE THE SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

UNITED STATES HOUSE OF REPRESENTATIVES

HEARING ON

"ASSESSING THE SAFETY OF OUR NATION'S DRUG SUPPLY"

May 9, 2007

A. Introduction

Mr. Chairman and members of the Subcommittee, thank you for the opportunity to testify today on issues surrounding the safety of the nation's drug supply. My name is Caroline Loew, Ph.D., and I am Senior Vice President of Scientific and Regulatory Affairs at the Pharmaceutical Research and Manufacturers of America, also known as PhRMA. PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. Our member companies invested more than $43 billion last year in discovering and developing new medicines for American patients. It is thus no overstatement to say that PhRMA companies are leading the way in the search for cures.

PhRMA and its member companies consider drug safety to be a top priority and support a number of initiatives and recommendations for improving the Food and Drug Administration's (FDA's) postmarket surveillance system, such as increased use of large medical databases and pharmacoepidemiology studies, which I will discuss in more detail later in my testimony. PhRMA wants to work with FDA and all stakeholders to improve the already robust drug safety system in a meaningful way that preserves innovation and patient access. PhRMA appreciates the opportunity to provide our views to this Subcommittee on this critical issue.

When considering potential drug safety legislation, PhRMA believes that Congress should keep in mind the following principles:

1. The current drug safety system is robust and effective but could be made even better with additional resources and better use of modern scientific techniques and resources for identifying and assessing risks.
2. Assessment of safety concerns must always be undertaken with full knowledge of the benefits (efficacy) of a drug. Drug safety is a balance between benefit and risk. This is critical as any assessment that focuses solely on risk will lead to decisions that will have an adverse impact on the public health and patients.
3. Drug safety is an ongoing process that begins long before a medicine enters the marketplace and continues long after it has been made available to patients. Drug safety does not stop at approval.
4. Any drug safety reforms should strengthen FDA's oversight capabilities without impeding innovation or interfering with patient access to needed medications. This is particularly important for patients with serious or life-threatening diseases and patients living in rural areas.

B. The FDA's Current Drug Safety System Is Robust and Effective

From the approval process through post-market surveillance, the current system, has and continues to work well in protecting Americans from dangerous drugs. Over the last 20 years, about 97 percent of all prescription medicines approved for patient use in the U.S. have safely remained on the market, while only about three percent of medicines have been withdrawn for safety reasons.

Before a drug is ever allowed on the market, it must undergo a rigorous premarket testing and approval process that often spans between 10 to 15 years. Drug safety is studied early in the development process through a series of laboratory tests, animal tests, and then with very small numbers of volunteer patients. Only after it is clear that the safety issues can be managed will it be tested in larger numbers of individuals in carefully controlled, monitored studies known as "clinical trials." Once this extensive testing process is concluded, FDA regulators then examine tens of thousands of pages of scientific data from these trials, and carefully weigh the benefits and risks of each medicine. FDA devotes fully half of its pharmaceutical review budget to safety issues in the pre- and post-market settings. Furthermore, for every 5,000 compounds that could become drugs, only five ever make it to a Phase 3 clinical study on patients, and only one is ever approved for sale by the FDA.

Because the science is constantly evolving, pre-approval safety testing is much more rigorous today than it was even ten or fifteen years ago. Companies now routinely test for safety issues that previously were poorly understood, could not be predicted well, and for which there were no accurate tests. For instance, today a company will often assess whether a drug causes QTc interval prolongation, a rare but serious side effect which could cause heart arrhythmia, and similarly will often assess the liver toxicity of a drug, which is again a rare but serious side effect associated with some drugs. As a result, we typically know far more about the safety profile of a drug that is approved under today's standards and science than ever before.

The FDA's post-market surveillance system also is robust and constantly improving. Once a drug is approved, safety is monitored continuously as long as it is on

the market through a collaborative process involving FDA, pharmaceutical companies, healthcare providers and patients. Physicians, nurses, and other healthcare providers are on the front-line of drug safety; they are often the first to learn of a potential problem with a medicine and are encouraged to report issues or concerns promptly to the FDA or the company concerned.

Pharmaceutical companies likewise play a critical role in assessing new and emerging risks with marketed medications. They spend considerable resources and have dedicated teams of experienced physicians and scientists whose jobs are to collect and analyze safety data on a daily basis - and immediately report any potential problems to government authorities. In many cases, this pharmacovigilance work includes post-approval safety studies, registries and pharmacoepidemiologic assessments of treatment populations.

FDA has broad statutory authority to monitor and ensure the safety of drug products after approval through adverse event reporting, annual reports (including new non-clinical and clinical data), and post-marketing study requirements.[1] FDA regulations require all manufacturers of prescription drug products to submit reports to FDA of adverse events associated with the use of their products.[2] Adverse events that are "serious and unexpected" (meaning that the event is serious and is not listed on the approved drug label) must be reported to FDA within 15 days of the initial receipt of the information by the manufacturer. Moreover, the manufacturer must promptly investigate these "serious and unexpected" adverse events and submit follow-up reports within 15

[1] *See* 21 U.S.C. §§355(k), 355a, 355c, 356, 356b.
[2] *See* 21 C.F.R. §§310.305, 314.80.

days of receiving new information. All other adverse events must be reported to FDA at quarterly intervals for the first 3 years after the date of approval, and annually thereafter.

FDA regulations also require manufacturers to submit an annual report within 60 days of the anniversary date of approval of a drug.[3] The annual report must contain, among other things, a summary of "significant new information from the previous year that might affect the safety, effectiveness or labeling of the drug product.[4] The annual report must contain both published and unpublished reports of "new toxicological findings" in animal and *in vitro* studies (e.g., animal studies bearing on the cancer risk of the drug).[5] Finally, the annual report must include any new clinical studies of the approved drug product, regardless of whether the study is published or unpublished.[6]

FDA also look for information on safety in large medical databases maintained by health plans and others. Access to these databases is costly and typically is purchased by the FDA and pharmaceutical companies. While these databases contain a wealth of safety information and can be used to conduct targeted epidemiological studies of particular drug risks, FDA is limited because of cost and the fact that there are no accepted "best practices" for conducting these types of epidemiological studies.

Postmarketing studies also provide useful safety information. Before or after granting marketing approval, FDA may ask a pharmaceutical company to conduct a "Phase 4" or "postmarketing study." Indeed, FDA routinely requests sponsors to conduct postmarketing studies as a condition of approval. A request is made if FDA concludes that additional information, while not essential for approval, is important in improving

[3] *Id.* §314.81.
[4] *Id.* §314.81(b)(2)(i).
[5] *Id.* §314.81(b)(2)(v).
[6] *Id.* §314.81(b)(2)(vi).

the prescribing and use of the product; product quality; or consistency in product manufacturing. Postmarketing studies may confirm existing data, raise or answer questions, or provide new data.[7]

In a 2004 study conducted by the Tufts Center for the Study of Drug Development, researchers found that between 1998 and 2003, FDA requested postmarketing studies in the vast majority of new drug approvals – 73%. Moreover, these requests for postmarketing studies are stringent, averaging 4.4 studies and 920 patients per new drug.

A recent FDA report on the performance of pharmaceutical and biologic firms in conducting post-marketing studies shows pharmaceutical companies are meeting their postmarketing study commitments. The report indicates that, of the studies concluded between October 1, 2005 and September 30, 2006, sponsors failed to meet study commitments only 5% of the time.[8] Likewise, the report indicates that only 3% of open studies for NDAs and ANDAs were delayed, meaning that the great majority of such studies – 97% -- had been submitted to FDA, were no longer needed or feasible, or were proceeding according to the schedule agreed to between the sponsor and FDA. These results demonstrate a commitment to postmarketing safety.[9]

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[7] FDA can require sponsors to conduct postmarketing studies for accelerated approval products or for other products to assess use in pediatric populations. 21 U.S.C. §§355c, 356.

[8] 72 Fed. Reg. 5069 (Feb. 2, 2007).

[9] Critics often contend that sponsors fail to even initiate studies in the vast majority of cases. These criticisms are based on a misunderstanding of FDA's statistics. While it is true that 71% of open commitments are considered "pending," these "pending" studies are in the preparatory phase of clinical trial development during which the protocol is drafted and submitted to FDA, IRB approval is obtained and the sponsor begins recruiting clinical investigators. *See, e.g.*, FDA Response to Congressman Markey at 5 (March 30, 2005) (clarifying that typically when a study is "pending" FDA and the applicant "are working together to design a study that will adequately address the objective of the commitment"). If sponsors simply failed to initiate such studies, the studies would be coded as "delayed" rather than "pending." However, only 3% of open studies are considered to be "delayed."

C. PhRMA Supports Efforts to Improve FDA's Drug Safety System

PhRMA believes that FDA's most urgent need is not for additional authority; rather, FDA's drug safety system could be improved with additional resources devoted to postmarket surveillance activities and a more modernized approach that takes full advantage of the latest scientific tools and resources, such as large medical databases and epidemiological expertise. PhRMA believes that the PDUFA-IV proposal addresses the FDA's most pressing drug safety needs.

PhRMA supports the FDA's proposal to reauthorize the Prescription Drug User Fee Act (PDUFA-IV) because it includes important new provisions and resources to enhance and modernize the drug safety system; increase FDA's oversight of direct-to-consumer (DTC) advertising; and facilitate the timely review of innovative medications. The PDUFA-IV proposal provides approximately $150 million of new money over five years to allow FDA to (1) hire 82 additional staff for postmarket safety activities, including experts in epidemiology; (2) increase use of modernized techniques, such as epidemiology studies and large medical databases, which contain a wealth of drug safety information; and (3) reduce FDA's reliance on spontaneous adverse event reports. The PDUFA-IV proposal also removes the three-year time limitation so that FDA can use funds from the user fee program to address safety issues whenever they emerge. This modernized approach should allow FDA to identify and assess safety risks more quickly and accurately.[10]

[10] While PhRMA and its member companies would prefer to see FDA's review and postmarket safety functions funded primarily through general appropriations rather than user fees, PhRMA recognizes that this may not be feasible given current federal budget constraints. In order to ensure that the FDA is adequately funded to perform its critical functions of expediting the development of life-saving medications while protecting the public health, PhRMA supports the FDA's current proposal even though it includes substantial increases in user fees. PhRMA would encourage Congress to explore options for reducing or

1. The PDUFA-IV Proposal Addresses All Relevant Recommendations of the Institute of Medicine (IOM)

While the PDUFA-IV proposal does not (and should not) address FDA's internal culture or possible new authorities, it does address the IOM's most important recommendations: the need for additional resources and improvements in the science of drug safety (see Exhibit A). Under PDUFA-IV, FDA will get more funding for drug safety activities and will markedly increase its scientific expertise and resources devoted to drug safety. This, in turn, will create a better, more responsive surveillance system.

Under the PDUFA-IV agreement, FDA will get an additional $150 million over five years for postmarket safety activities. With these additional funds, FDA will have the necessary resources to:

- Reduce the agency's reliance on the spontaneous reporting of adverse events and to conduct outside research to maximize the public health benefit associated with collecting and reporting adverse event information throughout a product's lifecycle (IOM Recommendation 4.1);
- Gain wider access to large healthcare databases for epidemiological studies (IOM Recommendation 4.2);
- Conduct assessments of the effectiveness of RiskMAPs, with input from industry, academia and others, to identify risk management and communication tools that are effective (IOM Recommendation 4.4);

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eliminating the Agency's reliance on industry user fees by the time the PDUFA program is scheduled for reauthorization in 2012.

- Hire 82 new employees, including experts in epidemiology (IOM Recommendation 4.6); and
- Develop a guidance document on epidemiological study best practices that will serve as a base for agency, academia and industry use (IOM Recommendation 4.6).

In addition, and as recommended by the IOM Report (IOM Recommendation 3.5), the PDUFA-IV proposal includes numerous safety-related performance goals. These include:

- Developing a 5-year plan describing agency activities that will lead to enhancing and modernizing FDA's drug safety system;
- Conducting a study on the value of adverse event reporting;
- Developing best practices for epidemiology studies;
- Developing and validating risk management and communication tools;
- Enhancing and improving coordination between the review divisions and the Office of Surveillance and Epidemiology;
- Developing guidance for industry on choosing proprietary names that do not pose a risk of confusion with existing drug names;
- Reviewing proprietary names within specified timelines to avoid confusion and potential medication errors;
- Reviewing DTC television advertisements within specified timelines to ensure compliance with regulatory requirements.

2. PhRMA Supports FDA's PDUFA-IV Proposal Because It Will Significantly Enhance FDA's Ability to Monitor Postmarket Drug Safety

Since its original passage in 1992, PDUFA has been a crucial program not only for FDA and the pharmaceutical industry, but also – and most importantly – for patients. Prior to passage of PDUFA-I in 1992, the average review time for a new drug application ("NDA") had increased to over 30 months, and there was a significant backlog of pending NDAs at the Agency. As a result, life-saving medications routinely were available to patients in Europe well before they were available to patients in the United States. With the increased funding provided under the PDUFA program, FDA was able to hire additional staff and quickly eliminated the backlog of pending NDAs. In addition, FDA made great strides to complete its reviews of new NDAs in a more timely manner, which not only added predictability to the drug review process but more importantly benefited patients by providing quicker and more widespread access to life-saving medications, such as treatments for HIV infection. The PDUFA program was reauthorized in 1997 and 2002.

Since PDUFA was originally enacted in 1992, FDA has approved more than 1,000 new drugs and roughly 100 new biologics, including new medicines for cancer (62), metabolic and endocrine diseases (109), anti-infective drugs (96), neurological and psychiatric disorders (103), and cardiovascular and renal disease (73).

It is important to stress that throughout the PDUFA programs of the past 15 years, the exacting standards by which FDA evaluates NDAs and BLAs have been maintained and, as a result of increased funding for drug safety, even strengthened. With more

resources provided by PDUFA, FDA has been able to complete its rigorous reviews more quickly and efficiently while maintaining its high standards for safety.

That tradition continues with the latest FDA proposal for the reauthorization of the PDUFA program. The Agency's PDUFA-IV proposal contains important new provisions and resources to (1) enhance and modernize the FDA drug safety program; and (2) add a new user fee program to give FDA additional resources to review and provide advisory opinions on direct to consumer television advertisements. PhRMA believes that the substantial new funding provided to enhance and modernize the FDA drug safety system– nearly $150 million dollars over the next five years – will continue to assure that FDA's pre- and post-market safety assessment system is the world's gold standard.

A key patient safety initiative is the allocation of a portion of this funding to improving the trade name review process. Trade names are reviewed within FDA's drug safety office to help ensure that new trade names cannot be confused with existing trade names in an effort to reduce possible medication errors. FDA will now have additional resources to review trade names during drug development and provide industry with guidance on "good naming practices." This will improve the predictability of the trade name review process.

The FDA's PDUFA proposal also includes a new user fee for DTC television advertisements. In 2005, PhRMA issued a set of voluntary guiding principles regarding DTC advertising. In those guiding principles, PhRMA member companies committed to submit all new DTC television advertisements to FDA prior to public dissemination to ensure that FDA's suggestions could be addressed before the advertisement was seen

widely by the public. The proposed new user fee would ensure that FDA has the necessary resources to review pre-submitted DTC television advertisements in a timely and predictable manner prior to public dissemination. This, in turn, will create incentives for companies to voluntarily submit advertisements prior to public dissemination, consistent with PhRMA's Guiding Principles.

The PDUFA program is vital to ensuring that FDA has the necessary resources to perform its critical functions of fostering drug development and innovation and protecting the public health. The PDUFA-IV proposal in particular will provide FDA with substantial new funding to enhance its oversight over drug safety and DTC advertising while ensuring that the drug review program is as robust and efficient as possible so that patients are not left waiting for needed cures.

3. PhRMA Supports Additional Activities to Improve Drug Safety

Over the past several years, PhRMA and its member companies have demonstrated a commitment to improving drug safety and transparency both before and after approval. For example, PhRMA has established a publicly available database of clinical study results; launched a Biomarkers Consortium in partnership with the FDA and the National Institutes of Health (NIH); is working to establish accredited training programs for physicians and other healthcare providers to better detect and report adverse drug events; is undertaking an extensive methodological study to develop a structured, transparent, semi-quantitative framework for the benefit-risk assessment of drugs over the full product lifecycle and has sponsored two academic studies to validate methodologies for datamining of large databases. These activities are described briefly below.

Clinical Study Results Database. PhRMA and its members support increased transparency of clinical trial information. In 2002, PhRMA issued its *Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results* (Clinical Trial Principles). Among other things, the Clinical Trial Principles announced the pharmaceutical industry's strong commitment to the "timely communication of meaningful results of controlled clinical trials of marketed products or investigational products that are approved for marketing, regardless of outcome." In other words, industry committed to communicate results regardless of whether they were positive, negative or inconclusive.

In 2005, PhRMA established a free, publicly available internet database to allow widespread access to company clinical trial results as described by our Principles, including unpublished results. The website can be accessed at www.clinicalstudyresults.org. As of late April 2007, the PhRMA website contained thousands of individual study results for approximately 331 different prescription drug products from 50 companies. More studies and drugs are added every week. The PhRMA website thus has been extremely successful in increasing the transparency of clinical trial results.

The pharmaceutical industry also supports expanding existing clinical trial registries to facilitate patient access to ongoing clinical trials. The primary purpose of a clinical trial registry is to inform patients who may have exhausted all other treatment options about ongoing clinical trials that they can participate in. The existing government database is limited to drugs intended to treat serious or life-threatening diseases or

conditions. In 2005, PhRMA adopted a position that companies should register all non-exploratory trials regardless of the condition or disease studied.

The Biomarker Consortium: This Consortium is an innovative, unique public-private biomedical research partnership between the NIH, FDA, PhRMA and the Foundation for the NIH, created to search for and to validate new biological markers, or biomarkers.

Biomarkers are important tools that are desperately needed to improve the flow of new healthcare technologies, medicines and diagnostics. Biomarkers can be predictors of a clinical outcome, be it the effectiveness of a drug, or a safety-related outcome (e.g. a certain type of side effect), and as such their use increases the timeliness, quality and accuracy of information collected during drug development. In just one example of their use, certain biomarkers can be used to indicate whether a patient will or will not respond to a treatment. This type of personalization ensures that only patients who are likely to experience a favorable outcome from a treatment will be exposed to it, demonstrating how biomarkers can be used to meaningfully improve drug safety. As such, these tools are critical to improving the process of discovering and developing the right medicine for the right patient, delivered at the right time, and the pharmaceutical industry is committing significant resources to their development.

The Biomarker Consortium was formed to help align all the stakeholders in the biomedical research enterprise so that they can work together, collaboratively, or pro-competitively on their highest priority and shared interest, to improve human health. The biopharmaceutical industry is committed to this effort. To date, thirteen major biopharmaceutical companies are participating in this effort with thirteen other patient

organizations, disease associations, and scientific societies to advance biomarker science critical to the future of human healthcare.

Reporting Adverse Events. Spontaneous reporting of adverse drug reactions ADRs) is useful in identifying those ADRs that occur rarely. Incorporation of these reports into company or regulatory agency databases serves as a starting point for signal identification, which then must be followed by extensive analysis and validation. One of the shortcomings of this system is the variable nature of reporting and the quality of reports. Ultimately, any database is only as good as the underlying data, and one of the chief difficulties with adverse event report databases is quality. Precious resources are often expended in contacting health care professionals regarding aspects of a report they have filed. In many instances, the reporter is unable or unwilling to provide sufficient detail for analysis. Privacy laws in some countries significantly impact the ability to get detailed information in reports that occur outside the United States. In addition, simply increasing the number of spontaneous reports is also not regarded as particularly useful. Increased reports may obscure potentially important safety signals by adding "noise" to the system.

PhRMA has been working to establish an accredited training program for physicians, medical students and healthcare providers on targeted issues designed to improve the detection of adverse events and the quality of adverse event reporting. One specific goal is training modules oriented towards both medical school students and continuing medical education (CME) programs focusing on practicing physicians and other healthcare providers. These training modules would explain the role and

responsibilities of healthcare professionals in reporting ADRs, how to identify and evaluate an ADR, and how to prepare and submit reports of high quality.

Pharmacovigilance Activities. In addition, PhRMA has worked collaboratively with the FDA and the Centers for Education and Research on Therapeutics (CERTs) in the areas of risk assessment and evaluation, benefit assessment, risk communication and drug safety. Another workshop in an ongoing series will be held later this month to explore opportunities related to proactive surveillance and other new pharmacovigilance methods. The topics at this workshop will include: use of datamining of large adverse event databases, use of active surveillance in community and managed care settings, and statistical approaches to signal identification and validation. This will make a significant contribution to the efforts of FDA, academia and industry.

***Benefit-Risk*:** Assessing the benefit-risk profile is the central element in the evaluation of drugs at any stage of their lifecycle. Understanding and trading off benefits and risks is central to pharmaceutical research, drug development, drug review and approval, prescribing, patient compliance and measuring and validating patient-centric outcomes.

However the issue of benefit-risk assessment of pharmaceuticals is one of the most prominent challenges facing all sectors of the healthcare continuum, from those involved in developing and approving new drugs, to physicians prescribing them, to patients trying to make informed treatment decisions. Approaches to the assessment of benefit and risk, and specifically balancing the two, have evolved over time, but today remain *ad hoc* at best, and as such could benefit significantly from the development of a more structured, transparent process and methodology for this assessment. Based on this

need PhRMA, in consultation with key stakeholders (including patients, physicians, the medical research community, regulators and industry), has an initiative underway to consider how to achieve more patient-focused, innovative, benefit-risk decision making.

Validation of Data mining Tools: In drug safety, data mining could potentially alert pharmacovigilance personnel of a safety signal before it would be detected using traditional methods, particularly in the case of unusual drug-event and drug-drug-event combinations. However, there is today much confusion and uncertainty regarding the potential value of using data mining methods in drug safety. Some of this arises because in fields such as finance and industry, data mining algorithms are used to make definitive decisions about processes and actions. In drug safety, data mining methodology cannot be the final "arbiter" of drug safety, but is rather only one component of a system that relies on the human judgment of astute clinicians. Another cause of confusion is that complexity has been built into drug safety data mining algorithms in an attempt to deal with the well-recognized data quality issues of safety databases. The danger here is the temptation to assume that with greater analytical complexity and sophistication also come greater precision and accuracy. A downside to data mining, especially when applied without context, is the wasted effort, which could be substantial, spent investigating "false positive signals." In addition, there is the potential negative impact of "false alarms" on public health which could arise from the disclosure of incomplete or inappropriate analysis. As such, before data mining can be used to its fullest potential in pharmacovigilance there is a real need to critically evaluate the data mining technology within this context.

To clarify the role of data mining, PhRMA on behalf of it members has engaged two independent contractors, the University of Maryland and Prosanos Corporation, to conduct research into aspects of data mining algorithms and the safety databases to which they are applied. The goal of the research is to reduce the current confusion in the field and to provide information regarding the appropriate application of data mining methods. In the studies, which are ongoing, various data mining algorithms are being compared and contrasted and the effects that reporting sources and other secondary factors and practices may have on data mining analysis will be tested. This effort was initiated in 2006 and will be producing its first results in the middle of this year, with full results in 2008, all of which will be published in peer-review scientific journals, presented at seminars, and made publicly available to regulators and pharmacovigilance scientists.

4. New Regulatory Authorities

The IOM Report recommends granting FDA broad new powers to, among other things, mandate labeling changes, order postmarketing studies, restrict distribution and use of drug products, and prohibit advertising. PhRMA believes that FDA's existing authorities are sufficient to ensure compliance with all applicable regulatory requirements, and that FDA's greatest need in the drug safety area is not new authority but rather additional resources and a more modernized approach to postmarket surveillance, both of which are provided by the PDUFA-IV proposal. Nevertheless, PhRMA would support targeted revisions to the Federal Food, Drug and Cosmetic Act (FFDCA) to clarify FDA's authority provided such revisions do not impede innovation or interfere with patient access to needed medications.

Clinical Trial Registries and Databases. PhRMA and its member companies are committed to the transparency of clinical trial information and supports a federal requirement that companies post information about ongoing clinical trials to a registry to assist patients who might want to participate in a trial. The registry, however, should be limited to hypothesis-testing trials and should not require the public dissemination of confidential commercial information.

In addition, PhRMA supports a federal requirement that companies post the results of completed studies to a national clinical trial results database. Like the registry, the results database should be limited to hypothesis-testing trials, which provide meaningful information that could be used to guide prescribing decisions. Moreover, the database should be limited to information about drug products that have been approved for at least one use, since physicians cannot prescribe drugs that have never been approved and are not on the market.

Clinical trial registries and results databases should balance the need for transparency with the need to protect confidential commercial information. Protections for trade secrets and confidential commercial information are vital for any innovative and highly competitive industry. When government policies weaken these important protections, they also weaken the incentives for companies to continue to innovate. In the pharmaceutical industry, such policies can have significant negative impacts on the public health. It is thus essential for policymakers to carefully balance the need for greater transparency against the need to protect confidential commercial information.

Finally, any federal requirement for a registry or database should preempt inconsistent state laws in order to foster uniformity and avoid confusion among patients

and their healthcare providers about where to find complete and relevant clinical trial information.

Postmarket Study Authority. PhRMA supports granting FDA explicit statutory authority to require a postmarketing study if, on the basis of new scientific information obtained after a drug is approved, FDA determines that (a) the drug may be associated with a significant new risk not listed on the current approved labeling; (b) a postmarketing study is necessary to assess the significant new risk; and (c) the information expected to be obtained from the postmarketing study would make a material contribution to the approved labeling for the drug. Moreover, the new authority should be limited to significant new risks associated with an approved use of the drug. Although physicians should remain free to prescribe a drug any way they deem appropriate as a legitimate exercise of the practice of medicine, companies should not be required to conduct research on a use they have not and do not intend to market. Finally, postmarketing studies can be extremely burdensome for sponsors and, in many cases, may be unnecessary to mitigate risks posed by a drug. Sponsors should have the option to take other equally effective but less burdensome actions before being ordered to conduct a postmarketing study (e.g., label change).

Labeling Authority. PhRMA supports proposals that give FDA greater authority to require a labeling change when warranted. PhRMA also supports the creation of an accelerated dispute resolution process for label changes that maintains the ability of the sponsor and FDA to engage in a meaningful dialogue but also places time limitations on such dialogue to ensure that new safety information is included on the approved labeling in a timely manner. Finally, PhRMA supports the requirement that FDA review and

approve all safety labeling changes prior to implementation within 30 days of submission. This will ensure that the FDA-approved labeling remains the primary source of information about a drug product and that safety labeling changes not subject to the dispute resolution process are implemented in a timely fashion.

Distribution Restrictions. PhRMA supports clarifying FDA's authority to approve drug products subject to certain distribution or use restrictions. However, because distribution and use restrictions create significant limitations on patient access to needed medications, they should be imposed only in exceptional circumstances. PhRMA is concerned that providing FDA explicit statutory authority to impose distribution and use restrictions could lead to the routine use of very onerous restrictions that should be reserved for exceptional circumstances. This would not only interfere with the legitimate practice of medicine but could unnecessarily limit drug availability, particularly in rural areas, to the detriment of patients. Consequently, any such authority should be limited so that it can be used only when absolutely necessary to ensure safe use of the product. Finally, distribution and use restrictions applicable to an innovative drug should likewise apply equally to any generic copy of the drug.

D. Conclusion

The evaluation of drug safety is an iterative process that continues throughout the lifecycle of a drug product, from earliest development, through clinical testing and approval, and continuing after approval during use by a diverse population. New information about the risks of a drug is constantly emerging and must be balanced against the known benefits of the drug. It is important to remember that drug safety cannot be

viewed merely in terms of a drug's risks; rather, it must be seen as a balance between a drug's risks and its benefits.

The current drug safety system is robust and effective, ensuring that drugs are rigorously tested before they are marketed and closely monitored after approval for any emerging safety signals that need to be factored into the benefit-risk equation. But there is no question that even a good system can be made better. Despite its critical role in monitoring drug safety and protecting the public health, FDA has been chronically underfunded for many years. FDA's most pressing needs, therefore, are for resources to fund its postmarket surveillance activities and a more modernized approach to drug safety that leverages new techniques and resources.

PhRMA believes that the robust drug safety provisions in the PDUFA-IV proposal address all of FDA's drug safety needs. These new provisions, along with FDA's own internal reforms, should be allowed to work to enhance and modernize the drug safety system. We are concerned that adding significant new authorities and a markedly different review paradigm, such as the Risk Evaluation and Mitigation Strategy (REMS) proposed in some bills, may actually be counter-productive. The REMS process creates a complicated and bureaucratic safety oversight system that may not be workable in practice. These additional processes may actually impair drug safety oversight by miring FDA safety officers in unproductive bureaucratic exercises rather than meaningful safety surveillance activities.

If Congress believes that the drug safety enhancements in the PDUFA-IV proposal are not sufficient and that FDA needs additional authorities, this should be accomplished through carefully targeted revisions to the FFDCA. For example, an

accelerated label revision process could be added to the Act in a relatively straightforward manner to ensure that labeling discussions on important safety issues do not extend too long. Significantly, this change and other targeted revisions can be accomplished *without* creating an entirely new bureaucratic maze.

PhRMA wants to work with FDA and all stakeholders to improve the already robust drug safety system in a meaningful way that preserves innovation and patient access. We believe that significant strides already have been made with the PDUFA-IV proposal, and we ask you to reauthorize PDUFA-IV as quickly as possible.

Exhibit A
Side-by-Side:
IOM Report and PDUFA Agreement -
Science of Safety and Funding Recommendations

ISSUE	IOM REPORT	PDUFA	Done
Safety-related Performance Goals in PDUFA	Recommends that PDUFA contain specific safety-related performance goals in 2007, such as: (1) target participation rates of OSE staff in NDA review teams, (2) prepare summary analysis of AE reports for new drugs within 18 months of launch, (3) review backlog of postmarketing commitments (4) review and act on drug advertisements and promotional material within specified timeframes (Rec. 3.5)	Contains many safety-related performance goals, including: (1) Developing a 5-year plan describing agency activities that will lead to enhancing and modernizing FDA's drug safety system; (2) Conducting a study on the value of adverse event reporting; (3) Developing best practices for epidemiology studies; (4) Developing and validating risk management and communication tools annually; (5) Enhancing and improving coordination between the review divisions and the Office of Surveillance and Epidemiology; (6) Developing guidance for industry on choosing proprietary names that do not pose a risk of confusion with other names; (7) timeline for reviewing promotional material, (8) timeline for reviewing tradenames	√

ISSUE	IOM REPORT	PDUFA	Done
Adverse Event Reporting System (AERS)	Recommends improving the generation of new safety signals by having CDER (a) conduct a systematic, scientific review of the AERS system; (b) identify and implement changes in key factors that could lead to a more efficient system; and (c) systematically implement statistical-surveillance methodologies on a regular basis for the automated generation of new safety signals (Rec. 4.1)	Provides funding for FDA to conduct outside research to maximize the public health benefit associated with collecting and reporting adverse event information throughout a product's lifecycle. Completion of studies is targeted at FY 11.	√
Use of Large Healthcare Databases	Recommends that CDER improve its formulation and testing of drug safety hypotheses by (a) increasing their intramural and extramural programs that access and study data from large automated healthcare databases; (b) include in these programs studies on drug utilization patterns and background incidence rates for adverse events; and (c) develop and implement active surveillance of specific drugs and diseases (Rec. 4.2)	Provides funding for FDA to obtain wider access to large healthcare databases for epidemiological studies.	√
Public-Private Partnerships to Fund Confirmatory Drug Safety and Efficacy Studies	Recommends that HHS, working with VA and DOD, develop a public-private partnership with drug sponsors, public and private insurers, health care provider organizations, consumer groups, and large pharmaceutical companies to prioritize plan and organize funding for confirmatory drug safety and efficacy studies of public health importance (Rec. 4.3).	No provision	

ISSUE	IOM REPORT	PDUFA	Done
Evaluation of Risk Minimization Action Plans (RiskMAPs)	Recommends that CDER assure the performance of timely and scientifically valid evaluations of RiskMAPs. This should include determining whether individual RiskMAPs are effective and an overall evaluation of the strategies used and processes of CDER staff and industry sponsors for planning and implementing RiskMAPs (Rec. 4.4).	Provides funding for FDA to conduct assessments of the effectiveness of RiskMAPs with input from industry, academia, and others. A public meeting will be held in FY 08, and FDA will conduct assessments on 1-2 RiskMAPs per year.	√
Development of Risk-Benefit Analysis Methods	Recommends that CDER develop and continually improve a systematic approach to risk-benefit analysis for use throughout the FDA in the pre-approval and post-approval settings (Rec. 4.5).	No provision	
Epidemiological Expertise	Recommends that CDER build internal epidemiologic and informatics capacity in order to improve the postmarket assessment of drugs (Rec. 4.6).	Provides funding for FDA to develop increased expertise in epidemiology, including developing a guidance document on epidemiology best practices and hiring more experts in epidemiology.	√

ISSUE	IOM REPORT	PDUFA	Done
FDA's Scientific Research Capacity	Recommends that FDA demonstrate commitment to building scientific research capacity by (a) appointing a Chief Scientist; (b) designating FDA's Science Board as the extramural advisory committee to the Chief Scientist; (c) including research capacity in the Agency's mission statement; (d) applying resources to support intramural research; and (e) ensuring that adequate funding for research is requested in the annual budget (Rec. 4.7).	Provides funding for FDA's Critical Path Initiative.	√
Advisory Committees – Review All NMEs	Recommends that FDA have its advisory committees review all new molecular entities (NMEs) either prior to approval or soon thereafter to advise on drug safety/efficacy and managing risks (Rec. 4.8).	No provision	
Advisory Committees – Pharmaco-Epidemiologists	Recommends that all FDA drug product advisory committees include a pharmacoepidemiologist or other individual with comparable public health expertise in studying the safety of medical products (Rec. 4.9).	Provides funding for FDA to increase its epidemiological expertise.	√

ISSUE	IOM REPORT	PDUFA	Done
Advisory Committees - Conflicts of Interest	Recommends that FDA establish a requirement that a substantial majority (60%) of the members of each advisory committee be free of significant financial involvement with companies whose interests may be affected by the committee's deliberations (defined as involvements that currently require only disclosure, not waiver (Rec. 4.10).	No provision	
Clinical Trial Registration	Recommends that Congress require industry sponsors to register all Phase 2 through 4 trials on clinicaltrials.gov if the data from the trials are intended to be submitted as part of an NDA, sNDA or to fulfill a postmarket commitment. In addition, sponsors should be required to post a summary of the results of such trials, including (a) primary hypothesis, (b) experimental design, (c) primary pre-defined outcome measure, (d) planned and actual sample size per treatment arm, (e) number and type of serious AEs, (f) overview of results, and (g) risk-benefit summary. Recommends harmonizing registration requirements with emerging international standards, such as WHO (Rec. 4.11).	No provision.	

ISSUE	IOM REPORT	PDUFA	Done
Disclosure of Review Packages	Recommends that FDA post all NDA review packages on the agency's web site (Rec. 4.12).	No provision	
CDER Review Teams	Recommends that CDER review teams regularly and systematically analyze all postmarket study results and make public their assessment (Rec. 4.13).	No provision	
Increased Funding	Recommends that the Administration request and Congress approve substantially increased resources in both funds and personnel for FDA (Rec. 7.1). The IOM favors appropriations from general revenues rather than user fees to support new drug safety responsibilities.	Includes several million dollars per year in increased user fees for drug safety activities.	√
Independent Drug Safety Center	Strong recommendation ***not*** to create a separate drug safety center. Believes that safety and effectiveness should not be separated.	Provides increased funding for drug safety activities, which will increase staffing for the Office of Surveillance and Epidemiology (formerly Office of Drug Safety).	√