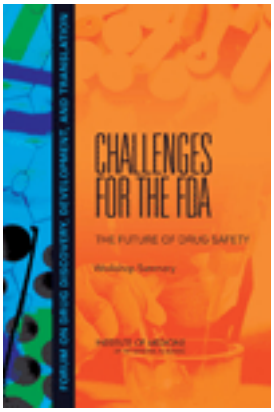

Challenges for the FDA: The Future of Drug Safety, Workshop Summary

Leslie Pray and Sally Robinson, Rapporteurs, Forum on Drug Discovery, Development, and Translation

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CHALLENGES FOR THE FDA

THE FUTURE OF DRUG SAFETY

Workshop Summary

Leslie Pray and Sally Robinson, *Rapporteurs*

Forum on Drug Discovery, Development, and Translation

Board on Health Sciences Policy

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We wish to thank the following individuals for their review of this report:

Catherine Bonuccelli, AstraZeneca Pharmaceuticals
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Alastair J. Wood, Symphony Capital LLC

Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the report before its release. The review of this report was overseen by **Hellen Gelband**, Scholar-in-Residence, Institute of Medicine. Appointed by the National Research Council and Institute of Medicine, she was responsible

for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authors and the institution.

Preface

Americans rely on the drug safety system to ensure that the medications they take are safe and effective. In carrying out its central role within this system, the U.S. Food and Drug Administration (FDA) faces a daunting task: it must balance the public's desire for rapid introduction of new drugs against the availability of limited safety and efficacy data, as well as monitor drugs after they are on the market. As a result of increases in the number of drugs used by Americans, coupled with greater potential for drug interactions, improved patient access to information, and recent advances in drug development technologies, the public's expectations of the drug safety system are higher than ever. But recent events—including highly publicized safety concerns and recalls of approved drugs—have shaken the public's confidence in the ability of the system to meet those expectations.

While the public would like the drug safety system to perform flawlessly, few understand the enormous constraints faced by the FDA in carrying out its critical functions. The number and complexity of drugs that the FDA must track are continually increasing even as drugs are spending less time in review. And while the world of drug discovery and development has undergone revolutionary change, shifting from cellular to molecular and gene-based approaches, the FDA's evaluation methods have remained largely unchanged over the last 50 years. Funding for the FDA has not kept pace with the evolution of the underlying science of drug development and the expanding scope of the agency's mission. Furthermore, the FDA's limited resources must be allocated to safety

assurance not only for drugs, but also for biologics, medical devices, food products, and cosmetics. Indeed, it has been estimated that the FDA regulates products representing nearly a quarter of consumer spending in the United States.

CONCERNS THAT LED TO THE INSTITUTE OF MEDICINE'S STUDY ON DRUG SAFETY

In 2005 the FDA commissioned the Institute of Medicine (IOM) to perform an independent assessment of the current U.S. drug safety system. In September 2006, the committee impaneled by the IOM to conduct this study released its report—*The Future of Drug Safety: Promoting and Protecting the Health of the Public*—which included 25 recommendations for improving the system for drug safety review. Since the report was issued, the FDA has taken a number of steps toward implementing those recommendations. Yet the FDA is financially strained by its existing responsibilities as a result of its many unfunded mandates and minimal annual increases in its congressional appropriations. Fully implementing the improvements to the drug safety system recommended in the IOM report will therefore require significant new financial commitments. The IOM report addressed some of the costs associated with its recommendations, but left many unanswered questions about the resources required to fully achieve the envisioned improvements. Absent substantial increases in agency funding, making the recommended improvements in the agency's ability to identify safety problems with new drugs, monitor routinely submitted safety data, and relay the resulting information to the public would require the diversion of funds from other mission-critical areas.

THE ROLE OF THE FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

The Forum on Drug Discovery, Development, and Translation was created in 2005 by the IOM's Board on Health Sciences Policy to provide an opportunity for leaders from government, academia, industry, patient advocacy, and other stakeholders to meet and discuss issues of mutual interest in a neutral setting. While the Forum was not involved in the IOM's drug safety study, it closely followed the committee's work. In October 2006, shortly after the release of the report, members of the committee and IOM staff presented the study findings to the Forum. Among the topics discussed at this meeting was the FDA's ability to implement the changes called for in the report given the resources likely to be required for the purpose.

Attempting to understand these resource requirements is a difficult

undertaking. Limited data are available to support such an exercise, and predicting the nature and level of effort associated with the new programs recommended in the drug safety report is even more difficult. In the report, the budget implications of enhancing certain aspects of drug safety science at the FDA are outlined, and a general increase in FDA funding is called for. But the funding required to implement the majority of the report's recommendations is not enumerated, nor does the report suggest the total investment required to achieve its broad, agency-wide objectives.

In the context of current congressional deliberations on reauthorization of the Prescription Drug User Fee Act (a substantial source of FDA funding) and growing pressure for improved drug and food safety processes, concern arose within the Forum that a lack of realistic budget estimates could lead to new legislative demands being placed on the FDA without funds commensurate with those demands being appropriated. This concern led to the Forum's decision to convene a national symposium aimed at achieving a better understanding of the types and magnitude of resources required to achieve the goals articulated in the IOM report.

Participants in the symposium included an impressive range of experts from industry and academia, government officials, policy makers, and patient advocates. Speakers included a former Secretary of Health and Human Services, two former FDA commissioners, many current and former FDA officials, and numerous other experts and stakeholders. Topics discussed included strengthening the scientific base of the agency, integrating pre- and postmarket review, enhancing postmarket safety monitoring, conducting confirmatory drug safety and efficacy studies, enhancing the value of clinical trial registration, and enhancing the FDA's postmarket regulatory and enforcement authority.

The symposium saw spirited, informed, and constructive discussion of the merits of the current drug safety system, the need for more FDA resources, and the ways in which new resources should be deployed. The discussion did not address every recommendation from the IOM report, but focused on selected recommendations with substantial resource implications. Recommendations for organizational and cultural changes at the FDA, for example, were not addressed. Moreover, while the symposium generated numerous insights into the types and magnitude of resources required to enhance the drug safety system, it did not result in detailed budget estimates.

Important discussions took place that were tangential to the goal of enumerating costs. One such discussion involved possible formation of a public–private partnership that would consolidate data from multiple stakeholders—such as the Centers for Medicare and Medicaid Services,

private health plans, and large provider systems—to support postmarket assessments of drug safety. While many technical challenges would be involved, several speakers suggested that not only is the capacity to accomplish this consolidation is within reach, but also that the costs could be substantially lower than those of using traditional clinical trial methods to achieve the same objectives.

Another key discussion involved the human resources needed to meet the challenges of ensuring drug safety and effect the recommended transformation of the FDA. The problem of how to train an adequate workforce of epidemiologists and translational scientists led to discussion of a key concept—the development of a Jet Propulsion Laboratory–style initiative that would generate a cooperative and aggressive training program designed to equip translational scientists with the necessary skills.

The symposium provided a valuable opportunity for the broad community of stakeholders who think hard and care passionately about drug safety to further delineate the recommendations of the IOM report and explore ideas for enhancing the drug safety system that is so important to all Americans. I would like to thank all of the individuals who contributed to and participated in the symposium—the panelists, the members of the planning committee, and the members of the Forum who gave so much of their valuable time and generously shared their expertise and guidance. I would also like to thank the Forum staff for their dedication and commitment to making the symposium a success.

Gail Cassell, *Symposium Chair*
Co-Chair, Forum on Drug Discovery,
Development, and Translation

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Summary[1]

As the principal agency regulating food, drugs, medical devices, and biological products used by Americans, the U.S. Food and Drug Administration (FDA) serves one of the most critical consumer protection functions of the federal government. The FDA's reach is enormous, regulating products that represent roughly 25 percent of all consumer spending in the United States (Coalition for a Stronger FDA, 2007).

Since 1992, however, federal funding for the agency has diminished, and the FDA's Center for Drug Evaluation and Research (CDER) currently relies on the fees it receives from the industry it regulates to fund the majority of its drug regulation functions. Prescription drug safety is receiving heightened press coverage and congressional scrutiny as a result of recent, highly publicized events, such as the recall of Vioxx because of its link to heart attacks, and the link between certain antidepressants (selective serotonin reuptake inhibitors, or SSRIs) and an increased risk of suicidal ideation in children. There is growing public concern about the ability of the current drug safety system to prevent future Vioxx-like events.

To address these concerns, the FDA in 2005 commissioned the Institute of Medicine (IOM) to conduct an independent assessment of the current U.S. drug safety system. In September 2006, the IOM committee

[1]The Forum's role was limited to planning the workshop. This report was prepared by the workshop rapporteurs as a factual summary of the presentations and discussions.

released its report—*The Future of Drug Safety: Promoting and Protecting the Health of the Public*—which included 25 recommendations for improving the system for drug safety review. The committee identified four major vulnerabilities in the U.S. drug safety system: (1) chronic underfunding; (2) organization problems, particularly inadequate integration of pre- and postmarket data review; (3) a range of technical problems related to the insufficient quantity and quality of postmarket data and inadequate capability to systematically monitor the risks and benefits of drugs after marketing; and (4) unclear regulatory authority and insufficiently flexible regulatory tools (IOM, 2007a).

Since the IOM report was issued, the FDA has taken a number of steps toward implementing the recommended improvements. Like many government agencies, however, the FDA is financially strained by its existing responsibilities, and fully implementing the recommended improvements to the drug safety system would require significant financial commitments. The IOM report addressed some of the costs associated with its recommendations, but left many unanswered questions about the resources required to fully achieve the envisioned improvements. Without substantial increases in agency funding, making the recommended improvements in the agency's ability to identify safety problems in new drugs, monitor routinely submitted safety data, and relay that information to the public would require the diversion of funds from other mission-critical areas.

To better understand the types and magnitude of resources required to achieve the goals of the IOM report, the IOM's Forum on Drug Discovery, Development, and Translation convened a 1-day symposium in March 2007. The symposium's presentations and discussions were in most cases framed by selected recommendations from the report, and are summarized here in seven key areas:

- addressing the FDA's resource challenges;
- strengthening the scientific base of the agency;
- integrating pre- and postmarket review;
- enhancing postmarket safety monitoring;
- conducting confirmatory drug safety and efficacy studies;
- enhancing the value of clinical trial registration; and
- enhancing the FDA's postmarket regulation and enforcement.

The presentations and discussions included the types and magnitude of resources required in these areas. A session at the close of the symposium looked to the future, exploring prerequisites for revitalizing the U.S. drug safety system and the future of drug safety regulation. It should be noted that, while the IOM report suggested some organizational and cultural changes at the FDA, those recommendations were not a focus of the dis-

cussions during the symposium. Additionally, participants did not deliberate upon whether the FDA in its current form is properly configured to lead the efforts that were discussed.

ADDRESSING THE FDA'S RESOURCE CHALLENGES

A central theme of the symposium was that many of the weaknesses of the national system for drug safety stem from a lack of resources. Since the passage of the Prescription Drug User Fee Act (PDUFA) in 1992, funding for the FDA has increasingly shifted from appropriations to user fees, which, until PDUFA III was authorized in 2002, could not be used for postmarket safety activities. Despite the dedication of monies for postmarket safety activities in PDUFA III, Congress rescinded much of that funding and reprogrammed the remainder elsewhere in the agency. Since 1992, the FDA has doubled the number of staff performing new drug reviews from approximately 1,300 to 2,600. Yet congressional appropriations paid for only 11 of those 1,300 additional staff; the remainder were funded by PDUFA. Further, over the last 10 years the FDA has lost some 1,000 staffers from the food, drug, and medical device safety programs not supported by PDUFA fees. User fees now represent more than 50 percent of the drug regulation budget, and some expect that PDUFA IV legislation may increase that figure to 80 percent or more. Alta Charo, University of Wisconsin–Madison, and member of the IOM Drug Safety Committee, stressed that, although the FDA regulates an extraordinary proportion of the products on the American market, it operates with a budget that is not commensurate with this broad regulatory authority. She noted that the committee responsible for the IOM report highlighted its consensus conclusion that more public funding is needed for the FDA, specifically more general appropriations. The Coalition for a Stronger FDA, a group of consumer, patient, industry, and nonprofit groups, has recommended a total increase of $175 million in appropriations for 2008 (over the fiscal year 2007 budget and over PDUFA IV increases).[2]

STRENGTHENING THE SCIENTIFIC BASE OF THE AGENCY

The committee that authored the IOM report was charged with reviewing the U.S. drug safety system and providing recommendations for how to improve it. While the majority of the report's recommendations focus on postmarket safety, there are opportunities to improve safety

[2]In light of recent events regarding food safety, the Coalition for a Stronger FDA has begun advocating for a $310 million increase in appropriations for 2008 rather than the $175 million previously called for.

throughout the drug development pathway. Gaining a better understanding of the safety profile of a drug and being able to discriminate more precisely among drugs within the same class before clinical testing begins would strengthen the drug safety system before a drug ever reaches the market.

A primary goal of the FDA's Critical Path Initiative is to increase the efficiency of the drug development process by building safety into products throughout their development life cycle. Panelists at the symposium described a broad spectrum of urgent safety science research needs and indicated that because the FDA is limited in its ability to conduct such research, one of its primary goals must be to collaborate with industry and academia to form public–private partnerships. Formation of these partnerships is important because by nature, this type of research requires access to people and resources outside the FDA. Given the agency's unique role, panelists encouraged the FDA to promote collaboration among stakeholders in the research and development of publicly available scientific methodologies and technical tools that all stakeholders could use to design safer and more effective products more efficiently. Garret FitzGerald, University of Pennsylvania, characterized FDA–industry partnerships as a necessary component of an improved drug safety system. He argued that an enhanced training ground is needed to develop a workforce of scientists with an integrative understanding of drug safety evaluation, and he proposed a Jet Propulsion Laboratory–style public–private partnership to fund this critical training.

INTEGRATING PRE- AND POSTMARKET SAFETY REVIEW

A major focus of the symposium was the integration of pre- and postmarket review. There are fundamental differences in the way data are collected and analyzed in the pre- and postmarket environments. Premarket data are generally collected from focused, randomized controlled preclinical studies and clinical trials, whereas postmarket data are collected from a broader array of sources, including controlled and uncontrolled observational studies. Integration of the two datasets is difficult, and there have been reported tensions between reviewers in the FDA's Office of New Drugs (OND) and Office of Surveillance and Epidemiology (OSE).

Discussion of the integration of pre- and postmarket review was framed by IOM recommendations calling for

- joint authority of OND and OSE for postapproval regulatory decisions;
- timely review of Risk Minimization Action Plans (RiskMAPs);
- establishment of a systematic approach to benefit–risk analysis;

- systematic review and publicizing of all postmarket study results; and
- evaluation of all data on new molecular entities within 5 years following approval.

Panelists asserted that providing increased training opportunities for epidemiologists and clinical reviewers would help create a workforce capable of overcoming some of the scientific challenges to implementing the IOM recommendations. Additionally, panelists considered ways of developing better methods for data capture through sharing of best practices, one of many potential collaborative efforts discussed throughout the day.

ENHANCING POSTMARKET SAFETY MONITORING

A conclusion of the IOM report was that the FDA's current postmarket surveillance system is neither as comprehensive nor as systematic as it needs to be to detect, interpret, and analyze safety signals effectively and efficiently. The current system for monitoring adverse events—the Adverse Event Reporting System (AERS)—is passive, with reports being submitted voluntarily by patients and physicians. While this passive surveillance system may be capable of detecting rare serious adverse events, it has several limitations, including underreporting, biased reporting, and difficulties in attributing an adverse event to a specific drug. Additionally, when analyzing postmarket epidemiological data collected through passive surveillance, it is difficult to know accurately how many people have taken a drug (i.e., to determine a denominator) and therefore to conclude the rate at which an event would take place.

Multiple panelists discussed how rejuvenating the passive surveillance system and augmenting it with an active system would be a feasible next step toward a stronger and more effective drug safety system. Several panelists suggested establishing a public–private partnership comprising various federal agencies, pharmaceutical and biotechnology companies, and health care organizations to create an integrated health care claims database. This database would be enhanced and linked with other databases, including full-text medical records, pharmacy claims data, physician and facility claims data, laboratory test results data, and demographic and other consumer information. It was speculated that such a system, including data from 100 million persons and capable of being accessed in real time and in a web-based, interactive manner, would help detect future drug safety signals much more rapidly (within months rather than years) than is possible with the current system.

CONDUCTING CONFIRMATORY DRUG SAFETY AND EFFICACY STUDIES

The IOM report noted that the FDA is limited in its ability to conduct the larger studies sometimes necessary to follow up on signals and reduce uncertainty associated with the benefit–risk balance of approved drugs. Accordingly, the report recommended the development of public–private partnerships to prioritize, plan, and fund confirmatory drug safety and efficacy studies. The ideas expressed during this session dovetailed with those put forth in the previous session, as summarized above, supporting the necessity of and readiness for a public–private collaborative effort to improve postmarket safety and efficacy monitoring. Whereas the focus of the previous session was on the capacity of a linked public–private surveillance system to improve the detection of safety signals, panelists went a step further during this session by considering the potential of such a system to be used not just for detection, but also as a tool for addressing the broad spectrum of safety science research questions that arise over the course of a drug's lifetime. A collaborative effort to this end would be more cost-effective than multiple isolated efforts, as presenters in the previous session emphasized with regard to detection. It would give researchers access to a larger volume of information resources, and it would generate information of value to multiple stakeholders.

ENHANCING THE VALUE OF CLINICAL TRIAL REGISTRATION

Since the International Committee of Medical Journal Editors began requiring registration of trials in a public trials registry as a condition of consideration for publication, the number of trials registered in ClinicalTrials.gov has increased. Nevertheless, the value and the transparency of the system are not optimal. To address the weaknesses of the current system, the IOM report recommended enhancing clinical trial registration.

Four components of the IOM recommendation can be identified. The first is an expanded scope of mandatory trial registration. It was suggested that the system could readily handle an increase in the number of trials registered without requiring a significant budget increase. Second is the addition of a results database—a complex task that would cost an estimated $10–20 million annually. The third component of the recommendation—scientific review—would involve reviewing 40–200 trials weekly, with each review consisting of complex analyses and the gathering of other information. It is unclear who would be able to carry out these reviews or what the cost would be. The same can be said of the final component—monitoring and enforcement.

ENHANCING POSTMARKET REGULATION AND ENFORCEMENT

Once a drug has been approved by the FDA for marketing, the agency's authority over the drug and the manufacturer changes markedly. Prior to approval, the FDA has complete control over when and by whom the drug can be used, how it can be discussed, and how it is manufactured. After approval, if the FDA finds problems in the way a product is manufactured or marketed or if it becomes aware of safety concerns, it has two options: withdraw approval of the drug, or try to persuade the manufacturer to comply with the agency's requests. The IOM report called for clarifying and enhancing existing authority to regulate marketed drugs and for developing sufficient enforcement tools to ensure that regulatory requirements imposed at or after approval will be fulfilled. Some symposium panelists argued that additional resources, not new legal authorities, are the principal need, while others argued that enhanced FDA authority and enforcement are critical to success.

LOOKING TO THE FUTURE

In looking to the future, panelists began by outlining three prerequisites for revitalizing the U.S. drug safety system: reauthorization of PDUFA, thoughtful utilization of the FDA's existing resources, and an emphasis on preserving patients' trust in the drug safety regulatory system. Multiple panelists called for timely reauthorization of PDUFA; should this not occur, the FDA will be forced to cut staff, and new drug reviews will largely come to a halt. Thoughtful use of existing resources—for example, through enhanced coordination and increased collaboration—was suggested as a complement to the emphasis throughout the symposium on the FDA's need for additional resources. Finally, panelists stressed that the voice and views of patients must be heard during the current reassessment of the U.S. drug safety system. Whatever steps are taken to improve drug safety, it is critical that those actions not restrict access to appropriate medications or otherwise interfere with patients' rights to make informed decisions about drug use with their doctors, and that the risks and benefits of drugs be carefully weighed "in full public view."

With regard to the future of drug safety regulation, it is essential to take immediate steps to capitalize on the significant progress made since the release of the IOM report, especially in light of the opportunity represented by the anticipated reauthorization of PDUFA. The session closed with a summary of five key issues around which much of the symposium discussion revolved, and which can inform the next steps to be taken: (1) the FDA's limited resources and technical capabilities; (2) operations and management, particularly with regard to changing the FDA's culture and

the way the agency is structured; (3) the importance of improving information and communication about benefits and risks; (4) public–private collaboration so stakeholders can work together to accomplish shared goals; and (5) the agency's regulatory authority.

1

Introduction

Mission Statement of the U.S. Food and Drug Administration

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

SOURCE: FDA, 2007a.

The FDA regulates products representing roughly 25 percent of all consumer spending in the United States (Coalition for a Stronger FDA, 2007). Since 1992, when the Prescription Drug User Fee Act (PDUFA) was enacted, federal funding for the agency has diminished. Currently the FDA's Center for Drug Evaluation and Research (CDER) relies on the fees that it receives from the industry it regulates to fund its essential programs. At the same time, the issue of prescription drug safety has received widespread public and congressional scrutiny as a result of the highly publicized recall of the arthritis drug Vioxx because of its link to serious cardiovascular events, and more recently the increased risk of suicidal ideation among children being treated for depression with selective serotonin reuptake inhibitors (SSRIs). There is growing public concern about the ability of the current drug safety system to prevent future Vioxx-like events.

In light of this increased scrutiny, the FDA commissioned the Institute of Medicine (IOM) to convene an ad hoc committee of experts to conduct an independent assessment of the current U.S. drug safety system. A con-

sensus report with recommendations for the system's improvement—*The Future of Drug Safety: Promoting and Protecting the Health of the Public* (hereafter referred to as the IOM report)—was released on September 22, 2006. The IOM committee that produced the report identified four major vulnerabilities in the U.S. drug safety system: (1) chronic underfunding; (2) organization problems, particularly inadequate integration of pre- and postmarket data review; (3) a range of technical problems related to the insufficient quantity and quality of postmarket data and inadequate capability to systematically monitor the risks and benefits of drugs after marketing (an underlying issue being the use of modern information technology and informatics, and the human expertise and systems that enable their use); and (4) unclear regulatory authority and insufficiently flexible regulatory tools (IOM, 2007a).

Since the IOM report was issued, the FDA has taken a number of steps toward implementing the improvements recommended by the report (see Box 1-1). Like many government agencies, however, the FDA is financially

BOX 1-1 Highlights of the FDA's Response to the IOM Report

Strengthening the Science

Improving how the agency assesses risk is a central component of the FDA's efforts to improve pharmaceutical drug safety. The agency is operating in this area with the belief that new scientific discoveries and the expanded availability of new data sources for pharmacoepidemiological research are creating an emerging science of safety that will support a life-cycle approach to drug safety (e.g., by helping to build safety into products prior to approval and by targeting patients who are more likely to benefit from a given product). The FDA has already started or is taking steps toward initiating a pilot program to review systematically new safety data for new molecular entities (NMEs) approximately 18 months after approval; upgrading the electronic Adverse Event Reporting System* (AERS) and expanding safety database resources in an effort to strengthen epidemiological surveillance methods and tools; and employing several Critical Path Initiative** activities designed to improve safety evaluation and establish best practices for protocol reviews.

Improving Communication and Information Flow

Improving the FDA's communication and information flow is another key component of the agency's current efforts to strengthen the effectiveness of the U.S. drug safety system. The FDA believes that open and transparent communication among the agency, health care providers, and patients is paramount to the rapid and

strained by its existing responsibilities, and fully implementing the recommended improvements to the drug safety system would require significant financial commitments from the agency. Without providing a full analysis of the costs associated with its recommendations, the IOM report left open a number of questions about the ability of the agency to achieve the envisioned improvements. Attempting to implement the report's 25 recommendations without a substantial funding increase could further strain the FDA's resources, thereby making it more difficult to identify safety problems associated with new drugs, to monitor routinely submitted safety data, and to relay the resulting information to the public.

To address this gap, the IOM's Forum on Drug Discovery, Development, and Translation convened a 1-day symposium in March 2007 to consider the types and magnitude of resources needed to implement some of the most resource-intensive recommendations of the IOM report. The symposium's presentations and discussions were in most cases framed

effective dissemination of new drug safety information. Accordingly, the agency has already started or is taking steps toward strengthening the role of advisory committees, designing two pilot projects to evaluate different ways of involving Office of Surveillance and Epidemiology (OSE) staff in reviews and regulatory decision making, implementing new procedures for postmarket decision making, implementing a postmarket electronic tracking system, establishing a new advisory committee on communication, publishing an Internet newsletter on postmarket findings, and issuing new guidance on risk communication.

Improving Operations and Management

In its effort to improve its culture of safety throughout the life cycle of the products it regulates, the FDA is reinvigorating the senior management team of the Center for Drug Evaluation and Research and charging it with leading the organization in an integrated manner, enlisting external organizational consultants to address concerns about tensions between preapproval and postapproval staff and clarify their respective roles and responsibilities, and improving the way in which scientific disagreements are handled.

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*The Adverse Event Reporting System is a computerized information database that supports the FDA's postmarket safety surveillance program. It stores safety information for all approved drugs and therapeutic biologic products.

**The Critical Path Initiative is a national effort led by the FDA to prompt the development of new technologies and leverage those technologies to expedite the product development process for new drugs, biologic products, and medical devices.

SOURCE: Galson, 2007.

by selected recommendations from the report, and are summarized here in seven key areas:

- addressing the FDA's resource challenges;
- strengthening the scientific base of the agency;
- integrating pre- and postmarket review;
- enhancing postmarket safety monitoring;
- conducting confirmatory drug safety and efficacy studies;
- enhancing the value of clinical trial registration; and
- enhancing the FDA's postmarket regulation and enforcement.

The presentations and discussions included the types and magnitude of resources required in these areas. A session at the close of the symposium looked to the future, exploring prerequisites for revitalizing the U.S. drug safety system and the future of drug safety regulation. It should be noted that, while the IOM report suggested some organizational and cultural changes at the FDA, those recommendations were not a focus of the discussions during the symposium. Additionally, participants did not deliberate upon whether the FDA in its current form is properly configured to lead the efforts that were discussed.

2

Addressing the FDA's Resource Challenges

Recommendation on Resources from the IOM Report
The Future of Drug Safety:
Promoting and Protecting the Health of the Public

Recommendation 7.1 To support improvements in drug safety and efficacy activities over a product's lifecycle, the committee recommends that the Administration should request and Congress should approve substantially increased resources in both funds and personnel for the Food and Drug Administration.

The FDA today faces resource challenges in carrying out an expanding set of responsibilities. A central theme of the symposium was that these resource challenges must be addressed if the agency is to implement the recommendations of the IOM report.

HISTORICAL OVERVIEW[1]

At the beginning of the twentieth century, there were few regulations to safeguard foods, and no safety or efficacy standards for drugs or concoctions purported to be drugs. In 1906, public disclosure of unsanitary conditions in meat-packing plants as documented in Upton Sinclair's *The Jungle*, the use of poisonous preservatives and dyes in foods, and cure-all claims for worthless and dangerous patent medicines led to the enactment of the Federal Pure Food and Drug Act. This act authorized regulation

[1]This section is based on the presentation by Jane E. Henney, Senior Vice President and Provost for Health Affairs, University of Cincinnati Academic Health Center, and former Commissioner of Food and Drugs at the FDA.

of product labeling, prohibited the adulteration or misbranding of both foods and drugs, and ensured that drugs were consistent with national formulary standards.

During its 100-year history, food and drug regulation in the United States has evolved in response to a series of significant public health events. For example, the deaths of more than 100 people who had taken a new but untested sulfanilamide elixir led to the 1938 Food, Drug and Cosmetic Act, which established a requirement for premarket safety testing. When thalidomide (a sedative taken by pregnant woman to relieve morning sickness and aid sleep) caused thousands of European babies to be born with birth defects, Congress recognized the need for premarket safety and efficacy testing and passed the 1962 Kefauver-Harris Amendments. These amendments also called for the retroactive examination of all drugs introduced since 1938. Investigation of the nearly 3,500 drugs introduced between 1938 and 1962, as mandated by the Kefauver-Harris Amendments, was among the first of many increases in the scope of the FDA's regulatory responsibility that were unfunded by Congress. More recently, the Hatch-Waxman Act, enacted in 1984 to ease the entry of generic drugs into the market and respond to concerns about drug pricing, led to an increase in the number of applications the agency had to review.

Dr. Henney commented that while necessary for preserving and advancing public health, this continual expansion of the FDA's mandate has created financial challenges for the agency in the absence of corresponding funding. By the early 1990s, there was a substantial backlog of New Drug Applications (NDAs), and review times had increased. To quell growing industry frustration with the unpredictability of the FDA review process, as well as to meet the desperate need of AIDS patients for access to new therapies, Congress passed the Prescription Drug User Fee Act of 1992 (PDUFA).[2]

As noted in Chapter 1, recent public health events, such as the withdrawal of Vioxx and the association between the use of selective serotonin reuptake inhibitors (SSRIs) and increased risk of suicidal ideation in children, have renewed public concern about drug safety and the FDA's ability to regulate it. Public outcry resulting from these events has led FDA officials and lawmakers to reexamine the agency and the current legislation that governs its role in regulating drug safety. Currently, the 110th Congress is considering the reauthorization of PDUFA, as well as several legislative proposals to improve the U.S. drug safety system.

[2]PDUFA was enacted by Congress in 1992 and revised in 1997 and 2002. Under this program, the pharmaceutical/biotechnology industry pays fees to the FDA, and in return the FDA agrees to meet drug-review performance goals (e.g., reviewing NDAs and Biological License Applications [BLAs] within specified time periods).

CURRENT FDA FUNDING[3]

According to Mr. Thompson, the FDA has been chronically underfunded in carrying out its responsibilities for ensuring the safety of drugs, medical devices, and the nation's food supply. While the FDA is commonly viewed as the global gold standard for consumer protection, it faces stiff competition for scarce resources and over the past 20 years has been tasked to do far more with its limited resources. As noted in Chapter 1, for example, the Coalition for a Stronger FDA (www.fdacoalition.org), comprising consumer, patient, industry, and nonprofit groups, reports that the FDA regulates products representing roughly 25 percent of all consumer spending, yet it is expected to meet its expanding mandate with only a fraction of the budget of its sister public health agencies—the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH). In 1986, the FDA's budget was 97 percent of CDC's budget; by 1996, this figure was just 39 percent and by 2006, just 28 percent. Likewise, in 1986 and 1996, the FDA's budget was merely 8 percent of the NIH budget and by 2006, only 5 percent (Figure 2-1). Mr. Thompson noted that not only is the budget gap between the FDA and its sister agencies increasing, but the recent doubling of NIH's budget is likely to stimulate a flood of new drug discoveries and new development technologies that the agency will not be able to handle, given the difficulty of dealing with its current workload. He expressed concern that the agency's limited resources could slow the development and availability of new therapies for major diseases.

Dr. Henney argued that the FDA's challenge in overcoming a weakened drug safety system stems from its lack of the resources required to implement any major changes. She stressed that the FDA has been requesting funding in the form of user fees for postmarket activities since the early 1990s, yet these requests have been removed during budget negotiations; moreover, as specified in the PDUFA I and II legislation, monies derived from user fees were to fund only premarket review activities. Dr. Henney added that the FDA has consistently requested funding from Congress to implement state-of-the-art systems for monitoring the postmarket safety of drugs, biologics, and devices; however, those requests have likewise gone unmet. During authorization of PDUFA III in 2002, $71 million was earmarked to fund drug safety activities at the FDA; however, Congress rescinded much of that money and reprogrammed the remainder elsewhere in the agency. The FDA has experienced difficulty in receiving adequate funding not necessarily because appropriations

[3]This section is based on the presentations of Tommy Thompson, Honorary Chairman, Coalition for a Stronger FDA, and former Secretary of Health and Human Services, and Dr. Henney.

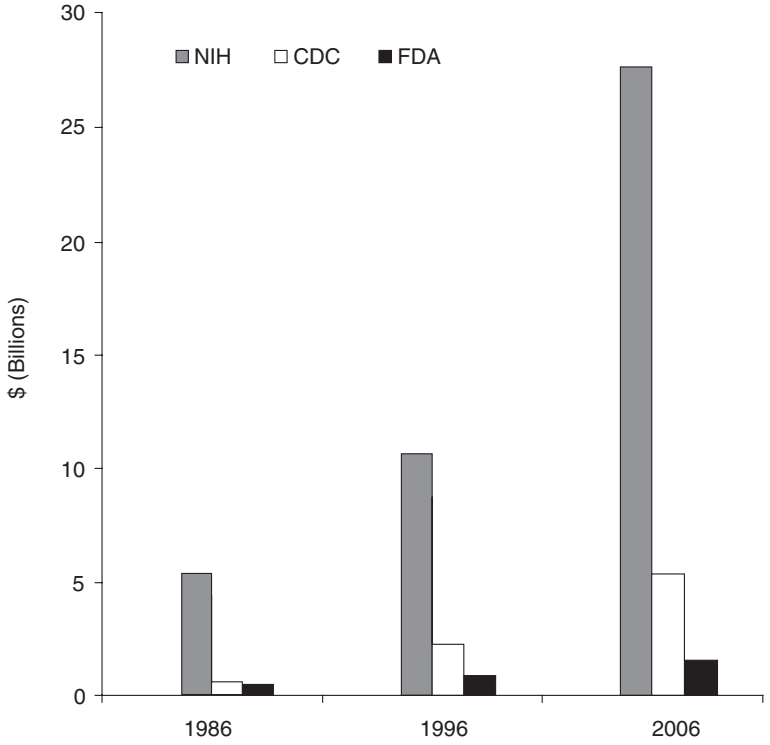

FIGURE 2-1 Comparison of NIH, CDC, and FDA budgets between 1986, 1996, and 2006. In 1986, FDA's budget was $416.7 million, CDC's was $429.4 million, and NIH's was $5.1 billion. In 1996, FDA's budget was $865 million, CDC's was $2.2 billion, and NIH's was $10.2 billion. In 2006, FDA's budget was $1.5 billion, CDC's was $5.2 billion, and NIH's was $27.7 billion.
SOURCE: Coalition for a Stronger FDA, 2007.

committees are unsympathetic to the agency's drug safety mission, but because the majority of resources are consumed by the agricultural sector. Dr. Henney concluded by expressing her hope that in fiscal year 2008, "both the administration and Congress will be mindful of the incredible needs of the agency."

INDUSTRY USER FEES

Mary Pendergast, President, Pendergast Consulting, asserted that since the authorization of PDUFA in 1992, Congress has increasingly relied on user fees rather than congressional appropriations to fund the

FDA, a situation that contrasts with the funding provided to CDC and NIH. She explained that since 1992, the FDA has doubled the number of staff performing new drug reviews from approximately 1,300 to 2,600, yet congressional appropriations paid for only 11 of those 1,300 new staff. User fees, originally representing about 30 percent of the FDA budget, now make up more than 50 percent, and PDUFA IV authorization may cause that figure to rise to as high as 80 percent or more. Not only is there active public debate about the FDA's accepting funding from the industry it regulates, but Dr. Henney asserted that the need for additional scientists to conduct the agency's drug safety–related activities is "more than obvious."

As discussed previously, Congress authorized PDUFA as a way to subsidize the FDA and help alleviate the backlog of NDAs. Following PDUFA, the FDA's congressional appropriations failed to keep pace with user fees. Further, Mr. Thompson remarked that while PDUFA has paid for nearly 1,300 new drug reviewers since 1992, over the last 10 years the FDA has lost some 1,000 staffers from the food, drug, and medical device safety programs not supported by PDUFA fees. Alta Charo, Professor, University of Wisconsin–Madison, and member of the IOM Drug Safety Committee, reiterated that the FDA regulates an extraordinary proportion of the products on the American market in the form of food, drugs, biologics, and medical devices, but operates with a budget that is not commensurate with this broad regulatory authority. Indeed, the committee responsible for the IOM report concluded that the agency's mission of promoting and protecting the health of the American public warrants more public funding in the form of general appropriations, as opposed to PDUFA funds. The committee further suggested that restrictions on the use of PDUFA funds be reduced to allow FDA management more flexibility in carrying out its mission. Echoing the IOM report, Ms. Pendergast encouraged Congress to increase appropriations for the FDA.

RESOURCE NEEDS

Dr. Henney noted that a late 1990s estimate of the resource requirements for strengthening the FDA's postmarket review system was in excess of $100 million.[4] However, this was an old estimate for a system less robust than that recommended by the IOM. Mr. Thompson commented that although the administration's 2008 budget request for the agency provides a modest increase for improvements in the right areas—

[4]Following the symposium, Dr. Henney specified that this $100 million included some one-time expenditures, such as new equipment, as well as annual increases in operations costs.

$11 million for drug safety, $7 million for medical device safety, and $10.6 million for food safety—funding for the agency remains insufficient. He noted that these increases will barely allow the agency to operate at last year's level, and will do little to make up for the steady loss of staff that the agency has endured for the past decade. Moreover, while the lack of national standards impedes the adoption of the information technology needed to improve the drug safety system, insufficient funding for the necessary purchases and upgrades would remain an insurmountable barrier even if such standards were in place.

As part of its call for a renewed public commitment to the FDA, the Coalition for a Stronger FDA is advocating a total of $175 million in increased appropriations for the agency for 2008 (over the fiscal year 2007 budget and over PDUFA IV increases).[5] This figure includes $40 million for drug reviews, $20 million for medical device programs, and $115 million for food safety programs. Among other improvements, the $40 million increase in the drug budget would enhance the agency's postmarket surveillance capabilities.

[5]In light of recent events regarding food safety, the Coalition for a Stronger FDA has begun advocating for a $310 million increase in appropriations for 2008 rather than the $175 million previously called for. This figure still includes $40 million for drug reviews and $20 million for medical device programs, but increases funding for food safety programs to $250 million.

3

Strengthening the Scientific Base of the Agency[1]

The committee that authored the IOM report was charged with reviewing the U.S. drug safety system—primarily the postmarket system—and providing recommendations for how to improve it. While the majority of the report's recommendations focus on postmarket safety, panelists emphasized that there are opportunities to improve safety throughout the drug development pathway. Gaining a better understanding of the safety profile of a drug and being able to discriminate more precisely among drugs within the same class before clinical testing begins would strengthen the drug safety system before a drug ever reaches the market. Postmarket safety is dependent upon a continuum of knowledge, including understanding of a drug's mechanism of action, as well as the information gained from clinical trials and epidemiological studies. Salient here are the drug safety recommendations in another (non-IOM) report, *Drug Safety and Drug Efficacy: Two Sides of the Same Coin*, which was based on feedback from the patient and clinical communities (Young et al., 2007). Key among these recommendations was the advancement of current scientific opportunities through the Critical Path Initiative (see below) in order to create a stronger, safer, science-based FDA. Dr. Sigal argued that "the new science" (e.g., molecular diagnostics and targeting)

[1]This chapter is based on the presentations of Ellen Sigal, Chairperson, Friends of Cancer Research; Janet Woodcock, Deputy Commissioner and Chief Medical Officer, FDA; and Garret FitzGerald, Professor of Medicine and Professor and Chair of Pharmacology, Department of Pharmacology, University of Pennsylvania School of Medicine.

will dramatically impact the future of drug safety and that advancing this science will require increased support.

In March 2004, the FDA released a document titled *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (FDA, 2004). The release of this document marked the launch of the agency's Critical Path Initiative, designed to revolutionize the drug development pathway. The FDA explained that, despite technological advances, the drug development community is still using the last century's methods to develop and test new drugs, biological therapies, and medical devices. In fact, a drug entering the Phase I clinical stage of development in 1985 was more likely to reach the market than one entering in 2000 (Lloyd, 2002–2003). During 1995–2000, an average of 1 out of 8 new compounds entering Phase I development reached the market, compared with an average of 1 out of 13 during 2000–2002. Thus between 1995 and 2002, the chance of reaching the market declined from 14 to 8 percent (Gilbert, 2003). One of the primary goals of the Critical Path Initiative is to increase the efficiency of the development process by building safety into products throughout their development life cycle.

RESEARCH NEEDED TO IMPROVE DRUG SAFETY: CURRENT FDA INITIATIVES TO EXPAND RESEARCH CAPACITIES

Dr. Woodcock emphasized the need for safety research and described the FDA's limited ability to take the lead in the conduct of such research. The type of postapproval research needed to improve drug safety extends well beyond the surveillance activities discussed in Chapter 5. Safety research is lacking in part because there is no particular body or entity charged with conducting it. While some research gaps can be filled through existing consortia, collaborations (e.g., with the National Institutes of Health [NIH] and the Centers for Education and Research on Therapeutics [CERTs]), and other mechanisms, the magnitude of the knowledge gap and the FDA's currently very limited capacity to fill that gap need to be recognized. The cost of a single large comparative safety study, for example, could exceed the entire appropriated budget of the Center for Drug Evaluation and Research (CDER). Considering that funding for CDER totals approximately $500 million for fiscal year 2007—of which about $240 million is from user fees, $225 million is base appropriations, and $16 million is dedicated for orphan drug research grants—less than a few million dollars remains to fund research (after infrastructure costs, salaries, document and adverse event processing costs, etc. are also subtracted).

Dr. Woodcock briefly outlined a broad spectrum of urgent safety science research needs, most of which focus on mechanisms, not just causal associations:

- *Drug toxicological research*—The system needs a way to predict and address drug toxicity questions before a drug reaches the market, as well as to address drug toxicity questions that arise after a drug has been marketed.
- *Predictive safety biomarkers*—The suite of biomarkers typically used for tracking during clinical trials, as well as after marketing, is inadequate, and most current safety tests are insensitive and nonspecific. Without good biomarkers, even skilled data mining of medical records will not provide adequate answers. The C-Path Institute's Predictive Safety Consortium, a group of 16 pharmaceutical firms based in Phoenix, Arizona, that shares and cross-validates new safety assays, could serve as a model for what the IOM report recommended.
- *Individualization of therapy*—While tests exist for drug-metabolizing enzymes (i.e., to identify slow metabolizers who are at risk for adverse events), outcome studies are needed to evaluate whether these tests really make drugs safer. Similarly, studies are needed to better understand how individuals vary with respect to target status (e.g., some people may have a slightly different molecular drug target that causes them to experience adverse events).
- *Abuse potential*—The animal model–based algorithm used for predicting the drug abuse potential of marketed drugs is very old and needs to be updated with better science.
- *Safety in special populations*—The FDA is one of the few organizations with a specific focus addressing many of the safety questions that pertain to special populations (e.g., women with asthma or pulmonary disease who take inhaled medications during pregnancy). Because of liability concerns, there is little involvement of the pharmaceutical companies in these activities.
- *Methodological research on how to use large databases and health records*—As discussed in Chapter 5, accessing data does not immediately translate into understanding the data.
- *Effective risk communication*—Research is needed to understand how information on adverse events and benefit–risk balance can be communicated effectively in a way that modifies prescriber behavior, and how safety information can be communicated effectively in drug advertisements.
- *Root causes of medication errors*—Research is needed to understand the causes of medication errors (e.g., mix-ups involving various strengths).[2]
- *New risk management programs being initiated by the FDA (and others)*—Research is needed to evaluate these programs.

[2]Medication errors were not discussed in detail at the symposium. Additional information on identifying and preventing medical errors is provided in the IOM's consensus report *Preventing Medication Errors* (IOM, 2007b).

Because of its limited ability to conduct the safety research outlined above, the FDA is promoting collaboration among stakeholders in the development of publicly available scientific and technical tools that all stakeholders could use to design safer and more effective products more efficiently. Dr. FitzGerald encouraged collaboration, arguing that FDA–industry partnerships would serve as a necessary component of an improved drug safety system. An enhanced training ground is needed to develop a workforce of scientists with an integrative understanding of drug safety evaluation, and Dr. FitzGerald proposed a Jet Propulsion Laboratory–style public–private partnership to fund this critical training (see the discussion in the next section). Barbara Alving, Acting Director, National Center for Research Resources, NIH, described the Clinical and Translational Science Award program funded by NIH, and gave several examples of current collaborative safety research efforts (see Chapter 5). For example, the University of Pennsylvania is working with the National Cancer Institute (NCI) to improve the capacity to report adverse events associated with cancer therapies.

BUILDING THE FDA'S CAPACITY FOR SCIENCE-BASED PREMARKET REVIEW

According to Dr. FitzGerald, a decade of revolution in drug discovery has resulted in more rationally selected drug targets and molecules directed against those targets than likely was ever anticipated. However, the number of new drugs emerging through the approval process has decreased (Figure 3-1). The current drug development model is not supporting drug discovery. Factors contributing to this "broken model of drug development" include pervasive concern about drug safety, with the "coxibs"[3] serving to illustrate the challenges faced by the U.S. drug safety system in balancing benefit and risk. In light of subsequent experience, it might be said that the traditional epidemiological drug safety approach detected merely "the tip of what turned out to be an iceberg." That is, while some studies detected a signal from the most selective drug (Vioxx) at a relatively high dose (50 mg/day), virtually all of the epidemiological studies conducted prior to the withdrawal of Vioxx from the market detected a signal at a lower dose (25 mg/day) or at any doses of Celebrex, and none detected a signal from Bextra. Yet placebo-controlled clinical tri-

[3]Merck & Co. withdrew rofecoxib (Vioxx), a drug for arthritis, from the market on September 30, 2004. Celecoxib (Celebrex) and valdecoxib (Bextra) are the only two COX-2 inhibitors ("coxibs") currently being marketed in the United States. However physicians now exercise extreme caution when prescribing those medications.

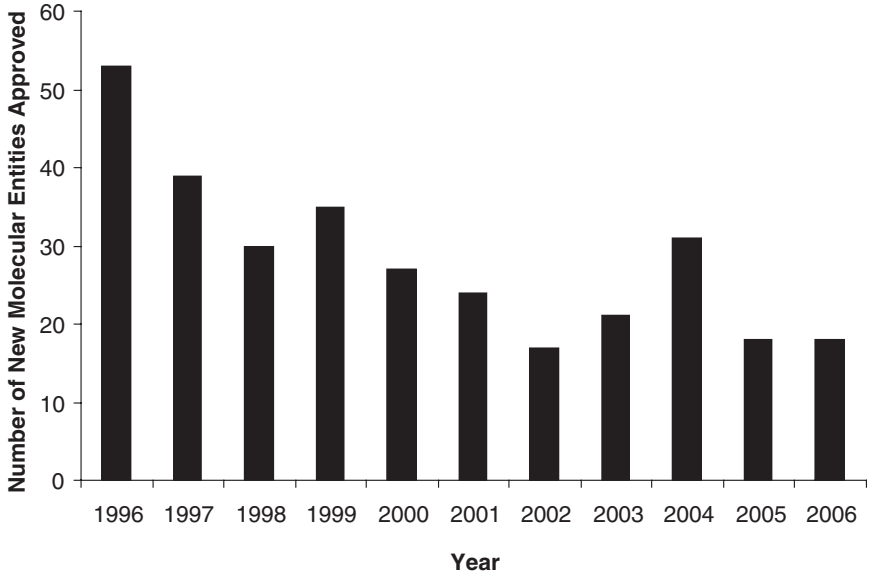

FIGURE 3-1 Number of new drugs approved in the last 10 years (1996–2006). SOURCE: Adapted by permission from Macmillan Publishers Ltd: Nature Reviews Drug Discovery (Owens, 2006 drug approvals: finding the niche), copyright 2007.

als designed to support new indications were able to detect safety signals for all three of these drugs. This example illustrates the importance of understanding the limitations of each scientific approach—human pharmacology, proof of principle in model systems, observational studies, and randomized trials—when drawing conclusions.

Dr. FitzGerald noted several lessons to be learned from the coxib experience:

- Industry had no incentive to invest in mechanistic research once the drugs had attained Investigational New Drug (IND) status.
- While the FDA may have detected and appreciated the relevance of the signals, limited resources made the agency poorly equipped to pursue them.
- The scientific results from both animals and humans poorly informed the epidemiological studies in terms of both design and analysis.

- Investigators did not appreciate the limitations of their respective approaches (i.e., epidemiological versus other types of approaches).
- The placebo-controlled trials that provided the final, compelling evidence were not designed to find that evidence, but to identify new indications.

In light of these lessons, Dr. FitzGerald suggested the need for "a radical new form of science that impinges on drug development in a way that is just as revolutionary as the changes that have occurred in drug discovery." This new science should have the capacity to (1) develop and project mechanism-based quantitative biomarkers from model systems to humans, (2) evoke phenotypic responses in humans to guide individualization in rational dose selection, and (3) harness unbiased technologies to select among molecules directed against a single target.

Dr. FitzGerald noted that in addition to the deficit of epidemiologists mentioned by Steve Galson, Director, CDER, FDA, and Hugh Tilson, Clinical Professor, University of North Carolina School of Public Health, there is a lack of experts with the integrated skill sets needed to pursue this new type of science (e.g., researchers capable of integrating molecular mechanistic science with clinical science and systems biology). The proposed Jet Propulsion Laboratory–style FDA–industry partnership could be used to address this deficit in human capital. Sites external to the FDA would serve as loci for mechanistic studies and the testing of proposed drug action hypotheses. One major roadblock to this type of initiative is funding, as neither the FDA nor NIH has money available for such an endeavor;[4] however, other organizations may be appropriate to spearhead the effort. The partnership could also leverage Clinical and Translational Science Awards and FDA investments in education and informatics. The integrative research challenges would be great, necessitating three or four external centers focused on major disease areas and extramural investments on the order of $10 million annually. Yet Dr. FitzGerald stressed that the investment would be worthwhile because it holds promise for speeding the development of safe and effective medicines, accelerating understanding of the factors involved in personalized medicine, and generally enhancing the benefit provided by the drug development industry.

Many of the symposium panelists expressed similar views on this issue. Gail Cassell, Vice President, Scientific Affairs, and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company, encouraged the audience to consider additional ways of increasing the availability of and interest in epidemiology training programs, perhaps in

[4]Currently NIH has only one training grant for pharmacoepidemiology; this grant has slots for only two researchers per year.

collaboration with the FDA and other organizations. Ellis Unger, CDER, FDA, said that the FDA would be interested in having a fellowship program similar to that of NIH. Finally, Dr. Tilson emphasized that before embarking on these programs, it will be important first to understand what competencies the scientists being trained need to have and then develop the appropriate training accordingly.

4

Integrating Pre- and Postmarket Review

Recommendations on Integrating Pre- and Postmarket Review from the IOM Report
The Future of Drug Safety:
Promoting and Protecting the Health of the Public

Recommendation 3.4 The committee recommends that CDER [Center for Drug Evaluation and Research] appoint an OSE [Office of Surveillance and Epidemiology] staff member to each New Drug Application review team and assign joint authority to OND [Office of New Drugs] and OSE for postapproval regulatory actions related to safety.
Recommendation 4.4 The committee recommends that CDER assure the performance of timely and scientifically-valid evaluations (whether done internally or by industry sponsors) of Risk Minimization Action Plans (RiskMAPs).
Recommendation 4.5 The committee recommends that CDER develop and continually improve a systematic approach to risk-benefit analysis for use throughout the FDA in the preapproval and postapproval settings.
Recommendation 4.13 The committee recommends that the CDER review teams regularly and systematically analyze all postmarket study results and make public their assessment of the significance of the results with regard to the integration of risk and benefit information.
Recommendation 5.4 The committee recommends that the FDA evaluate all new data on new molecular entities no longer than 5 years after approval. Sponsors will submit a report of accumulated data relevant to drug safety and efficacy, including any additional data published in a peer-reviewed journal, and will report on the status of any applicable conditions imposed on the distribution of the drug called for at or after the time of approval.

A major focus of the symposium was the integration of pre- and postmarket review. There are fundamental differences in the way data are collected and analyzed in the pre- and postmarket environments. Premarket data generally come from focused, randomized con-

trolled clinical trials; the scientists who review those data are well trained in evaluating them. Postmarket data are collected from a broader array of sources, including controlled clinical studies, as well as from single-arm observational studies that lack comparator data. Further, because it is difficult to determine how many people received a drug, benefit–risk calculations are complex, and therefore postmarket data are more likely to reflect safety problems than beneficial results. Like the scientists who review premarket data, those who review postmarket data are well trained in evaluating them. However, integration of the two datasets is difficult, and there have been reported tensions between reviewers in the FDA's Office of New Drugs (OND) and Office of Surveillance and Epidemiology (OSE). As Dr. FitzGerald said, "We are all conscious of the limitations that apply to other people's work. We are a little less conscious of those that apply to our own." Discussion of the integration of pre- and postmarket review was framed by the recommendations of the IOM report listed above.

OPERATIONAL CHALLENGES TO INITIATING A LIFE-CYCLE APPROACH TO DRUG REVIEW[1]

Dr. Tilson identified and discussed four major sets of operational challenges to the implementation of a life-cycle approach to drug review:

- *Methodological challenges*—Knowledge of product safety does not readily build over time and in a linear fashion; rather, gaining such knowledge is a complex and nuanced process. The methodological challenges include understanding how to determine a calculus for benefit-to-risk balance, how to recalculate benefit–risk balance on an ongoing basis (see IOM Recommendation 4.5), how to monitor effectiveness (Recommendation 5.4), and how to manage risk and evaluate Risk Minimization Action Plans (RiskMAPs) (Recommendation 4.4).
- *Human resource challenges*—Dr. Tilson echoed earlier comments stressing the need for more experts trained in epidemiology while also pointing out that improving the U.S. drug safety system will require an expanded workforce in all areas, not just epidemiology. He urged that a companion study be undertaken to consider not only who should do the work, but also where they should work (e.g., see Recommendation 3.4), what their competencies should be, what the mix of staffing should be, and what it will take to educate and train these new personnel, including the required academic infrastructure.
- *The need for evidence*—Benefit–risk data from preclinical, clinical, and postmarket spontaneous reports are all limited with respect to their

[1]This section is based on the presentation of Dr. Tilson.

predictive value and generalizability. The drug safety system needs better resources for capturing and analyzing population-based data and a way to harness the power of large, automated, multipurpose population-based databases (see Recommendation 4.13).

• *Organization challenges*—While many of the recommendations of the IOM report focused on the FDA and what that agency must do to improve the U.S. drug safety system, other stakeholders—including industry; health care organizations; and other government organizations, such as the Centers for Medicare and Medicaid Services (CMS) and the Agency for Healthcare Research and Quality (AHRQ)—have responsibilities as well. A culture of safety within the FDA will not be created simply by contracting with an outside organization, but will require the involvement of many outside partners, each with its own need to create a culture of safety. Moreover, the roles of industry, academia, and other organizations in the drug safety system need to be clarified and the best locus for work in each organization identified, and cross-organizational collaboration and public–private partnerships need to be developed, strengthened, governed, and funded. The Centers for Education and Research on Therapeutics (CERTs), created as the FDA's academic partner as part of the FDA Modernization Act of 1997, is an example of the type of public–private partnership (led by the FDA) needed to fulfill the agency's public health mission.

CURRENT INITIATIVES FOR INTEGRATING PRE- AND POSTMARKET REVIEW[2]

In response to the IOM report, the FDA provided a formal written statement detailing the programs and initiatives the agency will be employing to improve the U.S. drug safety system (see Box 1-1 in Chapter 1 for highlights of the FDA's response) (FDA, 2007b). The FDA's initiatives are geared toward effectively integrating the pre- and postmarket review programs, as well as strategically monitoring drugs throughout their life cycle so as to be able to determine their benefit–risk balance more accurately and relay that information to the public. These initiatives were discussed at the symposium within the context of Recommendations 3.4, 4.4, 4.5, 4.13, and 5.4 of the IOM report.

In response to Recommendation 3.4 (joint authority of OND and OSE for postapproval regulatory decisions), the FDA plans to (1) evaluate the feasibility of involving OSE staff earlier in the review process, a policy change that would be both labor- and resource-intensive; (2) evaluate

[2]This section is based on the presentations of Bob Temple and Ellis Unger, CDER, FDA, and Tim Franson, Vice President, Global Regulatory Affairs, Lilly Research Laboratories, Eli Lilly and Company.

models for more significant OSE involvement in postapproval decision making, including joint signatory authority (being considered for a pilot on a small scale); and (3) implement a process improvement initiative that will introduce a safety focus into OND's review divisions.

Dr. Temple expressed enthusiasm for the safety focus initiative in particular, partly because there is already a model for how it might work: the Division of Neuropharmacology, now the Division of Neurologic and Psychiatric Drug Products, has a safety group comprising about half a dozen clinical reviewers, most with epidemiological training, playing a role in both pre- and postapproval drug evaluation. In his view, it was the clear safety focus of the group and its regular meetings with OSE that led to fully cooperative interactions with OSE without the type of culture clash cited by the IOM report as part of the rationale for Recommendation 3.4. While some review divisions might not need a safety group this large, others would. Minimum personnel requirements under the current plan would be an associate director of safety and a safety regulatory project manager within each division. Dr. Franson cautioned that if designated OSE personnel are going to work with OND staff at the time of and after approval, OSE–OND processes and interactions must ensure timely review. Other relevant industry concerns from the perspective of Eli Lilly and Company include the need for common standards for benefit–risk criteria and review, and a way to ensure that all divisions across the FDA and all companies across the industry aspire to these standards. Additionally, Dr. Franson encouraged establishment of a process for reconciling disagreements.

One symposium panelist asked why the FDA response did not embrace the IOM recommendation regarding a formal and authoritative role for OSE staff in postapproval reviews and evaluations. Dr. Temple responded that while no one doubts the need for significant input from both OSE and OND, it is premature to reach a conclusion about what arrangement to this end would be best. Once pilot programs have been assessed, the agency will be better equipped to make that decision. Further, he emphasized that whoever has responsibility for sign-off, the postmarket review and assessment, as well as any revisions to labeling, must involve clinical judgment and understanding of both the risks and benefits of the therapy. Dr. Unger expressed his impression that there is not a great deal of clinical experience within OSE, and that OSE would need to expand its resources to include clinicians who understand both risk and benefit.

In response to Recommendation 4.4 (timely review of RiskMAPs), the FDA is planning to (1) identify risk management tools and programs and conduct assessments of the effectiveness of particular RiskMAPs and risk management and communication tools, using input from academia

and industry; (2) conduct annual systematic reviews and generate public discussion of the effectiveness of perhaps one or two RiskMAPs and one major risk management tool; and (3) post reports of these discussions on the Internet and hold a public workshop to obtain input on the prioritization of the plans and tools to be evaluated. Dr. Franson commented that this recommendation raises questions about how RiskMAPs will capture postapproval benefit information and incorporate benefit–risk over time. He stated that although virtually no health care entities currently capture postapproval benefit data, the system needs a plan for doing so. If risk data are the only information available, "all we are going to be talking about is problems." Additionally, Dr. Franson suggested that RiskMAPs might be renamed benefit–risk maps ("B/R maps").

In response to Recommendation 4.5 (establishment of a systematic approach to benefit–risk analysis), Dr. Temple remarked that the FDA already has a systematic approach to benefit–risk assessment, but added that it could be improved and better communicated. Benefit–risk analyses are complex and inevitably involve considerable judgment, and whether they can be compared on the same scale is unclear. That said, Dr. Temple noted that the FDA's assessment methodology and communication of that methodology could be improved. Dr. Franson supported this recommendation and proposed using the integrated summary of risk and benefit information that is submitted as part of every New Drug Application (NDA) as a springboard for subsequent benefit–risk assessments throughout the life cycle of the product. Dr. Unger explained that the FDA's formal written response to the IOM report described several initiatives aimed at improving quantitative benefit–risk assessment. He chose to highlight an initiative that began in March 2005—a postmarketing "Process Improvement Team." The goal was to identify best practices for improving safety processes that span the postmarket activities of OND and OSE so the two offices can better carry out their respective missions and enhance CDER's responsiveness to postmarket safety issues. The team formulated three key policy concepts: (1) create a postmarket safety entity within each OND review division (i.e., the safety focus initiative discussed above under Recommendation 3.4); (2) create an electronic postmarket safety tracking system[3] (this has been done, and each division is tracking its safety issues); and (3) initiate periodic, perhaps annual, assessments of recently approved new molecular entities (NMEs) (see the discussion of Recommendation 5.4 below).

[3]The electronic postmarket safety tracking system will replace individual systems that were office- and division-specific. This single system will ensure that all units within CDER have access to the same information and should help reviewers prioritize their work and monitor safety issues more effectively (FDA, 2007b).

In response to Recommendation 4.13 (systematic review and publicizing of all postmarket study results), Dr. Franson agreed that regular CDER review and dissemination of postapproval benefit–risk assessments would enable a more thoughtful approach to communicating benefit–risk information. Not only can a one-time adverse event frighten as much as warn the public, but the burden of proof for safety is usually only a single adverse event, in contrast to the randomized controlled study that is required to establish benefit. Drs. Galson and Unger reported that the FDA plans to publish a newsletter on the agency's website that will include summaries of the methods and results of postmarket drug reviews; given the proprietary nature of most predecisional information, however, this will be done on a case-by-case basis.

In response to Recommendation 5.4 (evaluation of all data on NMEs within 5 years following approval), the FDA initiated a pilot program to examine whether a periodic review of all data at 18 months postapproval can adequately identify potential safety issues and whether more frequent reviews are needed. Dr. Temple reported that this will be a resource-intensive effort, as it will involve reviewing all data sources (e.g., the Adverse Event Reporting System, further trials, literature reports) and will require using informed human judgment in addition to the data. The pilot program involves four NMEs, whose names the FDA has not yet made public. The reviews will be conducted consecutively using currently available staff and budgeted resources (i.e., review divisions and OSE). Dr. Franson stressed that it is important to look at the information accrued throughout a product's life cycle, not just through 18 months or 5 years. The above reviews raise questions about how standards will be set and what actions will be taken based on these reviews.

5

Enhancing Postmarket Safety Monitoring

Recommendations for Enhancement of the Postmarket Surveillance System from the IOM Report
The Future of Drug Safety:
Promoting and Protecting the Health of the Public

Recommendation 4.1 The committee recommends that in order to improve the generation of new safety signals and hypotheses, CDER [Center for Drug Evaluation and Research] (a) conduct a systematic, scientific review of the AERS [Adverse Event Reporting System], (b) identify and implement changes in key factors that could lead to a more efficient system, and (c) systematically implement statistical-surveillance methods on a regular and routine basis for the automated generation of new safety signals.

Recommendation 4.2 The committee recommends that in order to facilitate the formulation and testing of drug safety hypotheses, CDER (a) increase their intramural and extramural programs that access and study data from large automated healthcare databases and (b) include in these programs studies on drug utilization patterns and background incidence rates for adverse events of interest, and (c) develop and implement active surveillance of specific drugs and diseases as needed in a variety of settings.

Recommendation 4.6 The committee recommends that CDER build internal epidemiological and informatics capacity in order to improve the postmarket assessment of drugs.

A conclusion of the IOM report was that the FDA's current postmarket surveillance system is neither as comprehensive nor as systematic as it needs to be to detect, interpret, and analyze safety signals effectively and efficiently. The current system relies primarily on data collected through passive surveillance. These data are housed in the

Adverse Event Reporting System (AERS) database, which comprises three datasets: adverse event data reported voluntarily through MedWatch (generally by physicians, other health care practitioners, and consumers), mandatory periodically reported data from product manufacturers, and mandatory 7- and 15-day expedited report data from manufacturers following notification of a serious and unexpected adverse event. While this passive surveillance system may be capable of detecting rare serious adverse events, it has several limitations, including profound underreporting, biased reporting, and difficulties in attributing an adverse event to a specific drug. Additionally, when analyzing postmarket epidemiological data collected through passive surveillance, it is difficult to know just how many people have taken a drug (i.e., to determine a denominator), it is difficult to know how many events occurred (i.e., to determine the numerator) because of underreporting, and therefore it is difficult to conclude the rate at which an event would take place (e.g., event x would occur in 1 of every 100,000 persons).

Discussion at the symposium focused on how to enhance the current postmarket safety monitoring system by implementing the recommendations of the IOM report listed above, including upgrading AERS, developing an active surveillance system based on automated health care databases, and building internal epidemiological and informatics capacity at the FDA. Multiple panelists expressed the view that rejuvenating the passive surveillance system and augmenting it with an active system would be a specific feasible next step toward a stronger and more effective drug safety system.

FDA INITIATIVES FOR IMPROVING DRUG SAFETY MONITORING[1]

Revamping the AERS System

Dr. Dal Pan described several initiatives to enhance the FDA's current postmarket safety surveillance system. In response to Recommendation 4.1 of the IOM report (improving the generation of new safety signals and hypotheses), the Center for Drug Evaluation and Research (CDER) plans to upgrade to AERS II by adding functionalities that will allow for signal tracking, signal management, and data mining capability. Although the project is currently unfunded in the 2007 budget, the agency is evaluating system requirements and estimates the system could be operational in about 2 years once funded.

[1]This section is based on the presentation of Gerald Dal Pan, Director, Office of Surveillance and Epidemiology, CDER, FDA.

Enhancing the Agency's Use of Observational Data

In fiscal year 2008, in addition to initiating the development of guidance on best practices for observational pharmacoepidemiological studies, CDER plans to expand its intramural capabilities to use observational data by hiring additional epidemiologists trained in the methods of analytical observational epidemiology, statistical programmers, and properly trained statisticians capable of working on complex statistical and epidemiological issues. Pilot programs are currently being conducted with the Centers for Medicare and Medicaid Services (CMS) and the Agency for Healthcare Research and Quality (AHRQ) to examine the feasibility of using CMS data and to identify the practical barriers involved. Expanding this effort would require increased resources. Additionally, the FDA plans on issuing a request for proposals for evaluation of adverse event reporting and inviting outside groups to study such reporting so as to determine how to maximize its public health impact.

The Sentinel Network

Another agency-wide initiative being considered is the formation of a Sentinel Network.[2] In March 2007, the FDA sponsored a meeting of experts from all sectors involved in postmarket safety monitoring to discuss how the public and private sectors could work together to generate and use safety data most productively. Panelists noted the difficult informatics and methodological challenges to integrating public- and private-sector postmarket safety monitoring systems. Among the multitude of ways postmarket safety data could be used, the panelists agreed on three areas appropriate for active surveillance: (1) monitoring for specific adverse events related to a particular drug (based on pharmacological data and possible signals from clinical trial data); (2) monitoring for adverse events of concern with any drug, especially those events that have a low background rate and are often drug-induced, such as aplastic anemia or acute liver failure; and (3) monitoring for unexpected adverse events.

[2]The Sentinel Network would be a virtual, federated, electronic network designed to integrate existing and planned efforts to collect, analyze, and disseminate safety information on medical products to health care practitioners and patients at the point of care.

PUBLIC–PRIVATE PARTNERSHIP FOR DEVELOPING A NATIONAL ACTIVE SURVEILLANCE SYSTEM[3]

The FDA is planning initiatives aimed at responding to Recommendation 4.6 of the IOM report (developing an active surveillance system based on automated health care databases). These initiatives are aimed at the development of an active surveillance system that could be used to access data that already exist, looking for patterns of adverse events that may be related to specific drugs that would not be noticed through passive surveillance. However, Dr. Dal Pan noted that this effort will require additional funding, including significant resources for developing, testing, and validating such a system.

Dr. Dal Pan discussed CDER's pilot work with CMS, in conjunction with AHRQ, to gain experience with large databases that could potentially be useful for an active surveillance system and identify practical barriers to gaining access to such databases. While this work is currently focused on epidemiological analysis of specific drug safety questions (and not on active surveillance), FDA epidemiologists have learned much about the CMS system. Although CDER already works with four outside organizations, the FDA is interested in increasing this number (adding, for example, other federal agencies such as AHRQ, the Department of Veterans Affairs [VA], and the Department of Defense [DoD]), as well expanding the funding allocated to each organization. Dr. Dal Pan noted that this expansion would require increasing FDA staffing resources, as well as financial resources for contracts to manage the programs. The FDA is also interested in gaining broader access to drug utilization data (CDER already accesses a large number of such databases but does not have access to some types of drug use data, such as data on drugs administered in outpatient clinics).

Considerations for Creating an Active Surveillance System

Dr. McClellan suggested that, while many of the FDA-proposed changes to the postmarket safety monitoring system that were discussed by Dr. Dal Pan and that are included in current legislative proposals may be beneficial for improving the U.S drug safety system, they are still based primarily on drug-by-drug or manufacturer-by-manufacturer approaches.

[3]This section is based on the presentations of Dr. Dal Pan; Mark McClellan, Visiting Senior Fellow, AEI Brookings Joint Center for Regulatory Studies, and former Commissioner of Food and Drugs, FDA; Ronald Krall, Senior Vice President and Chief Medical Officer, GlaxoSmithKline; Richard Platt, Professor and Chair, Harvard Medical School and Harvard Pilgrim Health Care; and Alec Walker, Senior Vice President for Epidemiology, i3 Drug Safety, Ingenix.

The proposed changes do not involve the type of routine, systematic collection and analysis of use and outcome data necessary for the system to progress. For example, pending legislation supports the additional use of existing electronic population-based databases, but there is no comprehensive infrastructure in place to link the various databases. In short, while steps are being taken in the right direction, they are not enough.

Dr. McClellan pointed to several key questions that should be taken into account in planning a national active surveillance system to monitor drug safety. Will the proposed system have the greatest impact on reducing the likelihood of the recurrence of a drug-induced serious adverse event (for example, a Vioxx-induced myocardial infarction or increased risk of suicide due to a selective serotonin reuptake inhibitor [SSRI])? In particular, will the new system have greater capacity to identify potential risks and areas in which heightened surveillance might be warranted? Will it have greater capacity to identify safety signals and affected patients more quickly and reliably than the current system? Will it utilize existing capacity to do a much better job of identifying circumstances under which drugs are used differently than they were in clinical trials? Will it aid in targeting efforts toward the type of postmarket clinical studies needed when a safety signal is unclear? Will it accomplish these tasks without unnecessary costs?

Dr. Krall stressed that, although it is important for the FDA to play a role in the development of a national system for active surveillance of drug safety, the agency should not have sole responsibility for the effort. Moreover, it is important that each health plan, each company with an approved drug, and each regulatory authority not build its own system, a strategy that would be unnecessarily costly and inevitably increase disputes over whose findings were valid. Consequently, Dr. Krall and other symposium panelists proposed that such a system be built as a public–private partnership.

To address the issue of how to create a comprehensive rather than a piecemeal system, Dr. Platt argued that health plans—which serve large, defined populations and share many priorities with public health agencies—could play a substantial role in forming such a public–private partnership. Specifically, health plans' administrative and claims databases, enhanced by other data, such as laboratory test results, and with access to full-text medical records (especially to electronic medical records, which are becoming increasingly available), could serve as an important resource for active surveillance. Drs. Platt and McClellan both indicated that it should be feasible to create a system with access to information on 100 million persons, a number that would provide enough statistical power to answer important safety questions quickly. They further suggested that a database system of this size could have detected a signal of

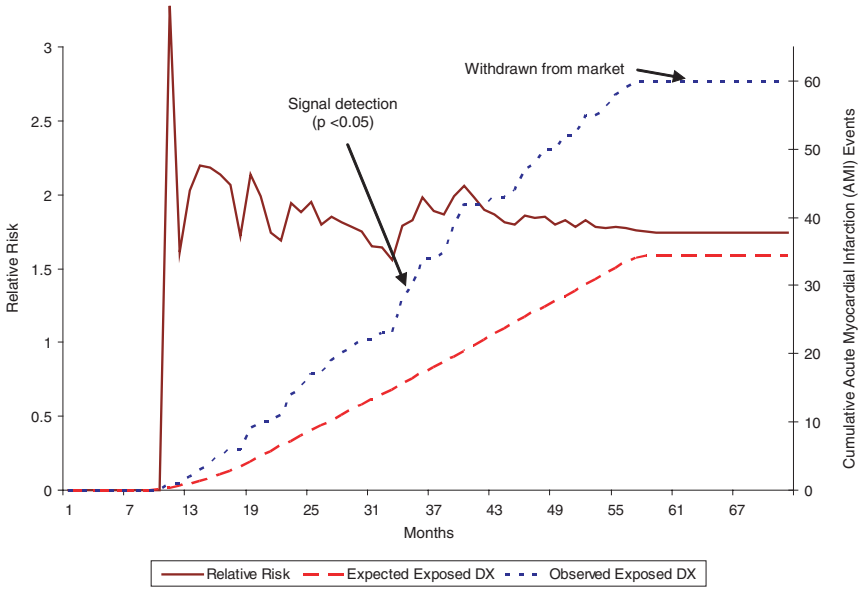

FIGURE 5-1 Monthly incidence of acute myocardial infarction (AMI) for Vioxx users.

Using data from the Health Maintenance Organization Research Network (HMORN) CERTs (Centers for Education and Research on Therapeutics) for a population of 7 million, researchers performed a retrospective month-by-month analysis of relative risk and occurrence of cumulative AMI events for new users of Vioxx in comparison with new users of naproxen. With a population of 7 million, signal detection for AMI occurred at 34 months. Dr. Platt argued that using a database of 100 million people would have enabled signal detection after 2 to 3 months.

NOTE: Comparator = naproxen. Adjusted for age, sex, health plan. DX = drug reaction.

SOURCE: Platt, 2007.

myocardial infarction risk among Vioxx recipients within a few months (Figure 5-1).

In addition to allowing for earlier detection, a large, defined population of 100 million (spread across multiple databases) could serve a critical role in follow-up. Dr. Platt used a recent public health example to demonstrate the limitations of an existing surveillance system, the Centers for Disease Control and Prevention's (CDC) Vaccine Safety Datalink database.

The question has arisen as to whether a meningococcal conjugate vaccine (Menactra),[4] approved in 2005, causes Guillain-Barre Syndrome (GBS), an inflammation of the peripheral nerves. Within 15 months following the vaccine's approval, there were 15 spontaneous reports of GBS occurring soon after immunization. However, the Vaccine Safety Datalink database has limited capacity and has data on only about 100,000 of an estimated 5.7 million distributed vaccine doses, while the background rate of GBS is only about 1.5 events per 100,000 person-years. Therefore, it would take several more years before the Vaccine Safety Datalink would be expected to detect a signal unless the excess risk were very great. A substantially larger population would make it possible to detect safety signals much sooner. Dr. McClellan proposed a postmarket system for detecting drug risks that would have four major components, all with FDA oversight: better data, public–private collaboration, a systematic strategy for analysis, and supplemental clinical studies.

Better Data

Dr. McClellan explained that the system needs a mechanism for pooling relevant data from public and private databases on prescription use and health outcomes in a much more systematic and ongoing way than is currently done or proposed. He suggested that the infrastructure built for this purpose should make use of private health plan, Medicare, and VA/DoD data. Dr. Platt noted that data sources should include health plans' claims data, which would exist in standard format files and be preprocessed to allow rapid queries. The system should allow access to full-text medical records, as needed, and other data, such as laboratory test results, as they become available. Dr. Walker added that everything that is paid for through the health insurance industry is recorded in its databases. These data could be organized into a chronological file and enhanced and linked with other databases, including those containing pharmacy claims data, physician and facility claims data, laboratory test results, and demographic and other consumer information (Figure 5-2). The data could then be accessed in real time and in a web-based, interactive manner. Multiple panelists agreed that using enhanced claims data, including links to full-text medical records, would be an efficient way to conduct postmarket monitoring on a real-time basis.

[4]Menactra was licensed to prevent meningococcal disease (meningitis), an infection of the membranes that surround the brain.

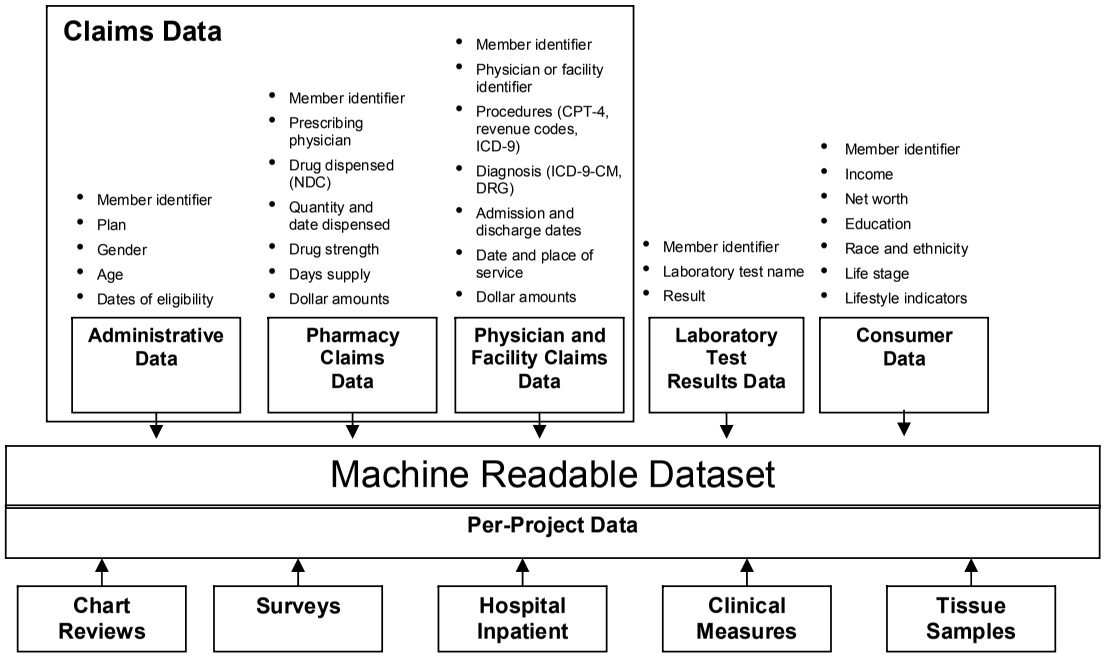

FIGURE 5-2 Proposed composition of an enhanced claims database.
NOTE: CPT-4 = *Current Procedural Terminology*, 4th Edition; DRG = Diagnosis Related Grouping; ICD-9 = *International Classification of Diseases*, 9th Revision; ICD-9-CM = *International Classification of Diseases*, 9th Revision, Clinical Modification; NDC = National Drug Code.
SOURCE: Walker, 2007. Copyright 2007 i3, used with permission.

Public–Private Collaboration

While the FDA is very interested in having available the type of enhanced infrastructure for postmarket safety data described above, the agency has neither the resources nor a plan to implement it. Therefore, Dr. McClellan suggested that the acquisition of better data and the implementation of a systematic strategy for analysis will require additional support for postmarket surveillance, the development of a comprehensive implementation plan, and effective public–private collaboration to carry it out. Dr. Platt described the developing Centers for Education and Research on Therapeutics (CERTs) Health Plan Consortium for Public Health, whose goal is to "improve the safety and safe use of marketed vaccines and prescription drugs by studying their use in large populations of health plan members." The consortium could be an important component of a national active surveillance system that would include other data sources. As Dr. Tilson noted, the CERTs were created under congressional mandate and have robust processes that already make them good hosts for a public–private partnership. Plans are for partners in the consortium to include health plans, federal agencies, industry, foundations, the academic community, and the public. Federal public health agencies (e.g., CMS, AHRQ) are already collaborating with the FDA on stimulating analyses of this type, the private sector has expressed willingness to help, and academia must be engaged. The FDA currently has postmarket surveillance contracts with medical record–linked claims databases from the Health Maintenance Organization Research Network (HMORN), United Healthcare, Tennessee and Washington State Medicaid, and the VA, which collectively cover about 26 million persons. However, Dr. Platt argued that these systems are insufficient and should also include databases from Medicare (Parts A, B, and D), Medicaid from most large states, and private health plans.

As envisioned by Dr. Krall, the public–private partnership would (1) have the mandate to carry out surveillance on behalf of all stakeholders (health systems, companies, and the FDA); (2) acquire data, develop analysis methodology, and conduct and report the results of analyses, with the regulatory authority and companies interpreting the results as they do today; and (3) operate transparently, with the FDA having the right of first call on the partnership's analytical capability. Drs. Platt and McClellan both agreed that transparency and confidentiality are critical to establishing a public–private database for use in active surveillance of drug safety. Dr. McClellan added that if non-FDA partners were to help in identifying priority questions and mechanisms for answering those questions, this would have to be done through a transparent process.

Systematic Strategy for Analysis

Once the necessary infrastructure has been established, the new system will need a strategy for conducting analyses. While this strategy could be based on expert guidance, Dr. McClellan suggested that the FDA should continue to have a central role in the effort as it will be making ultimate judgments about risks and benefits for labeling and other purposes. Dr. Krall proposed that the system should have the capability to (1) focus on the period of uncertainty following approval; (2) detect classic "drug list" events, drug- or class-specific events, increases in events with large public health consequences, and unsuspected events; (3) confirm benefit or effectiveness; (4) serve as a source of hypothesis-driven studies to validate signals; and (5) provide quantitative, real-time output. Dr. Platt asserted that prospective evaluation for "anticipated" adverse outcomes should be the primary objective of the system. "Anticipated" would include the FDA's list of Designated Medical Events, which has been responsible for a large fraction of product withdrawals, plus other outcomes of concern because of the chemical class involved or events observed during preclinical evaluation. When asked whether more could be gained from developing and refining data mining methods that would point in unexpected directions and help in formulating the right questions, Dr. Platt agreed that this should be one of the goals of postmarket surveillance. However, the science here is much less well developed, and he maintained that the first investment should be in building a system that can deal rapidly with problems there is reason to expect.

Another question was raised about the extent to which the system would be used to go beyond signal detection and enable the quantitative evaluation of benefit. Dr. Krall replied that initially, the new system would complement existing systems by providing crucial information that is currently lacking; eventually, however, it would enable an enhanced understanding of benefit and risk. Dr. Walker added that, although epidemiologists traditionally avoid benefit studies because of their greater potential for confounding, the data needed for the purpose do exist.

Several panelists discussed the important need to study off-label use of prescription drugs. When the FDA approves a drug, it does so based upon the risk and benefit data collected on the drug when it was tested in the indicated population. Thus if a drug is used for other than what is specified on the label (i.e., off-label), the drug may not have been tested for safety and efficacy in that situation. Dr. Alving stated that off-label use should not necessarily be prohibited. However, she stressed that if drugs are to be used off-label, it is important to have available a public database that can be used to report and track those data. Dr. Walker added that such a database should also collect data on concomitant medicines, as

they may have an impact on drug reactions. A public–private partnership could play a large role in capturing and analyzing data for off-label use.

A final question was related to psychiatric medications and why investigation of their safety lags so far behind that of other, nonpsychiatric drugs. Dr. McClellan responded that this is just such a problem that a large-scale effort could address. Psychiatric drugs are often used in patients with comorbid conditions, for off-label conditions, and over long periods of time. These factors are difficult to address in premarket studies. The postmarket monitoring effort discussed here would provide a way to learn more systematically about these types of drugs.

Supplemental Clinical Studies

Dr. McClellen suggested that even if the system has access to good population-based data, not all questions would be answerable with observational data alone. Consequently, resources would still be required for postmarket clinical studies focused on cases in which detection of safety signals is insufficient for resolving whether a drug causes an elevated risk of an adverse event.

Active Surveillance Prototypes

According to Dr. Walker, a prototype of the kind of surveillance system envisioned, though on a much smaller scale, already exists. This prototype, developed by i3 Drug Safety using United Healthcare's population of 12 million, is "a general-purpose medical data warehouse built on a health insurance transaction platform" and incorporates diverse data sources. The prototype was up and running about 6 months after its development. While it covers only 12 million people, it is scalable to datasets of any size. The retrieval time is only about 1 or 2 minutes, and a database of 100 million persons would probably not take much longer. Dr. Walker emphasized that, while i3's prototype is not the last word in automated prescription surveillance, it demonstrates that the principal obstacles to developing such a system are not technological.

Dr. Krall described in some detail a prototype system validated by GlaxoSmithKline. The system uses two health care databases (totaling approximately 45 million persons with more than 22 months of exposure) and a methodology for comparing terminology between the two databases. While the analyses are not simple, each requiring substantial custom design, Dr. Krall argued that it should be possible (at least for classic drug-related events) to develop a methodology that would be applicable to most drugs, would be repeatable over time, and could serve as the foundation for a systemwide surveillance system.

Drs. Walker and Krall were asked to comment on what they thought would be necessary to scale up the efforts they described in their presentations. Dr. Krall replied that the greatest need is a mechanism for drawing the various stakeholders together to coalesce their common interests, ideas, and approaches.

Implementation and Funding

Dr. Platt suggested that remarkably few resources would be needed to establish the proposed public–private partnership for surveillance of drug safety. Dr. McClellan also stated that only limited additional funding would be needed, noting that all the required building blocks are in place for a postmarket infrastructure to be feasible now. Dr. Platt pointed to AHRQ, the FDA, and CDC as being in a position to initiate the necessary dialogue, with CMS being a principal partner. Dr. McClellan also identified the CERTs, subject to FDA guidance, as a possible convener and a good home for the public–private partnership as they are already conducting analyses on some of the salient data, and there is considerable interest in expanding those efforts. With regard to time, Dr. Platt said that it is not unreasonable to expect to have at least a rudimentary system covering 100 million people up and running within a year. Electronic databases of private plans already collectively handle well over 100 million people annually. Additionally, the FDA is using electronic Medicare data (Parts A and B) on a pilot basis, and some state Medicaid programs are contributing data to similar efforts. Together, these various private and public databases encompass more than 100 million persons that could form the base for a single, comprehensive surveillance network.

Dr. Walker suggested that the concerns of stakeholders accustomed to controlling the flow of data are the main obstacle to the implementation of the system. Dr. Platt noted, however, that in his experience, the owners of the data are willing to have the data used for important public health purposes as long as they can be confident that these are the only uses involved. He emphasized that the system would be a federated one and that no single entity would have ownership of it. He pointed to CDC's Vaccine Safety Datalink as a pioneering effort in this regard: all the databases that contribute to that system reside separately but contribute to unified analyses.

The proposed public–private partnership would require funding, including both core funding to build the necessary infrastructure and develop routine postmarket surveillance, and separate funding for individual projects to follow up on and confirm potential safety signals. Dr. Krall and Gretchen Dieck, Senior Vice President, Safety and Risk Management, Pfizer, Inc., proposed that the partnership should accept both public

and private funding. Earlier in the symposium, Dr. Henney had alluded to decreased public confidence in the FDA because of its reliance on industry user fees. While multiple panelists discussed the need for mixed funding for the public–private partnership, several stressed the importance of a transparent process that could help build pubic confidence despite the reliance on private financing.

While such an endeavor would be costly, Dr. McClellan stressed that the alternative would be more costly still. Once the infrastructure was in place, the incremental cost of conducting further studies and the value of having a more comprehensive population database available for conducting analyses would translate into a much higher return on investment than would be obtained if the system continued to collect and analyze adverse event data on a drug-by-drug and manufacturer-by-manufacturer basis. Not only would a comprehensive approach be less expensive, but it would also generate better information and better-targeted and timelier postmarket clinical studies. And while statistical methods need to be refined to handle the complexity of the dataset and analyses, Dr. McClellan argued that if additional support were provided, existing resources could be leveraged so that work using the system could begin with relatively little delay.

Dr. Walker argued that cost is relative. For example, the cost of implementing the envisioned system pales in comparison with the billion dollars being spent to renovate the Hard Rock Café in Las Vegas. Moreover, as a joint public–private effort, the system could draw on the infrastructure already in place. When asked directly about ongoing costs for maintaining the system, Dr. McClellan said, "I think the low tens of millions is probably a good figure." He noted that this money is already being spent and that the enactment of the Prescription Drug User Fee Act (PDUFA) IV and pending drug safety legislation would result in more funding for postmarket surveillance activities. He stressed that just about every major stakeholder group has expressed the desire to see the further development of such a system, that the necessary technical capabilities exist, and that Congress is interested in addressing the problem. Drs. Platt and Krall stated that while the precise amount of funding required is unclear, they believe it is modest, agreeing that it is along the lines suggested by Dr. McClellan.

Governance

In addition to quality data, an accepted methodology, qualified expertise, and funding, a national surveillance system would require a governance mechanism. Because the system would be based on health claims data and medical record information, it would need to provide continued

assurance of patient confidentiality and appropriate use of the data. Panelists voiced concerns about issues of privacy, confidentiality, and informed consent with respect to data from clinical trials. Dr. Platt responded that this type of work has been conducted for several years now, and always with the full approval of Health Insurance Portability and Accountability Act (HIPAA) privacy boards and institutional review boards (IRBs). Dr. Walker added that there is more to be done, however, with respect to reframing the work in a public health context rather than as a research activity, in a way that engages the public and health care providers and familiarizes them with the idea that information derived from routine health care delivery can and should be used to improve health care itself. Additionally, he asserted that HIPAA works partly because it operates according to a clear set of rules. The new system would need a new set of rules for the use and interpretation of claims data so people would not be left wondering, for example, whether something is reportable. Once those rules had been formulated, there would likely be greater acceptance of the proposition.

Limitations of Automated Databases as a Resource for Drug Safety Studies[5]

Dr. Dieck discussed the benefits as well as the limitations of automated databases. She agreed with some of the earlier presenters that rapid epidemiological studies involving real-world data on large samples are the cornerstone of postmarket safety monitoring, and that they could also serve as an important resource for estimating background rates and drug effects. She cautioned, however, that there are issues to consider when thinking about using automated databases as a resource for drug safety studies:

- Scientific safety rather than available data should drive the process. Health care claims data are not collected for research purposes and therefore may be limited. They are collected for such purposes as billing and reimbursement, and the potential lack of specificity in the coding of public-use data could make them less sensitive and consequently less useful for addressing some safety issues.
- The data may not be collected uniformly across sites (although this is a technical issue that can be resolved), and some diagnostic or procedural codes may be inconsistent or rarely used. This point was also mentioned by Dr. Krall, who when discussing GlaxoSmithKline's active surveillance databases said that the company had devised a way to com-

[5]This section is based on the presentation of Dr. Dieck.

pare terminology used in two different databases. It is important to note that while this issue of developing common data standards and controlled vocabularies was not discussed in depth during the symposium, combining databases without standardization is nearly impossible and is a major challenge that must be overcome.

- Public-use data may derive from skewed populations that make the data problematic for answering certain types of safety questions. For example, VA data, as rich as they may be, are for a military population, Medicare data for the elderly, Medicaid data for those on government assistance, and heath maintenance organization (HMO) data for the working healthy.
- The ability to adjust for important confounders, such as sociodemographic factors, health behaviors, and use of over-the-counter products, is limited.
- Safety end-point data need to be validated with medical records. While some automated databases do this very well, others do not.
- In some instances, a medicine may not be reimbursable (e.g., Viagra), or its use may be restricted (e.g., COX-2 inhibitors), with different types of patients taking different drugs (e.g., COX-2 inhibitors versus nonsteroidal anti-inflammatory drugs [NSAIDs]). Thus limited claims data will be available for these drugs.
- The potential exists for channeling bias. For example, if people gained weight with their antischizophrenic medication, they may have been channeled toward Geodon because of its weight-neutral effects. However, because those individuals had previously gained weight, they would now generally be more susceptible to normal health risks as well as to the risks of Geodon.
- Many postmarket safety studies involve specialized populations that would likely not fall under the purview of a public–private partnership that relied on an automated database as its cornerstone. Pfizer's postmarket safety studies (some completed, others ongoing), for example, are each in some way specialized. One such effort is the Exubera VOLUME LST study, an 8-year trial that started in the third quarter of 2006. This study involves looking at abnormalities of lung function, something not normally included in electronic medical records or reimbursement codes since many such patients are asymptomatic.

Examples of Successful Public–Private Partnerships[6]

Dr. Alving described the public–private partnerships already being forged through Clinical and Translational Science Awards (CTSAs), which

[6]This section is based on the presentation of Dr. Alving.

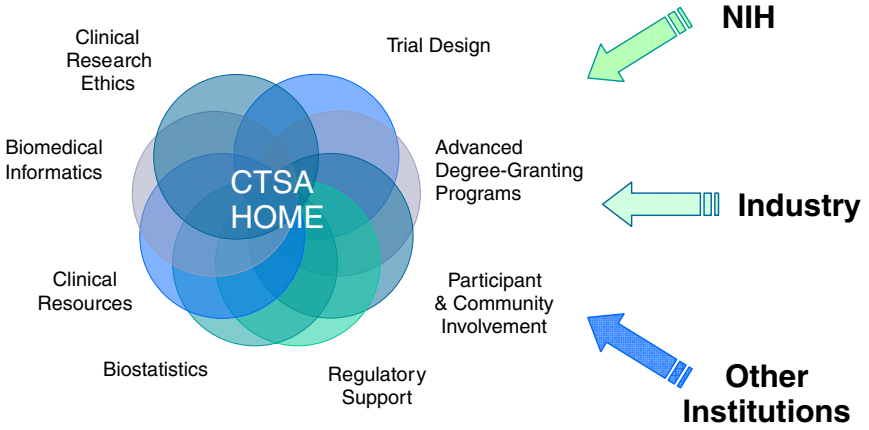

FIGURE 5-3 NIH's Clinical and Translational Science Awards: A home for clinical and translational science.
SOURCE: Alving, 2007.

she identified as one of the most significant outcomes of the National Institutes of Health (NIH) Roadmap (Figure 5-3). The goal of the CTSA program is to accelerate and encourage the translation of basic biomedical discoveries into clinical science and medical practice. CTSA centers serve as a means of removing interdisciplinary barriers and encouraging creative, innovative approaches to solving complex medical problems. The centers offer advanced degree-granting programs in clinical and translational science; involve investigators from a wide range of medical, veterinary, and other biomedical disciplines; and interact with the FDA, industry, and other institutions.

The ultimate objective is to build a national consortium and forge new partnerships with public and private health care organizations. CTSAs will be distributed among more than 60 academic health centers by 2012, with the first awards having been granted in 2006. Already, interdisciplinary pilot programs are under way at, for example:

- Duke University, where advanced informatics and health service delivery methods are being used to translate bench–bedside findings to populations;
- University of California–San Francisco, where opportunities are being pursued in conjunction with the San Francisco VA and Kaiser Permanente;

- Oregon Health and Science University, where investigators are developing new informatics capabilities to partner with Kaiser Permanente, the Northwest Center for Health Research, the Oregon Rural Practice Research Network, and the Portland VA Medical Center;
- University of California-Davis, where new community research centers are being developed to expand efforts addressing minority and medically underserved populations; and
- University of Pennsylvania, where robust efforts in cancer bioinformatics (CA BIG) are being led by the National Cancer Institute to improve the informatics capacity to report adverse events.

In addition to the partnerships cited above, NIH CTSA teams are being created to support efforts to develop new informatics capabilities. Additionally, the CTSA program has developed robust working relationships with the FDA and CMS. Updated information on the program is available at the CTSA website (http://ctsaweb.org).

Summary

Dr. McClellan summarized the discussion of a public–private partnership for the development of a national active surveillance network to monitor drug safety. He stated that it is "an issue whose time has come because . . . there is uniform agreement that this approach is feasible . . . and FDA reform is front and center in the legislative agenda and in the public agenda." He cited interest at the highest levels within the Department of Health and Human Services in building a much more interoperative electronically based health care system, and suggested that creating a public–private postmarket drug safety monitoring system linking multiple existing databases is a leading edge of that effort.

6

Conducting Confirmatory Drug Safety and Efficacy Studies[1]

Recommendations on Public–Private Partnerships for Conducting Large Research Studies from the IOM Report
The Future of Drug Safety:
Promoting and Protecting the Health of the Public

Recommendation 4.3 The committee recommends that the Secretary of HHS [Health and Human Services], working with the Secretaries of Veterans Affairs and Defense, develop a public-private partnership with drug sponsors, public and private insurers, for-profit and not-for-profit 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. Congress should capitalize the public share of this partnership.

The IOM report noted that the FDA is limited in its ability to conduct the larger studies sometimes necessary to follow up on signals and reduce uncertainty associated with the benefits and risks of approved drugs. Accordingly, the report recommended the development of public–private partnerships to prioritize, plan, and fund confirmatory drug safety and efficacy studies (Recommendation 4.3).

The ideas expressed in this session, particularly with respect to Recommendation 4.3, dovetailed with those put forth in the previous session, supporting the necessity of and readiness for a public–private collaborative effort to improve postmarket safety and efficacy monitoring. Whereas the focus of the previous session was on the capacity of a linked

[1]This chapter is based on the presentations of Dr. Dieck and Robert Califf, Director, Duke Translational Medicine Institute, Professor of Medicine, and Vice Chancellor for Clinical and Translational Research, Duke University Medical Center.

public–private surveillance system to improve the detection of safety signals, panelists went a step further during this session by considering the potential of such a system to be used not just for detection, but also as a tool for addressing the broad spectrum of safety science research questions that arise over the course of a drug's lifetime. A collaborative effort to this end would be more cost-effective than multiple isolated efforts, as presenters in the previous session emphasized with regard to detection. It would give researchers access to a larger volume of information resources, and it would generate information of value to multiple stakeholders.

Dr. Dieck elaborated on earlier discussions regarding the use of public–private partnerships for establishing and conducting active surveillance studies. While industry is interested in supporting such partnerships because of their potential to lower the costs associated with larger safety studies and provide better benefit–risk information, costly studies for specialized populations unlikely to be included in an automated, linked database would still be necessary. Such specialized postmarket safety studies are expensive, costing from $500,000 to $110 million (i.e., the Exubera VOLUME LST study).

Dr. Califf identified two fundamental changes necessary to establish a large public–private partnership to prioritize, plan, and organize funding for confirmatory drug safety and efficacy studies of public health importance. First, stakeholders need to be proactive and take responsibility for establishing such a partnership. These stakeholders include pharmaceutical, biotechnology, and medical device companies; government agencies (the Department of Health and Human Services [DHHS], the National Institutes of Health [NIH], the Agency for Healthcare Research and Quality [AHRQ], the Centers for Medicare and Medicaid Services [CMS], and the Department of Veterans Affairs [VA]); private health plans; academic health centers (which have largely discouraged this kind of activity in the past); and consumer groups. Dr. Califf suggested that bringing these groups together would have not just an additive but a synergistic effect, particularly with regard to workforce standardization and interoperability. Second, it will be necessary to modernize the "incredibly inefficient" clinical research system to eliminate wasteful spending and build efficiency into the system.

Dr. Califf echoed statements made earlier by Drs. Krall and McClellan about what will happen if public–private partnerships and the associated lower costs are not achieved. If the various stakeholders developed their own systems, the resulting bureaucracy would be highly complex; moreover, it would be dangerous to have every health care organization publicizing results and making coverage decisions based on its own limited datasets. Dr. Califf suggested that the IOM conduct a study on the cost of developing such a partnership, hypothesizing that the total cost

would be less than the cost of having multiple separate entities, as argued by Dr. McClellan.

A public–private partnership would do more than save money, stressed Dr. Califf. Given the reality that every drug has both benefits and risks, along with the heterogeneity of individual responses, the system risks shelving good products in the absence of a systematic way of responding to and putting into context the signals detected by an automated surveillance system. A public–private partnership would minimize that possibility by setting priorities and, through consensus, deciding on the most important safety research questions. The partnership could also deal proactively with the design of studies intended to clarify putative safety signals. These studies could include larger surveillance studies, more focused prospective registries, pragmatic trials, or mechanistic laboratory-based studies to determine biological mechanisms. Dr. Califf proposed that industry be rewarded for prioritizing in the public interest, and that government agencies focus on prioritizing according to impacts on public health. The hope is that a public–private partnership would be nimble enough to respond to the needs of the public while avoiding the types of bureaucracy that create rules and expensive procedures with the expectation that "armies of people following processes" will lead to better research answers. Rather, the bureaucracy should be efficient, focused on standardizing data collection and nomenclature and optimizing the yield of useful research results per dollar spent. Failure to develop common data standards and controlled vocabularies would make it exceedingly difficult to combine datasets, which is critical to integrating databases.

With respect to cost, Dr. Califf suggested that while a new system would require investment, much of the current $90+ billion being spent each year on biomedical research and development worldwide is being spent unnecessarily. He pointed to the 2005 time-adjusted estimated cost of drug development—$1.318 billion ($439 million preclinical, $879 clinical) (Figure 6-1)—remarking that some of that expense is due to the complexity of the billing system. For example, when a patient comes to the Duke health care system for clinical care and then is also enrolled in a research study, organizing the billing becomes extremely complicated. Indeed, at Duke the time of an estimated 1,200 people is devoted to billing. Additionally, some of the high cost of clinical trials can be attributed to the way they are conducted. A typical industry-funded outcome clinical trial costs on the order of $100–600 million, a figure that could be reduced by simplifying protocols, developing interoperability in data management, and reducing redundancy.

Concluding, Dr. Califf emphasized that the way to establish the envisioned public–private collaboration is through federated informatics: linking existing networks so that clinical studies and trials can be con-

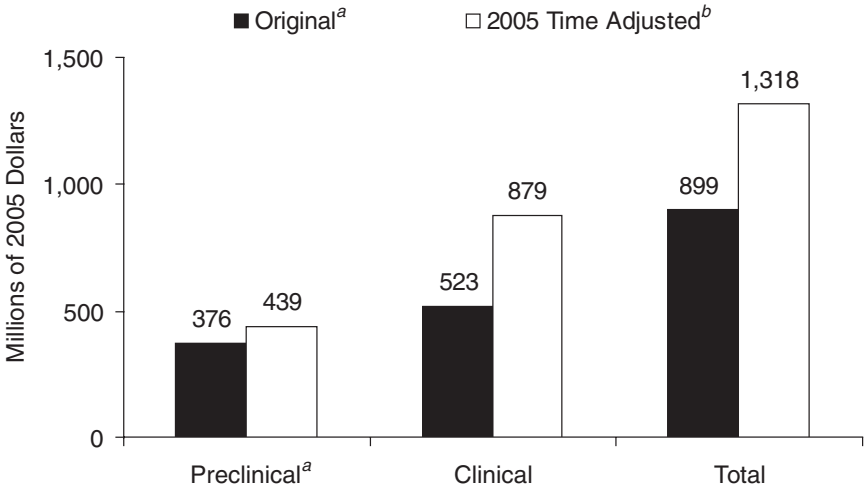

FIGURE 6-1 2005 time-adjusted comparative preapproval capitalized cost estimate per approved new molecule.
[a] All research and development costs (basic research and preclinical development) prior to initiation of clinical testing.
[b] Based on a 5-year shift and prior growth rates for the preclinical and clinical periods.
SOURCE: Adapted from Dimasi and Grabowski, 2007. Copyright 2007, John Wiley & Sons Limited. Reproduced with permission.

ducted more effectively, and establishing a data-coordinating center to ensure that patients, physicians, and scientists are using the same data standards and nomenclature. Dr. Califf was asked about the "Wilensky proposal" (Wilensky, 2006), which calls for a distinct comparative effectiveness entity that would set priorities and be directed largely toward postapproval activities, systematic reviews, and observational studies. He responded that he would not want to see different structures built to address comparative effectiveness and postmarket safety because the two functions have so much in common; rather, he would hope that there would be "conceptually one effort, but tailored for different purposes." Dr. Woodcock expressed her view that for the partnership to work effectively, it would require proper governance and attention to the privacy concerns associated with the variety of entities that could use the system for various purposes. She also echoed the idea that the partnership would pool efforts to meet common needs and thereby be less costly than having

many separate groups. The questioner then emphasized the importance of including this perspective in other dialogues on this issue because once stakeholders start to gather resources and evaluate proposals, it will be more difficult to introduce a larger, broader agenda.

7

Enhancing the Value of Clinical Trial Registration[1]

Recommendation on Registration of Clinical Studies on ClinicalTrials.gov from the IOM Report
The Future of Drug Safety:
Promoting and Protecting the Health of the Public

Recommendation 4.11 The committee recommends that Congress require industry sponsors to register in a timely manner at clinicaltrials.gov, at a minimum, all phase 2 through 4 clinical trials, wherever they may have been conducted, if data from the trials are intended to be submitted to the FDA as part of an NDA [New Drug Application], sNDA [supplemental New Drug Application], or to fulfill a postmarket commitment. The committee further recommends that this requirement include the posting of a structured field summary of the efficacy and safety results of the studies.

Since the International Committee of Medical Journal Editors began requiring registration of trials in a public trials registry as a condition of consideration for publication, the number of trials registered on ClinicalTrials.gov has increased. Nevertheless, the value and the transparency of the system are not optimal. To address the weaknesses of the current system, the IOM report recommended enhancing clinical trial registration (Recommendation 4.11). Dr. Zarin discussed approaches to achieving this goal and the cost of their implementation.

A major focus of the IOM report was improved communication with the public. ClinicalTrials.gov is already a valuable resource to the public; however, the modifications proposed in Recommendation 4.11 were

[1]This chapter is based on the presentation of Deborah Zarin, Director, ClinicalTrials.gov, National Library of Medicine.

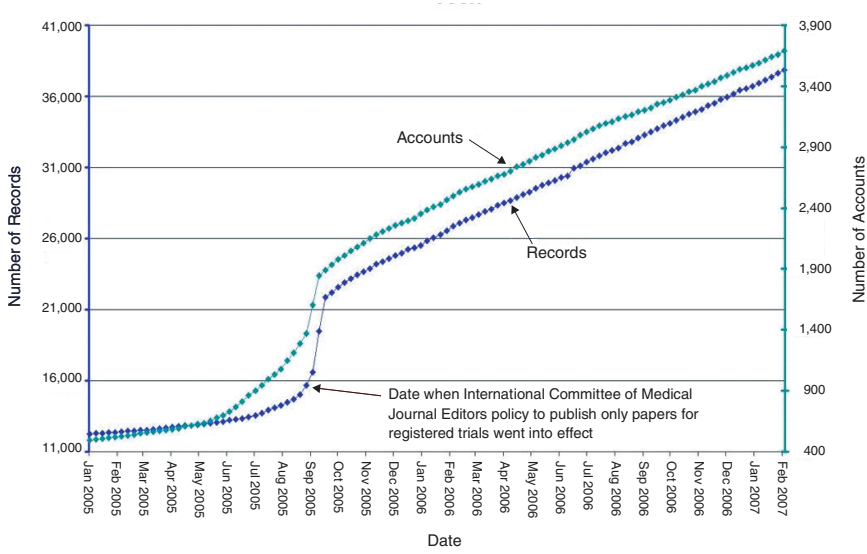

FIGURE 7-1 Monthly registration of trials on ClinicalTrials.gov. Presently, journal editors will publish papers only for registered trials. As indicated by the constant slope, even after this policy went into effect, the National Library of Medicine was capable of handling large increases in the number of trials registered.
SOURCE: Zarin, 2007.

intended to increase its value. Dr. Zarin discussed the resource challenges of what she identified as four components of Recommendation 4.11, noting that none of those components will be easy to implement:

- *Expanded scope of mandatory trial registration*—The system has yet to reach a steady state, and could readily handle an increase in the number of trials registered without requiring a significant budget increase (Figure 7-1). While the current budget for ClinicalTrials.gov is just over $3 million per year, the system taps the National Library of Medicine's (NLM) $300 million annual budget for search engine capabilities, hardware, personnel, etc. Some key functions of the registry, however, would be affected by and could benefit from policy changes:

  – Providing objective criteria for determining whether mandated trials are registered. Examples of criteria that would be easy to monitor include intervention type (e.g., drug trials), phase, and number of subjects. Examples of criteria that would be difficult to monitor include those that use subjective language (e.g., "serious conditions").

– Giving the National Institutes of Health (NIH) the flexibility to define "acceptable" entries and input rules so that information in the registry will be meaningful.

– Enabling users to find the information they want. Currently, about 20 percent of industry drug records use untracked serial numbers instead of the names of drugs, thereby hindering searches for information on the drug trials. An example of how a policy change could improve this situation is Maine's recent bill requiring drug companies to post a form indicating all previous names or aliases of each drug.

• *Addition of a results database*—ClinicalTrials.gov is already linked to published results whenever possible and could be linked to drugs@fda if trial identifiers were used. For de novo results, however, quality assurance is complex, and validation of all results would be challenging since these data are more complex than other trial data, the stakes are higher, and NIH would not have access to the full results dataset. The current validation system is based on both automated and manual checks, correction of errors when found, and an archived site that tracks changes. But difficult-to-detect errors still occur. The resource needs for adding results data would depend on the number of trials. As of 2006, the system was receiving an average of about 923 new trial registrations a month (Figure 7-2), and between 160 and 500 trials in the registry are being completed each month.

• *Scientific review*—Between 40 and 200 trials would need to be reviewed each week, and it is important to note that the FDA reviews for one of these trials could consist of 30+ pages of complex analyses and other information. It is unclear who would be able to review database entries for their concordance with complex FDA reviews.

• *Monitoring and enforcement*—It is unclear within the various bills currently before Congress what the roles of the FDA and NIH would be, although several proposals to keep those roles simple have been put forth (e.g., using objective definitions of scope, using NCT numbers[2] and incorporating them into business processes).

In summary, expanding the number of trials in the registry could probably occur at no significant increase in cost to ClinicalTrials.gov. Adding a structured results database, however, would be a complex task costing on the order of $10–20 million annually in addition to what is being spent on the registry. With respect to scientific review and monitoring and enforcement, it is unclear what would need to be done and how much it would cost.

[2]NLM's unique identifier for a particular record, found at the end of each record.

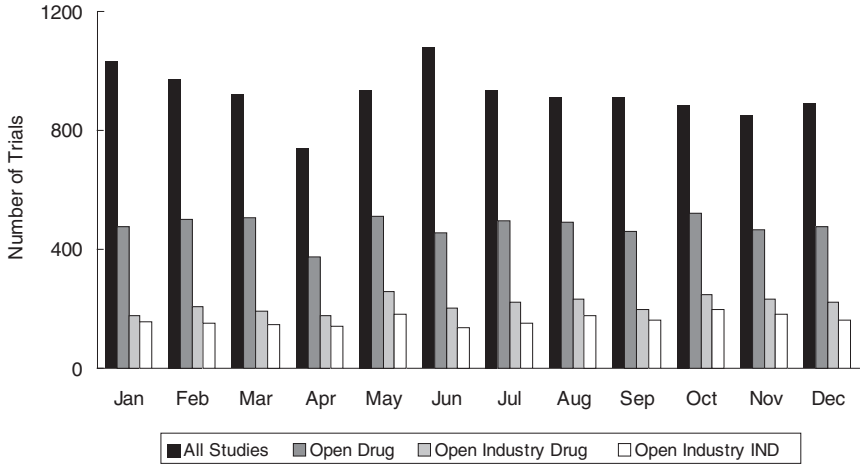

FIGURE 7-2 New trials received by ClinicalTrials.gov in 2006. The average total number of new trial registrations received per month was 923; the average number of open drug trials received per month was 478; the average number of open industry drug trials received per month was 215; and the average number of open industry IND trials received per month was 162.
NOTE: IND = Investigational New Drug.
SOURCE: Zarin, 2007.

When questioned about the history and mandate of the ClinicalTrials.gov registry, Dr. Zarin responded that the registry has been functioning since 2000, although some sponsors (NIH and some drug companies) have registered older studies. The current mandates for registration include the Food and Drug Modernization Act, Section 113, which mandates registering all Investigational New Drug (IND) studies with efficacy end points for serious and life-threatening conditions, and the above-mentioned requirement of the International Committee of Medical Journal Editors to register trials for any intervention that is clinically directed as a condition for publication. Again, one of the challenges is determining whether a trial that is mandated to be registered is actually registered. In response to another question, Dr. Zarin noted that while ClinicalTrials.gov accepts and welcomes data on nonclinical trials (i.e., observational data), it cannot enforce their inclusion.

8

Enhancing Postmarket Regulation and Enforcement

Recommendations on Enhancing Postmarket Regulation and Enforcement from the IOM Report
The Future of Drug Safety:
Promoting and Protecting the Health of the Public

Recommendation 5.1 The committee recommends that Congress ensure that the Food and Drug Administration has the ability to require such postmarketing risk assessment and risk management programs as are needed to monitor and ensure safe use of drug products. These conditions may be imposed both before and after approval of a new drug, new indication, or new dosage, as well as after identification of new contraindications or patterns of adverse events. The limitations imposed should match the specific safety concerns and benefits presented by the drug product. The risk assessment and risk management program may include:

a. Distribution conditioned on compliance with agency-initiated changes in drug labels.
b. Distribution conditioned on specific warnings to be incorporated into all promotional materials (including broadcast direct-to-consumer [DTC] advertising).
c. Distribution conditioned on a moratorium on DTC advertising.
d. Distribution restricted to certain facilities, pharmacists, or physicians with special training or experience.
e. Distribution conditioned on the performance of specified medical procedures.
f. Distribution conditioned on the performance of specified additional clinical trials or other studies.
g. Distribution conditioned on the maintenance of an active adverse event surveillance system.

Recommendation 5.2 The committee recommends that Congress provide oversight and enact any needed legislation to ensure compliance by both the Food and Drug Administration and drug sponsors with the provisions listed above. FDA needs increased enforcement authority and better enforcement tools directed at drug sponsors, which should include fines, injunctions, and withdrawal of drug approval.

Recommendation 5.3 The committee recommends that Congress amend the Food, Drug and Cosmetic Act to require that product labels carry a special symbol such as the black triangle used in the UK or an equivalent symbol for new drugs, new combinations of active substances, and new systems of delivery of existing drugs. The Food and Drug Administration should restrict direct-to-consumer advertising during the period of time the special symbol is in effect.

Once a drug has been approved by the FDA for marketing, the agency's regulatory authority over the drug and the manufacturer changes markedly. Prior to approval, the FDA has complete control over decisions about how and by whom the drug can be used and how it is manufactured. More important, the potential for rejection of the application gives the FDA strong leverage in dealings with the company, including, for example, requests for data and negotiation of postmarket commitments. After approval, if the FDA finds problems in the way a product is manufactured or marketed or if it becomes aware of safety concerns, it has two principal options: withdraw approval of the drug, or try to persuade the manufacturer to comply with the agency's requests. Panel moderator Alta Charo, Warren P. Knowles Professor of Law and Bioethics, University of Wisconsin–Madison, explained that the FDA's current authority is grounded largely in its mandate to prevent the sale of adulterated or misbranded drugs, and that it is differing interpretations of the phrase "adulterated or misbranded" that lead to inconsistent application of the agency's authority from one administration to the next. This variation in the application of the FDA's authority led to the call in the IOM report for clarifying and strengthening the agency's existing authority to regulate marketed drugs, and for giving the FDA sufficient enforcement tools to ensure that regulatory requirements imposed at or after approval are fulfilled (see the recommendations listed above).

In his presentation, Peter Hutt, Senior Counsel, Covington & Burling LLP, argued that the FDA needs resources, not new legal authorities. This assertion prompted many comments by subsequent speakers and led to debate about the potentially beneficial versus harmful consequences of legally altering the FDA's authority or enforcement mechanisms.

THE FDA'S REGULATORY AUTHORITY[1]

Mr. Schroeder echoed Ms. Charo's comments about the inconsistent interpretation of the FDA's authority, "under which it has expanded under one chief counsel, only to shrink again under another." He further described the FDA's authority as not sufficiently nuanced to give the agency the flexibility required to implement a life-cycle approach to benefit–risk profiling. Currently, the agency either exercises its leverage or takes a withdrawal action, both of which involve prolonged negotiations with the manufacturer.

Mr. Schroeder emphasized that, although resource limitations are more important than the issue of regulatory authority, the authors of the IOM report concluded that some revision of the FDA's statutory authority would be consistent with and help reinforce the agency's ability to fully implement a life-cycle approach to benefit–risk profiling. While the FDA may be able to carry out many of its responsibilities in the postmarket environment under its existing mandates, there are some actions it cannot take.

The growing complexity of drug therapies and widespread patient misperceptions about drugs reinforce the argument for strengthening the FDA's regulatory authority. Mr. Schroeder suggested that the FDA needs more explicit postmarket authority to conduct adequate surveillance and to oversee and enforce safety studies. Preapproval trials frequently will not detect drug risks that are the result of drug interactions or variations in risk across the general population. The IOM report argued that enhanced postmarket authority would take some of the pressure off the preapproval process. Mr. Schroeder noted, however, that while the FDA will always be inclined to take advantage of its leverage in the preapproval period, approval is only one of many milestones at which the benefit–risk profile of a drug should be assessed. Having clearer postmarket authority would minimize the agency's incentive to make last-minute decisions prior to approval.

Strengthening postmarket regulatory authority may take some pressure off the preapproval process, but it is unlikely to compensate for failures earlier in the evaluation process. Moreover, Mr. Schroeder argued that once a certain level of comprehensiveness has been achieved (meaning that information has been acquired, and hypotheses have been generated, tested, and converted into actionable knowledge), the importance of strengthened authority is modest. However, the rationale for providing the FDA with a more flexible array of enforcement options is that if the agency does decide it needs to take action, it can do so swiftly.

[1]This section is based on the presentation of Chris Schroeder, Professor of Law and Public Policy Studies, Duke University School of Law.

THE FDA'S STATUTORY AUTHORITY[2]

Mr. Hutt asserted that the FDA has no need for additional regulatory authority. With respect to legal authority, he described the 1906 Food, Drug and Cosmetic Act, which was revised in 1938 and has since been amended more than 100 times, as an "old-fashioned statute" written in broad, sweeping terms, not addressing the minutiae dealt with by many modern statutes. Pointing to the definition of safety ("a drug must be proved safe by all tests reasonably applicable to show safety"), he observed that it is not an operational rule. He noted that since 1962, there has not been a single case of an FDA safety decision's having been overturned in court.

According to Mr. Hutt, a larger issue is the lack of scientific information and the reality that there are many questions about drug safety for which there are no answers. While FDA reviewers occasionally fail to take all the action that could be taken (and by doing so, leave an unsafe drug on the market), taking strenuous and immediate action can in many cases be more harmful than waiting for more information (by preventing a safe drug from reaching the market). These decisions are often difficult to make.

Mr. Hutt reiterated that the agency already has the strong legal enforcement mechanisms it needs. Formal mechanisms include seizure, injunction, and criminal action, the latter representing one of only two statutes in U.S. history that imposes criminal liability on corporate officials regardless of whether they had knowledge of or intent to commit a crime. More important are the FDA's informal actions—publicity and negotiations with industry. Mr. Hutt pointed to phenylpropanolamine and ephedra as two examples of the power of publicity. With regard to negotiating with industry, he noted that in most negotiations, both sides have relatively balanced power, either side can walk away, and therefore a balanced agreement must be forged. A company coming to the FDA with an Investigational New Drug (IND) application or a New Drug Application (NDA), by contrast, cannot walk away from the negotiations, a fact that gives the FDA the final word.

Mr. Hutt concluded by stating his view, noted above, that what the FDA needs is the resources to address the issues discussed during the symposium. Although these are not new issues—indeed, they have been discussed for more than 35 years—the technological tools needed to strengthen postmarket approval and surveillance now exist. The money to pay for these tools, however, is lacking.

[2]This section is based on the presentations of Mr. Hutt; Mary Pendergast, President, Pendergast Consulting; and Eve Slater, former Assistant Secretary for Health, U.S. Department of Health and Human Services, and Director, Vertex Pharmaceuticals and Theravance, Inc.

Ms. Pendergast seconded Mr. Hutt's point about the FDA's power in negotiations with industry, noting that in her 20 years with the FDA, she could not recall a single case in which she did not ultimately attain what the agency wanted from the negotiating process. According to Ms. Charo, on the other hand, it could sometimes be said that the process took too long. Ms. Pendergast responded that, to people at the FDA, this translates to their not having pressed hard enough. Even with Vioxx, she asserted, it was unclear whether the problem was a failure of information or a failure of will on the part of the FDA.

Dr. Califf suggested that the battle is unfair: an FDA employee with a myriad of other things to do and no administrative support is up against a large number of people who are highly paid, technically gifted, well supported, and highly focused on selling a product. He expressed the view that, although an extremely diligent FDA employee who stays on the case, sometimes to the detriment of other responsibilities, may be able to make things happen, in many cases the company's promise and initial effort to conduct a study are considered enough. Thus the remedy may not be legal, but a matter of resources. Mr. Hutt concurred with Ms. Pendergast that the will to press hard must exist, and he agreed with Dr. Califf that the problem is one of resources.

Disagreeing with the preceding speakers, Dr. Slater asserted that new, carefully considered regulations are necessary because the current system is failing. While this failure has been attributed to faster drug approvals, she argued that the Prescription Drug User Fee Act (PDUFA) did not accelerate review and approval as much as it redressed unwarranted delays. Furthermore, modern drugs intervene via much more complex pathogenetic and biochemical mechanisms than do older drugs and with multiple consequences that are difficult to determine. Dr. Slater cited other reasons for failure of the system, including alleged malfeasance by sponsors and within the FDA, which may or may not be the case, and well-documented deficiencies in the current safety surveillance system and its associated enforcement capabilities.

PHASE IV COMMITMENTS[3]

One area of particular concern cited in the IOM report was the FDA's lack of authority to enforce Phase IV commitments. At the time of approval, the FDA often negotiates hurriedly with a company to design a Phase IV

[3]This section is based on the presentations of Mr. Schroeder, Mr. Hutt, Dr. Califf, and Ms. Pendergast.

study.[4] While the company may have agreed to conduct the study prior to approval, the FDA has few options for ensuring that it actually meets that commitment once the drug is on the market. Because these studies may be negotiated quickly at the last moment, they can be poorly designed. As a result, a company may have difficulty gaining approval for such a study from an institutional review board (IRB) or enrolling subjects, or may conduct the study but end up with meaningless results. Mr. Schroeder supported the recommendation of the IOM report that the FDA be given the authority, both before and after approval of a new drug, to require such postmarket studies if needed to monitor and ensure the safe use of drug products (Recommendation 5.1). In response to this recommendation, Mr. Hutt argued that the FDA does not need statutory authority to regulate Phase IV studies. Rather, he suggested that there be a mechanism for reviewing postmarket Phase IV commitments to ensure that studies are well designed and executable, either before or after approval, and that the FDA follow up with a later review in the event a company claims it cannot gain IRB approval or enroll enough patients. Dr. Califf commented that it is easy to design a study that sponsors know is not going to succeed in enrolling enough patients, to which Mr. Hutt responded that identifying and penalizing those sponsors would be an effective way of resolving the issue, and something the FDA has the ability to do.

It was suggested that instead of penalties, incentives could be used—for example, rewards for shorter negotiation times or prompter actions. Dr. Califf mentioned a recent article on the Pediatric Rule describing how such an approach can work (Li et al., 2007). Another incentive suggested was that the guaranteed market exclusivity that usually comes with approval of a new drug could be contingent on completion of reasonably determined requirements for postmarket surveillance trials. Ms. Pendergast responded by noting the difficulty of differentiating good and bad excuses for not finishing a trial, and she suggested that every drug needs to be dealt with on a case-by-case basis. She added that the dialogue between companies and the FDA about postmarket studies should occur earlier in the FDA review process instead of at the time of approval. She proposed that a reasoned discussion of postmarket commitments take place perhaps 6 weeks before approval instead of during the last 24 hours.

While the FDA may not need more formal authority, Mr. Schroeder asked whether a statute enabling the FDA to order a Phase IV study after

[4]Phase IV studies are conducted once a drug has been approved and is on the market. There are many reasons for conducting Phase IV studies, for example, to monitor potential safety signals observed in premarket clinical studies, to look for interactions with other drugs, or to study particular populations (e.g., pediatric patients or pregnant women).

approval would relieve the pressure of the hurried negotiations that take place within the 24-hour period prior to approval. If everyone involved understood that there would be time after approval to discuss whether a postapproval study was necessary, this might eliminate some of the poorly conceived studies for which commitments are now made.[5] Mr. Hutt agreed with this concept, but asserted that it could be implemented without a new statute.

One panelist pointed to the Best Pharmaceuticals for Children Act (Public Law 107-109), a mandated safety review for products that receive exclusivity, as an example of how legislation has helped the FDA in establishing its priorities. All stakeholders know up front what is going to happen and when, and the system has worked. Mr. Hutt responded that while the new statute requires the FDA to act accordingly, the agency could have implemented this process without further statutory authority—as is the case for many of the safety initiatives described during the symposium. As with an earlier comment about the possibility of enacting legislation authorizing the FDA to undertake the combining of databases around the country, he stressed that the impediment is not a lack of authority, but insufficient resources.

Ms. Charo asked Mr. Hutt whether, given the varying interpretations of the FDA's authority over the years, as discussed earlier, and the apparent effect of a lack of clarity on the agency's internal behavior, there would be any harm in explicitly acknowledging the authority Mr. Hutt claimed the agency clearly has. She noted that IOM Recommendation 5.1 suggested not that the FDA consider a Phase IV study as a requirement for approval, but that it be permitted to impose new postmarket or Phase IV commitments at any time if it felt doing so was necessary. The IOM committee anticipated that this would not happen very often. Mr. Hutt disagreed. He argued that the number of Phase IV requirements would rise "exponentially" because those with the authority to impose such requirements would use it in any situation where they believed they or the FDA could be faulted in the future for not having done so.

RESOURCES FOR ENHANCED ENFORCEMENT[6]

Throughout the above discussion, Mr. Hutt, Ms. Pendergast, and Dr. Califf all cited a lack of resources as one of the major roadblocks to the FDA's postmarket regulatory enforcement. Ms. Pendergast stressed the

[5]In the FDA's 2006 report to Congress, there were 1,632 open postmarket commitments (1,259 NDAs or Abbreviated New Drug Applications [ANDAs], and 373 Biological License Applications [BLAs]).

[6]This section is based on the presentation of Ms. Pendergast.

importance of realizing what implementation of some of the IOM report's recommendations addressing postmarket compliance will cost in terms of both resources and time. An example is the amount of effort required to address the current backlog of postmarket commitments. The number of commitments is rising every year, but many of these trials never even get under way. Between 1991 and 2000, there were on average 1.5 postmarket commitments per drug; by 2003 and 2004, that number had risen to 5 per drug (with some companies having none and one company having as many as 26). In fiscal year 2006, there were 1,632 postmarket commitments, 63 percent of which had not been initiated (Table 8-1).

Ms. Pendergast gave an example to demonstrate how resource-intensive implementation of this recommendation would be. She explained that, to determine why a postmarket commitment had not begun, a first step would be to assign an FDA investigator, likely a clinical expert, to the case and identify the specific problem causing the delay. For example, the sponsor might be slow to undertake the study. The investigator would need to look into communications between the sponsor and the FDA division responsible for overseeing the product, and determine whether the commitment was a last-minute one just prior to approval or involved a meaningful dialogue about the trial and its design. The investigator would also need to interview company personnel, look through records, and perhaps investigate the IRB in an effort to learn from the company its reasons for the delay. Or maybe the investigator would determine that the problem lay with the clinical researchers or the study design. For example, the trial might be one that would never get published; it might require computer-assisted tomography (CAT) scans and magnetic resonance imaging (MRI) or other procedures that would be disruptive to a medical practice; or the subjects might not be highly motivated. In such cases, the company might not be at fault for the trial's not starting in a timely manner.

The investigator would need to examine a multitude of factors before the FDA could make an enforcement decision as to whether a particular trial was just slow getting off the ground or the company was culpable. Ms. Pendergast also noted that the same questions could be asked of a company that failed to complete a trial. Moreover, once the FDA had finished its investigation and deliberations and decided to pursue an enforcement action, it would have to convince the Department of Justice to join in taking action against the company. That itself would be a challenge because of the Department of Justice's own priorities and resource constraints.

TABLE 8-1 Summary of Postmarket Study Commitments (Numbers as of September 30, 2006)

	New Drug Applications (NDAs)/Abbreviated New Drug Applications (ANDAs) (% of Total)	Biological License Applications (BLAs)[a] (% of Total)
Number of Applicants with Open Postmarket Commitments	127	45
Number of Open Postmarket Commitments	1,259	373
Status of Open Postmarket Commitments		
• Pending	899 (71%)	127 (34%)
• Ongoing	184 (15%)	90 (24%)
• Delayed	31 (3%)	78 (21%)
• Terminated	1 (<1%)	2 (1%)
• Submitted	144 (11%)	76 (20%)
Concluded Studies (October 1, 2005, through September 30, 2006)	194	38
• Commitment Met	160 (83%)	33 (87%)
• Commitment Not Met	10 (5%)	0
• Study No Longer Needed or Feasible	24 (12%)	5 (13%)
Applications with Open Postmarket Commitments with Annual Reports Due, but Not Submitted Within 60 Days of the Anniversary Date of U.S. Approval	133 (37%)[b]	33 (47%)

[a]On October 1, 2003, the FDA completed a consolidation of responsibility for certain products formerly regulated by the Center for Biologics Evaluation and Research (CBER) into the Center for Drug Evaluation and Research (CDER). The previous association of BLA reviews only with CBER is no longer valid; BLAs are now received by both CBER and CDER. Fiscal year statistics for CDER BLA postmarket study commitments are counted under BLA totals in this table.

[b]Note that this statistic counts all annual reports submitted more than 60 days after the anniversary date of U.S. approval as overdue, including reports that may have been submitted on a modified reporting schedule in accordance with prior FDA agreement. Of the applications categorized as having overdue annual reports using this definition, annual reports were subsequently submitted in fiscal year 2006 for 133/133 (100%) of NDAs/ANDAs and 15/33 (45%) of BLAs.

SOURCE: Federal Register, 2007.

THE FDA'S REGULATORY AUTHORITY OVER DRUG LABELING[7]

Panelists discussed whether the FDA has the authority to force labeling changes once a product is on the market. One panelist questioned why, if the agency has that authority, it is not used, and FDA leaders instead refer to the process as one of negotiation. Mr. Hutt responded that the FDA does have the authority, but the problem is, first, a matter of priorities—the FDA cannot always grant an immediate meeting with a company—and, second, a consequence of the reality that the agency does not know everything about a drug, and should therefore negotiate and engage in discussion with a company about labeling. While negotiating is necessary, however, it need not be prolonged. Dr. Slater observed that, although limited resources are a hindrance in dealing with labeling issues, in reality no amount of money is going to fix the problem unless a well-developed infrastructure is in place to support the volume and complexity of the work involved—one that might enable a labeling meeting within 30 days instead of, say, 75. Indeed, one of the reasons the drug industry can mobilize its resources more quickly than can the FDA is because it is a regulated industry and over the years has had to invest a great deal in infrastructure. According to Dr. Slater, the FDA has the will but not the funding to do the same.

Advertising or marketing of a drug falls within the purview of drug labeling; therefore, the FDA's mandate does not include approving advertising and promotional materials beyond the labeling negotiations that occur prior to approval. While advertising materials must be submitted to the FDA at the time of use, they need not be approved by the agency before being used. The IOM report recommended that the FDA restrict direct-to-consumer (DTC) advertising of all new drugs for a period to be determined by the agency (Recommendation 5.3). Dr. Slater cautioned against moving quickly to place a moratorium on DTC because it has the potential to become a much more effective method of communicating drug information to the public. Rather, she suggested that a revised concept of DTC could serve as a valuable tool for providing information to both prescribers and patients, and eventually could replace drug detailing. Considering that there is no way to impede the flow of information to patients (with information being posted on blogs and elsewhere on the Internet), it would be just as well to lend as much FDA expertise and authority to the process as possible.

[7]This section is based on the presentations of Mr. Hutt and Dr. Slater.

PATIENT SAFETY AND ACCESS[8]

The IOM report cautioned against assuming that simply altering the statute governing the FDA's regulatory authority will resolve the difficulties related to that authority. Several additional challenges will need to be addressed:

- New legislation will take time.
- Because enforcement through litigation is time-consuming, most of the benefits of enhanced enforcement are realized only post hoc.
- Even if the FDA gained increased funding, execution of the recommendations would require a well-structured and -supported infrastructure.
- Many of the enhancements proposed in the IOM report (e.g., extensive risk management plans) would cost money and time, which would likely translate into higher drug prices.
- If restrictions were placed on DTC advertising, the flow of information about new drugs to practitioners and patients could suffer.
- Enhanced enforcement could unintentionally drain critical resources from areas of more urgent need (e.g., study of the science of drug safety).
- Restricted use of a drug in the name of safety could limit access to the drug by those who need it.

In addition, as discussed in Chapter 3, the science of safety needs to be strengthened, a new cohort of drug safety professionals needs to be trained, practitioner and patient education needs to be enhanced, and the public needs to be engaged.

INDUSTRY PERSPECTIVE[9]

Dr. Haffner remarked that drug safety is not the responsibility of a single group, but the collective responsibility of patients, providers, regulators, and industry, all of whom have vested interests in optimizing the benefit–risk balance of therapeutic molecules. Moreover, the responsibility for drug safety does not end at approval, but demands continuing assessment and improvement of the benefit–risk profile throughout a product's lifetime. Effective continuing assessment, in turn, requires partnerships across the health care spectrum. To be effective, those partnerships require governance, transparency, and clarity about the roles and responsibilities of each partner. With respect to the IOM report's Recommendation 5.2 (that the FDA should have increased enforcement

[8]This section is based on the presentation of Dr. Slater.

[9]This section is based on the presentation of Marlene Haffner, Executive Director, Global Regulatory and Intelligence Policy, Amgen, Inc.

authority and better enforcement tools, including fines, injunctions, and withdrawals), Dr. Haffner suggested that if the FDA is given more authority, there must be a clear description of that authority, how it is to be exercised, and how it can and should be exercised with input from other stakeholders. Moreover, that authority should be used only outside the political arena. While industry benefits from a strong and scientifically based FDA, and while the FDA should have the authority to withdraw a product, Dr. Haffner emphasized that this must be done with care and only under rare circumstances.

The IOM report recommended that the FDA have increased authority to restrict drug distribution (Recommendation 5.1). With respect to Recommendation 5.1.a—conditional distribution based on agency-initiated changes in drug labels—Dr. Haffner argued that imposition of this condition (1) must include dialogue with industry, (2) should be a transparent process involving communication of risk to patients, and (3) should involve only thoughtful changes that meet the perceived safety need. With respect to Recommendation 5.1.d—distribution restricted to certain facilities, pharmacists, or physicians with special training or experience—Dr. Haffner noted that to some extent, the FDA already has this authority and uses it. Once again, however, she emphasized that such restrictions should be used only in the appropriate circumstances, that patient access should be taken into account, and that patients should be properly accommodated when necessary.

9

Looking to the Future

The final session of the symposium looked to the future. Panelists began by outlining three prerequisites for revitalizing the U.S. drug safety system: reauthorization of the Prescription Drug User Fee Act (PDUFA), thoughtful utilization of the FDA's existing resources, and an emphasis on preserving patients' trust in the drug safety regulatory system. This was followed by a summary of the symposium discussions on the future of drug safety regulation.

PREREQUISITES FOR REVITALIZING THE U.S. DRUG SAFETY SYSTEM

Reauthorization of PDUFA

PDUFA III is set to expire on September 30, 2007. As of this writing, Congress is deliberating the act's reauthorization (PDUFA IV), and a vote is planned for sometime during the summer. If Congress does not pass this legislation before August, the FDA will have to initiate reductions in its workforce, many FDA staff will lose their jobs, and new drug reviews will likely come to a halt. Throughout the symposium, multiple panelists called for timely reauthorization of PDUFA. In her presentation, for example, Myrl Weinberg, President, National Health Council, stressed the urgent need for Congress to reauthorize PDUFA and increase appropriations to ensure that the FDA is adequately resourced to monitor drug safety. It is also important for Congress to support the FDA's Critical Path

Initiative so the agency can modernize the way in which the agency deals with new channels of scientific discovery. Dr. Franson likewise stated that reauthorization of PDUFA is absolutely vital.

The FDA's proposal for PDUFA IV includes programs and funding dedicated to measures aimed at increasing the regulation of postmarket drug safety. Ms. Pendergast stressed that if PDUFA IV is authorized, the resources dedicated to the FDA for drug safety must stay focused on drug safety. She explained how 5 years ago, during authorization of PDUFA III, the FDA received $71 million from industry to pay for large database studies and new drug safety reviewers. However, Congress rescinded much of that money and reprogrammed the small remainder elsewhere in the FDA. As a result, the Office of Drug Safety is no better off than it was 5 years ago.

Thoughtful Utilization of Existing Resources

Most of the panelists attributed some portion of the current drug safety problems and the FDA's inability to initiate programs to improve the U.S. drug safety system to chronic underfunding and a lack of adequately trained personnel. However, some panelists suggested that the FDA needs to use its existing resources more wisely. Ms. Pendergast stated that the FDA has an obligation to be a steward of the money it receives and to spend that money wisely. Referring to the FDA-commissioned Breckenridge report (Breckenridge Institute, 2006), she remarked that, while the agency received a large sum of money ($25 million) to improve its information technology, it did not spent the money wisely, as the Adverse Event Reporting System (AERS) is no better today than it was many years ago.

Dr. Franson suggested that, given the thousands of people throughout the pharmaceutical industry who are working on the same issues as the FDA, improving the U.S. drug safety system should be a process based on collaboration. The challenge is to coordinate these efforts in a way that will enable shared learning—particularly in precompetitive areas—and enable those involved to utilize resources more effectively by capitalizing on each other's capabilities. If the current resources of the FDA, industry, and other stakeholders were inventoried, many complementary disciplines (e.g., epidemiology) and best practices would likely be identified. For example, with respect to using potential biomarkers to define risks and benefits in databases, it should be possible to collaborate with large health care organizations that routinely capture at least some of this information. According to Dr. Franson, the need for such coordination is a larger issue than the FDA's inadequate resources.

Preserving Patients' Trust in the Drug Safety Regulatory System

Ellen Sigal, Chairperson, Friends of Cancer Research, and Ms. Weinberg both urged that the voice and views of patients be heard during the current reassessment of the U.S. drug safety system. Dr. Sigal emphasized that there is declining public trust in the FDA-led drug safety system and posited that the lack of public participation in the debate on how to improve the system may reinforce this lack of trust. She also expressed concern that a one-size-fits-all regulatory approach and excessive regulatory requirements would slow approval, increase drug prices, and discourage innovative product development, thereby making it more difficult for patients to gain access to much-needed drugs. Ms. Weinberg asserted that no drug is 100 percent safe, and that drug safety must be viewed within the context of a benefit–risk balance and consumer choice. She cited the case of a boy with epilepsy who benefits from a medication that carries a black box warning, illustrating how patients (or their parents) are willing to take risks "for just a shot at a normal life."

The National Health Council has formulated several key research-based findings that shed light on drug safety issues from the patient's point of view:

- A patient's assessment of risks and benefits is highly complex, involving both analytical and emotional factors (e.g., prior experience with a drug, severity of symptoms or condition, trust in doctors, credibility of outside information sources). Patients' trust in the benefit–risk information they receive is critical to their willingness to take medications.
- People have incorrect assumptions about the benefit–risk correlation, usually believing that as benefit increases, risk decreases. In reality, the opposite may be true. It is unlikely that providing more detailed statistical information about risks in packaging or advertising is the best way to proceed. In fact, it is more likely that patients will pay less attention to the actual correlation.
- While patients are willing to take risks to improve their quality of life, they expect full disclosure about both risks and benefits so they can make informed decisions. Moreover, even patients who understand that no drug is completely safe are not always aware that the full risks cannot be known at the time of approval. Patients and the public need to understand that generally, detection of safety problems in premarket studies is limited to common adverse events occurring after a relatively short-term exposure and brief period of follow-up. These studies are not adequately powered to detect rare adverse events; therefore, postmarket surveillance is necessary to identify additional safety issues.
- Many patients fear restricted access to medications that carry risks but may nonetheless improve and/or prolong their lives, and they view

any limitations on their access to such drugs as a violation of their right to make personal health decisions with their physicians.

- Health care providers play a central role in patients' understanding of the risks and benefits of medications, so it is critical that this bond between patient and provider be strengthened.

In summary, Ms. Weinberg emphasized that, whatever steps are taken to improve drug safety, it is critical that those actions not restrict access to appropriate medications or otherwise interfere with patients' right to make informed decisions about drug use with their physicians. She asserted that the system needs to do a better job of putting the patient's needs first. There must be a balance between access to drugs that help individuals lead independent, productive lives and attention to safety concerns, with the risks and benefits of prescription drugs being carefully weighed "in full public view."

THE FUTURE OF DRUG SAFETY REGULATION

Dr. McClellan reflected on the many challenges to and opportunities for enhancing drug safety that had been discussed throughout the symposium. He also shared his thoughts on necessary next steps if the FDA is to be able to meet these challenges and exploit these opportunities.

Significant progress has already been made since the IOM report was released in September 2006:

- The issue of drug safety is in the forefront of the American public's awareness.
- The FDA made a formal point-by-point response to the IOM report (see Box 1-1 in Chapter 1 for highlights of the FDA's response). That response included many new initiatives, some of which were discussed during the symposium. The strong attendance of FDA staff at the symposium illustrates the staff's commitment to doing the best job possible with the available resources.
- All stakeholders (e.g., industry, consumer groups, patient advocates, medical and statistical experts) are engaged in and contributing to the debate. Some have even issued secondary reports on drug safety.

Dr. McClellan emphasized the importance of taking immediate steps to build on this progress because of the forthcoming congressional action on the issue of drug safety in conjunction with the reauthorization of PDUFA. Because of its potential impact on the FDA's activities related to drug safety, this upcoming action is the most significant legislative opportunity for the FDA in at least a decade.

Dr. McClellan identified five key issues around which much of the symposium discussion had revolved:

- The FDA's limited resources and technical capabilities. The agency is regulating products representing 25 percent of the U.S. economy with a budget of under $2 billion, which amounts to a few cents per member of the population—far lower than the funding level of any other public health agency. This inadequate funding is compounded by the additional responsibilities the agency continues to accrue even as its budget remains the same.
- Operations and management, particularly with regard to changing the culture of the FDA and the way the agency is structured.
- The importance of improving information and communication about benefits and risks.
- Public–private collaboration—opportunities for stakeholders to work together to accomplish shared goals.
- The FDA's regulatory authority.

Dr. McClellan then summarized the discussions of pre- and postmarket components of the drug safety system that touched on these key issues.

Premarket Enhancements

Most of the discussion on enhancing premarket components of the drug safety system focused on two key concepts. First is the need to develop a better safety science that involves identifying biomarkers and other predictors of individual responses to drugs and characterizing individual differences in risk and benefit. Second is the idea that profiling and managing the risks and benefits of a drug should be a continuous learning process, one that employs a systematic life-cycle approach in which potential areas of concern requiring postmarket evaluation are identified during the premarket process. The view was widely expressed that there are at least two necessary next steps for achieving these goals:

- Provide the FDA with additional resources to support its Critical Path Initiative and related efforts aimed at improving drug safety. Currently, the agency has virtually no financial support in these areas.
- Change the culture of the FDA so it supports a continuous learning process and a life-cycle approach, and integrates perspectives from throughout the agency.

Postmarket Enhancements

Most of the symposium discussions focused on the postmarket setting, including the need for better evidence on risks and benefits, for communication of information in a way that impacts clinical practice, and for greater clarity about postmarket regulation.

Need for Better Evidence on Risks and Benefits

Discussion of the gathering and analysis of benefit–risk information in the postmarket setting focused on the need for and advantages of adopting a broad population-based approach. Multiple speakers stated that the time has come to adopt a more population-based approach to determining safety signals. Such an approach could also provide more insight into how drugs are being used, both on and off label. A better infrastructure for understanding risks and safety signals and other aspects of drug utilization would enable more effective targeting of costly follow-up clinical studies. Several steps must be taken to develop a population-based approach, some of which the FDA has announced and others of which will require additional resources:

- FDA initiatives that have already been announced include enhanced tracking and follow-up of postmarket issues, planned improvements in AERS, and pilots of new postmarket drug-monitoring strategies. All of these steps are possible with existing funding and authority.
- There were repeated calls throughout the symposium for development of a federated public–private partnership to detect signals and support follow-up studies. It was asserted that with the proper funding and governance, such a partnership would provide better evidence at lower overall cost relative to multiple separate efforts. This partnership would also serve as a step toward a more complete electronic clinical database with greater interoperability, which would reduce the costs of follow-up clinical studies.

Need for Better Communication of Information

Discussion of the need to communicate information in a way that impacts clinical practice revolved around three major sets of needs. First is the need for increased transparency and clarity about FDA benefit–risk evaluation processes and regulatory conclusions. Second is the need for more comprehensive and useful information on clinical trials, made publicly available through the registration of trials and the reporting of results. Finally, information about risks and benefits needs to be communicated more effectively to both patients and physicians so they can make

more informed treatment choices. Several steps will be required to meet these needs, some of which the FDA has announced and others of which will require additional resources:

- The FDA has announced efforts to provide transparency in the review and advisory committee processes.
- While there have been some legislative proposals for reporting of clinical trials on ClinicalTrials.gov and elsewhere, more resources are required to meet this need.
- The FDA has outlined a number of steps toward providing timelier and clearer updates on the latest safety-related evidence. However, patients do not always get their information from product labels or mainstream medical literature. Thus it is necessary to take a new look at how people access information on the risks and benefits of drugs, for example, by sharing information on blogs.

Need for Clarity About Postmarket Regulation

Discussion of postmarket regulation focused on two key concepts. First, the IOM report urged more clarity and the development of "graded" tools for evaluating benefit–risk profiles, including new enforcement steps that would lie somewhere between the exercise of the agency's leverage and the removal of drugs from the market. Special attention was directed at the way new drugs are marketed and distinguished in the minds of clinicians and the public. At the same time, however, serious concern was expressed about this recommendation and whether the proposed regulatory authority would really respond appropriately and efficiently to the types of issues (e.g., the case of Vioxx) that have led the system to its present state. Two major steps currently being taken address this need:

- The FDA is taking the administrative actions necessary to evaluate the Risk Minimization Action Plan (RiskMAP) strategy on a pilot basis and does not anticipate that implementing this strategy would require additional authority beyond the usual monitoring performed by the agency.
- Congress is in the midst of a legislative debate on this topic, and further legislative action is likely that will provide the FDA with more powerful tools encompassing additional enforcement responses. Dr. McClellan emphasized the importance of bringing the best ideas to light to help guide that legislative process.

Conclusion

In concluding, Dr. McClellan emphasized the following points:

- The FDA needs additional resources and technical capabilities to achieve the goals of the IOM recommendations. While additional regulatory authority, organizational change, and better information are necessary, they are not sufficient and will in fact require yet more resources, including personnel and expertise.
- A great deal is already being spent on safety in the health care system, and still more will be spent with the reauthorization of PDUFA and the passage of pending drug safety legislation. Additionally, health plans are investing considerably in systems for identifying how drugs are being used and with what consequences.
- Taking a more collaborative approach to addressing safety issues through public–private partnerships—particularly in the conduct of postmarket surveillance—would be much more cost-effective than the current piecemeal approach.
- There are a number of other opportunities for such public–private collaboration to achieve consensus on how to move forward. These include improving safety science; developing better postmarket evidence on the risks and the actual use of drugs; developing more individualized and effective benefit–risk communications; assessing the development and use of new regulatory tools; and ultimately, continuing to improve the regulatory system while avoiding unnecessary costs and delays in access, creating a health care system that delivers the best possible treatment to each patient.

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Appendix A

Workshop Agenda

Symposium on the Future of Drug Safety: Challenges for FDA

March 12, 2007
Hotel Monaco, Paris Ballroom
700 F Street NW, Washington, DC

Symposium Objective: The Institute of Medicine recently released a report, *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. This report includes recommendations for improving the U.S. drug safety system. These recommendations would likely entail significant new commitments for an agency that some consider to be financially strained by existing responsibilities. The meeting will consider the types and magnitudes of resources needed to achieve the goals of the IOM report. It will focus on a subset of IOM recommendations (attached) which were deemed to have significant resource implications—these are grouped into five topic areas: increased FDA funding; integration of pre- and postmarket review; enhancing postmarket safety monitoring; conducting confirmatory drug safety and efficacy studies; and enhancing postmarket regulation and enforcement. The complete list of recommendations can be found in the report or the executive summary at http://www.nap.edu/catalog/11750.html. For each topic, presenters will describe the relevant IOM recommendations, the FDA's current capacities and initiatives; and the resource implications of those recommendations. Perspectives will include FDA officials (for information on current operations and plans), industry, patient advocates, and other experts.

7:30 am **Coffee/Refreshments**

8:00 am **Welcome**

GAIL CASSELL, SYMPOSIUM CHAIR AND MODERATOR
Co-Chair, Forum on Drug Discovery, Development, and Translation
Vice President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases
Eli Lilly and Company

Session 1: Preserving the Public Trust: Ensuring Drug Safety, Efficacy, and Availability

Session Objectives: The IOM drug safety report recommended that the FDA receive "substantially increased resources" to support improvements in the system for ensuring drug safety and efficacy (**Recommendation 7.1**). This session will provide an overview of the role of the FDA in protecting the public, and the magnitude of resources appropriate to the task, from the perspectives of a former Secretary of Health and Human Services, a former FDA Commissioner, and an advocate for patients. In addition, the FDA's official response to the IOM recommendations will be presented.

8:10 am Ensuring commitment to safety through a strong FDA.

TOMMY THOMPSON
Honorary Chairman
Coalition for a Stronger FDA
Former Secretary for Health, U.S. Department of Health and Human Services

8:20 am Reflections on the historical challenges of regulating drug safety and efficacy.

JANE HENNEY
Senior Vice President and Provost for Health Affairs
University of Cincinnati Academic Health Center
Former Commissioner of Food and Drugs, U.S. Food and Drug Administration

8:30 am Preserving public trust in the drug safety regulatory system.

ELLEN SIGAL
Chairperson
Friends of Cancer Research

8:40 am The FDA response to the IOM drug safety report.

STEVE GALSON
Member, Forum on Drug Discovery, Development, and Translation
Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

8:50 am **Q & A**

Session 2: Integration of Pre- and Postmarket Review

Session Objectives: The IOM Drug Safety report recommends adoption of a lifecycle approach to drug review, including integration of pre- and postmarket review (**Recommendations 3.4, 4.4, 4.5, 4.13, and 5.4**). This session will describe the FDA's drug review process, the IOM recommendations for implementing a lifecycle approach to drug safety review, and the levels and types of resources needed to address the IOM report goals. In addition, the session will consider approaches to strengthening the scientific basis of premarket review.

9:05 am Overview of key IOM recommendations and introductions.

ALTA CHARO, PANEL MODERATOR
Member, IOM Drug Safety Committee
Professor
University of Wisconsin

Panel: Each panelist will make brief remarks followed by a Q&A period at the conclusion of the presentations.

9:15 am Operational challenges for instituting a lifecycle approach to drug review.

HUGH TILSON
Clinical Professor, Public Health Leadership
University of North Carolina School of Public Health

9:25 am Building FDA's capacity for science-based premarket review.

GARRET FITZGERALD
Member, Forum on Drug Discovery, Development, and Translation
Professor of Medicine, Professor and Chair of Pharmacology, Department of Pharmacology
University of Pennsylvania School of Medicine

9:35 am Current FDA initiatives to integrate pre- and postmarket review.

BOB TEMPLE
Director, Office of Drug Evaluation
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

ELLIS UNGER
Deputy Director for Science (Acting)
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

9:55 am Industry's role in the institution of a lifecycle approach to drug safety review.

TIM FRANSON
Vice President, Global Regulatory Affairs
Lilly Research Laboratories
Eli Lilly and Company

10:05 am **Q & A**

10:35 am **Break**

Session 3: Enhancing Postmarket Safety Monitoring

Session Objectives: The IOM drug safety report recommends significant changes in the FDA's postmarket review process (**Recommendations 4.1, 4.2, and 4.6**). This session will describe the FDA's current initiatives and the IOM recommendations for improving postmarket monitoring and drug safety review, and discuss the resources required to achieve the goals of the IOM report. Presentations will also consider ways to leverage existing resources to enhance postmarket safety monitoring, including the innovative use of databases and resources from other agencies, health plans, and industry.

10:50 am Overview of key IOM recommendations and introductions.

ANDY STERGACHIS, PANEL MODERATOR
Member, IOM Drug Safety Committee
Professor of Epidemiology and Adjunct Professor of Pharmacy
University of Washington

Panel: Each panelist will make brief remarks followed by a Q&A period at the conclusion of the presentations.

11:00 am FDA initiatives for improving drug safety monitoring.

GERALD DAL PAN
Director, Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

11:10 am Innovative use of existing data bases to aid in drug safety monitoring.

MARK MCCLELLAN
Visiting Senior Fellow
AEI Brookings Joint Center for Regulatory Studies
Former Commissioner of Food and Drugs, U.S. Food and Drug Administration

11:20 am Mining health plan patient data for drug safety monitoring.

Richard Platt
Professor and Chair
Harvard Medical School and Harvard Pilgrim Health Care

11:30 am Leveraging non-FDA resources for drug safety surveillance.

Barbara Alving
Acting Director, National Center for Research Resources
National Institutes of Health

11:40 am Feasibility of implementing new approaches to enhance postmarket safety monitoring.

Alec Walker
Senior Vice President for Epidemiology
i3 Drug Safety, Ingenix

11:50 am Industry initiatives for utilizing health care data.

Ron Krall
Member, Forum on Drug Discovery, Development, and Translation
Senior Vice President and Chief Medical Officer
GlaxoSmithKline

12:00 pm **Q & A**

12:30 pm **Lunch/Roundtable Discussion**

Session 4: Conducting Confirmatory Drug Safety and Efficacy Studies

Session Objectives: The FDA is limited in its ability to conduct studies on drugs that are already approved to assess the safety concerns or efficacy of drugs in clinical use. The IOM drug safety report calls for the development of public–private partnerships to prioritize, plan, and fund confirmatory drug safety and efficacy studies (**Recommendation 4.3)**. Panelists will discuss the FDA's current capacity to organize such studies, consider approaches to expanding this capacity, and examine the costs of

implementing these approaches. In addition, the IOM recommendation calling for enhanced clinical trial registration will be discussed (**Recommendation 4.11**).

1:30 pm Overview of key IOM recommendations and introductions.

ANDY STERGACHIS, PANEL MODERATOR

Panel: Each panelist will make brief remarks followed by a Q&A period at the conclusion of the presentations.

1:40 pm Current FDA initiatives to expand research capabilities.

JANET WOODCOCK
Member, Forum on Drug Discovery, Development, and Translation
Deputy Commissioner for Operations and Chief Medical Officer
U.S. Food and Drug Administration

1:50 pm Funding large research studies.

ROBERT CALIFF
Member, Forum on Drug Discovery, Development, and Translation
Director, Duke Translational Medicine Institute
Professor of Medicine
Vice Chancellor for Clinical and Translational Research
Duke University Medical Center

2:00 pm Enhancing the value of clinical trial registration.

DEBORAH ZARIN
Director, ClinicalTrials.gov
National Library of Medicine

2:10 pm An industry perspective on expanding the capacity for postmarket studies and regulation of ClinicalTrials.gov.

GRETCHEN DIECK
Senior Vice President, Safety and Risk Management
Pfizer Inc

2:20 pm **Q & A**

2:50 pm **Break**

Session 5: Enhancing Postmarket Regulation and Enforcement

Session Objectives: The IOM report calls for clarification or strengthening of existing authority to regulate drugs already on the market, new methods to address direct-to-consumer advertising, and sufficient enforcement tools to ensure that regulatory requirements imposed at or after approval are fulfilled (**Recommendations 5.1, 5.2, and 5.3)**. This session will describe how the FDA currently deals with concerns about drugs that are on the market, will consider various approaches to enhancing the FDA's ability to regulate drugs following approval, and will examine the resource implications for both the FDA and industry of alternative approaches.

3:05 pm Overview of key IOM recommendations and introductions.

Alta Charo, Panel Moderator

Panel: Each panelist will make brief remarks followed by a Q&A period at the conclusion of the presentations.

3:15 pm Providing FDA with clear and unambiguous regulatory authority.

Chris Schroeder
Member, IOM Drug Safety Committee
Professor of Law and Public Policy Studies
Duke University School of Law

3:25 pm Effective use of existing FDA authorities.

Peter Barton Hutt
Senior Counsel
Covington & Burling LLP

3:35 pm Anticipated impact of new regulations upon patient safety and access.

EVE E. SLATER
Director
Vertex Pharmaceuticals and Theravance, Inc.
Former Assistant Secretary for Health, U.S. Department of Health and Human Services

3:45 pm Making resources for postmarket compliance a priority.

MARY PENDERGAST
President
Pendergast Consulting

3:55 pm Industry perspectives on enhanced regulatory authority.

MARLENE HAFFNER
Executive Director, Global Regulatory and Intelligence Policy
Amgen, Inc.

4:05 pm **Q & A**

Session 6: Drug Safety Regulation: Looking to the Future

Session Objectives: Panelists will reflect on the challenges and opportunities for enhancing drug safety discussed throughout the day, and share their thoughts on the steps necessary to ensure the continued ability of the FDA to meet the challenge.

4:40 pm **MYRL WEINBERG**
President
National Health Council

4:50 pm **MARK MCCLELLAN**

5:10 pm **Q & A**

Closing Remarks

5:20 pm **GAIL CASSELL, SYMPOSIUM CHAIR**

5:30 pm **Adjourn**

Selected Recommendations from the IOM Report *The Future of Drug Safety*, Referred to in the Symposium[1]

Session 1: Preserving the Public Trust: Ensuring Drug Safety, Efficacy, and Availability

7.1: To support improvements in drug safety and efficacy activities over a product's lifecycle, the committee recommends that the Administration should request and Congress should approve substantially increased resources in both funds and personnel for the Food and Drug Administration.

Session 2: Integration of Pre- and Postmarket Review

3.4: The committee recommends that CDER [Center for Drug Evaluation and Research] appoint an OSE [Office of Surveillance and Epidemiology] staff member to each New Drug Application review team and assign joint authority to OND [Office of New Drugs] and OSE for postapproval regulatory actions related to safety.

4.4: The committee recommends that CDER assure the performance of timely and scientifically-valid evaluations (whether done internally or by industry sponsors) of Risk Minimization Action Plans (RiskMAPs).

4.5: The committee recommends that CDER develop and continually improve a systematic approach to risk-benefit analysis for use throughout the FDA in the preapproval and postapproval settings.

4.13: The committee recommends that the CDER review teams regularly and systematically analyze all postmarket study results and make public their assessment of the significance of the results with regard to the integration of risk and benefit information.

5.4: The committee recommends that FDA evaluate all new data on new molecular entities no later than 5 years after approval. Sponsors will submit a report of accumulated data relevant to drug safety and efficacy, including any additional data published in a peer-reviewed journal, and will report on the status of any applicable conditions imposed on the distribution of the drug called for at or after the time of approval.

[1]To see all 25 recommendations, refer to the full report or the summary at http://www.nap.edu/catalog/11750.html.

Session 3: Enhancing Postmarket Safety Monitoring

4.1: The committee recommends that in order to improve the generation of new safety signals and hypotheses, CDER [Center for Drug Evaluation and Research] (a) conduct a systematic, scientific review of the AERS [Adverse Event Reporting System], (b) identify and implement changes in key factors that could lead to a more efficient system, and (c) systematically implement statistical-surveillance methods on a regular and routine basis for the automated generation of new safety signals.

4.2: The committee recommends that in order to facilitate the formulation and testing of drug safety hypotheses, CDER (a) increase their intramural and extramural programs that access and study data from large automated healthcare databases and (b) include in these programs studies on drug utilization patterns and background incidence rates for adverse events of interest, and (c) develop and implement active surveillance of specific drugs and diseases as needed in a variety of settings.

4.6: The committee recommends that CDER build internal epidemiologic and informatics capacity in order to improve postmarket assessment of drugs.

Session 4: Conducting Confirmatory Drug Safety and Efficacy Studies

4.3: The committee recommends that the Secretary of HHS [Health and Human Services], working with the Secretaries of Veterans Affairs and Defense, develop a public-private partnership with drug sponsors, public and private insurers, for-profit and not-for-profit 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. Congress should capitalize the public share of this partnership.

4.11: The committee recommends that Congress require industry sponsors to register in a timely manner at clinicaltrials.gov, at a minimum, all phase 2 through 4 clinical trials, wherever they may have been conducted, if data from the trials are intended to be submitted to the FDA as part of an NDA [New Drug Application], sNDA [supplemental New Drug Application], or to fulfill a postmarket commitment. The committee further recommends that this requirement include the posting of a structured field summary of the efficacy and safety results of the studies.

Session 5: Enhancing Postmarket Regulation and Enforcement

5.1: The committee recommends that Congress ensure that the Food and Drug Administration has the ability to require such postmarketing risk assessment and risk management programs as are needed to monitor and ensure safe use of drug products. These conditions may be imposed both before and after approval of a new drug, new indication, or new dosage, as well as after identification of new contraindications or patterns of adverse events. The limitations imposed should match the specific safety concerns and benefits presented by the drug product. The risk assessment and risk management program may include:

a. Distribution conditioned on compliance with agency-initiated changes in drug labels.
b. Distribution conditioned on specific warnings to be incorporated into all promotional materials (including broadcast direct-to-consumer [DTC] advertising).
c. Distribution conditioned on a moratorium on DTC advertising.
d. Distribution restricted to certain facilities, pharmacists, or physicians with special training or experience.
e. Distribution conditioned on the performance of specified medical procedures.
f. Distribution conditioned on the performance of specified additional clinical trials or other studies.
g. Distribution conditioned on the maintenance of an active adverse event surveillance system.

5.2: The committee recommends that Congress provide oversight and enact any needed legislation to ensure compliance by both the Food and Drug Administration and drug sponsors with the provisions listed above. FDA needs increased enforcement authority and better enforcement tools directed at drug sponsors, which should include fines, injunctions, and withdrawal of drug approval.

5.3: The committee recommends that Congress amend the Food, Drug and Cosmetic Act to require that product labels carry a special symbol such as the black triangle used in the UK or an equivalent symbol for new drugs, new combinations of active substances, and new systems of delivery of existing drugs. The Food and Drug Administration should restrict direct-to-consumer advertising during the period of time the special symbol is in effect.

Appendix B

Speaker Biographies

SYMPOSIUM MODERATORS

GAIL H. CASSELL, PhD (Member, IOM Forum on Drug Discovery, Development, and Translation), is currently Vice President, Scientific Affairs, and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company, Indianapolis, Indiana. She is former Charles H. McCauley Professor and Chair of the Department of Microbiology, University of Alabama Schools of Medicine and Dentistry at Birmingham, a department that ranked first in research funding from the National Institutes of Health (NIH) during the decade of her leadership. She obtained her BS from the University of Alabama in Tuscaloosa and in 1993 was selected as one of the top 31 female graduates of the twentieth century. She obtained her PhD in microbiology from the University of Alabama at Birmingham and was selected as its 2003 Distinguished Alumnus. She is past President of the American Society for Microbiology (the oldest and single largest life sciences organization, with a membership of more than 42,000). She was a member of the NIH Director's Advisory Committee and of the Advisory Council of the National Institute of Allergy and Infectious Diseases. She was named to the original Board of Scientific Councilors of the Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), and served as chair of the board. She recently served a 3-year term on the advisory board of the Director of CDC and as a member of the Secretary of Health and Human Services' Advisory Council of Public Health Preparedness. Currently she is a member of the Science Board of the U.S. Food and Drug Administration (FDA). Since

1996 she has been a member of the U.S.–Japan Cooperative Medical Science Program, responsible for advising the respective governments (U.S. State Department/Japanese Ministry of Foreign Affairs) on joint research agendas. She has served on several editorial boards of scientific journals and has authored more than 250 articles and book chapters. Dr. Cassell has received national and international awards and an honorary degree for her research in infectious diseases. She is a member of the Institute of Medicine (IOM) and is currently serving a 3-year term on the IOM Council, the institution's governing board. Dr. Cassell has been intimately involved in the formulation of science policy and legislation related to biomedical research and public health. For 9 years she was chair of the Public and Scientific Affairs Board of the American Society for Microbiology; she has served as an advisor on infectious diseases and indirect costs of research to the White House Office of Science and Technology Policy, and has been an invited participant in numerous congressional hearings and briefings related to infectious diseases, antimicrobial resistance, and biomedical research. She has served two terms on the Liaison Committee on Medical Education (LCME), the accrediting body for U.S. medical schools, as well as other national committees involved in establishing policies on training in the biomedical sciences. She recently completed a term on the Leadership Council of the School of Public Health of Harvard University. Currently she is a member of the Executive Committee of the Board of Visitors of Columbia University School of Medicine, the Executive Committee of the Board of Directors of the Burroughs Wellcome Fund, Research!America, and the Advisory Council of the Johns Hopkins School of Nursing.

R. ALTA CHARO (Member, IOM Drug Safety Committee) is Warren P. Knowles Professor of Law and Bioethics, University of Wisconsin at Madison, where she is on the faculty of the Law School and the Medical School's Department of Medical History and Bioethics. She also serves on the faculty of the university's Masters in Biotechnology Studies program and lectures in the Master of Public Health program of the Department of Population Health Sciences. She received her BA in biology from Harvard University in 1979 and JD from Columbia University School of Law in 1982. She has been elected to membership in the Wisconsin Academy of Sciences, Arts and Letters and the IOM. Ms. Charo serves on the expert advisory boards of several organizations with an interest in stem cell research, including CuresNow, the Juvenile Diabetes Research Foundation, the International Society for Stem Cell Research, and WiCell, as well as on the advisory board of the Wisconsin Stem Cell Research Program. In 2005 she was appointed to the ethics standards working group of the California Institute for Regenerative Medicine. Also in 2005, she

helped draft the National Academies' Guidelines for Embryonic Stem Cell Research, and in 2006 she was appointed to co-chair the National Academies' Human Embryonic Stem Cell Research Advisory Committee. In 1994 Ms. Charo served on the NIH Human Embryo Research Panel, and from 1996 to 2001 she was a member of President Clinton's National Bioethics Advisory Commission. Since 2001 she has been a member of the National Academy of Sciences' Board on Life Sciences. She served as its liaison to the Committee on Research Standards and Practices to Prevent Destructive Applications of Biotechnology, as well as serving on its Advisory Committee on Human Embryonic Stem Cell Research. She also served as a member of the IOM's Committee on Smallpox Vaccination Program Implementation, and in 2006 was appointed to the IOM's Board on Population Health and Public Health Practice. In 2005–2006, she served on the IOM Committee on the Assessment of the U.S. Drug Safety System, which reviewed the FDA and the U.S. national system for the assurance of drug safety.

ANDY STERGACHIS, PhD, MS, RPh (Member, IOM Drug Safety Committee), is Professor of Epidemiology and Adjunct Professor of Pharmacy and Interim Chair, Department of Pathobiology, School of Public Health and Community Medicine, University of Washington. He was previously Chair of the university's Department of Pharmacy and founding Director of its Program in Pharmaceutical Outcomes Research and Policy. Through his affiliation with the university's Northwest Center for Public Health Practice, he focuses on education, training, and research in emergency preparedness in collaboration with the public health and pharmacist communities. Dr. Stergachis has served on NIH's Epidemiology and Disease Control Study Section; the Agency for Healthcare Research and Quality's (AHRQ) Health Systems Research Study Section; committees of the National Committee on Quality Assurance; and the IOM's Committee on Poison Prevention and Control and Committee to Study the Interactions of Drugs, Biologics, and Chemicals in the U.S. Military. He held several positions with Group Health Cooperative of Puget Sound and served on its Pharmacy and Therapeutics Committee for 12 years. In 1998 he joined drugstore.com, for which he has served as Vice President and Chief Pharmacist and currently serves as Pharmacy Advisor. He co-founded and served as principal of Formulary Resources and presently serves as the company's consultant on managed care pharmacy. Dr. Stergachis is also pharmacoepidemiology consultant to United HealthCare for its pharmacoepidemiology cooperative agreement with the FDA. He was the 1990 American College of Preventive Medicine/Burroughs Wellcome Scholar in Pharmacoepidemiology. The American Association of Pharmaceutical Research Scientists presented him with the 1994 Research Achievement

Award in Economic, Marketing and Management Sciences. In 1999 he was selected as one of the 50 Most Influential Pharmacists in the United States by American Druggist. He was awarded the 2002 Pinnacle Award by the American Pharmaceutical Association Foundation for career contributions toward improving the quality of care through the medication use process. Dr. Stergachis' research in the prevention of pelvic inflammatory disease helped lead to new recommendations from CDC and to the Health Plan Employer Data and Information System (HEDIS) measure "Chlamydia Screening in Women." Dr. Stergachis serves as board member for the American Pharmacists Association Foundation and the Group Health Community Foundation, and he is a fellow of the International Society for Pharmacoepidemiology. His research interests include pharmacoepidemiology and the epidemiology of biological and chemical hazards. He received his PhD and MS from the University of Minnesota and his BPharm from Washington State University.

Session 1: Preserving the Public Trust: Ensuring Drug Safety, Efficacy, and Availability

TOMMY THOMPSON, JD, was Secretary of Health and Human Services (HHS) from 2001 to 2005 and four-term Governor of Wisconsin, 1987 to 2001; he made state history when he was reelected to office for a third term in 1994 and a fourth term in 1998. He is Chair of the Deloitte Center for Health Solutions and a partner at the law firm of Akin Gump Strauss Hauer & Feld LLP. He also serves as Honorary Chair of the Coalition for a Stronger FDA. Secretary Thompson has dedicated his professional life to public service and is one of the nation's leading advocates for the health and welfare of all Americans. At Deloitte and Akin Gump, he is building on his efforts as HHS Secretary and Governor of Wisconsin to develop innovative solutions to the health care challenges facing American families, businesses, communities, and states and the nation as a whole. The focus is on improving the use of information technology in hospitals, clinics, and doctors' offices; promoting healthier lifestyles; strengthening and modernizing Medicare and Medicaid; and expanding the use of medical diplomacy around the world.

JANE E. HENNEY, MD, is Senior Vice President and Provost for Health Affairs at the University of Cincinnati. Beginning in 1980, she served for 5 years as Deputy Director of the National Cancer Institute. Subsequently, she joined the University of Kansas Medical Center as Vice Chancellor for Health Programs. She then served as the FDA's Deputy Commissioner for Operations until assuming the position of First Vice President for Health Sciences at the University of Mexico. In 1998 she was appointed

Commissioner of the FDA by President Clinton, a position she held until 2001. After leaving the FDA, Dr. Henney was appointed Senior Scholar in Residence at the Association of Academic Health Centers. She serves on a number of boards of directors related to her work in Cincinnati, including UC Foundation, UC Physicians, University Hospital, Health Alliance of Greater Cincinnati, Hoxworth Blood Center, Medical Center Fund of Cincinnati, Bio/Start, and OMERIS. Additionally, she serves on the boards of The Commonwealth Fund and the China Medical Board in New York City, AmerisourceBergen Corporation and CIGNA Corporation in Philadelphia, and AstraZeneca PLC in London. Dr. Henney has received many honors and awards in her field, including election to the IOM and the Society of Medical Administrators and honorary membership in the American Colleges of Health Care Executives. Dr. Henney received her undergraduate degree from Manchester College and her medical degree from Indiana University, and completed her subspecialty training in medical oncology at the M.D. Anderson Hospital and Tumor Institute and the National Cancer Institute.

ELLEN V. SIGAL, PhD, is founder and Chair of Friends of Cancer Research, a nonprofit organization based in the Washington, DC, metropolitan area. She serves on the National Cancer Institute's Board of Scientific Advisors; the NIH Foundation Board, chairing its Public-Private Partnerships Committee; the American Association for Cancer Research Foundation Board; the M. D. Anderson Cancer Center External Advisory Board; the Johns Hopkins Cancer Center Advisory Council; the Duke University Cancer Center Board of Overseers; and the Howard University Cancer Center Board of Visitors. She served on the NIH's prestigious Director's Council of Public Representatives from 2003 to 2006. She was a presidential appointee to the National Cancer Advisory Board from 1992 to 1998, chairing its Budget and Planning Committee, which oversees the federal cancer budget. She is a past member of the American Society of Clinical Oncology Foundation Board. Dr. Sigal received the Association of American Cancer Institutes' Public Service Award, the American Society of Clinical Oncology Special Recognition Award, the Sidney Kimmel Cancer Center National Leadership Award, and the American Association for Cancer Research National Leadership Award. She has been honored by Research!America, George Washington University Cancer Institute, International Spirit of Life Foundation, and *Washingtonian* magazine as a Washingtonian of the Year.

STEVEN K. GALSON, MD, MPH (Member, IOM Forum on Drug Discovery, Development, and Translation), was named Director of the FDA's Center for Drug Evaluation and Research (CDER) in July 2005. He pro-

vides leadership for the center's broad national and international programs in pharmaceutical regulation. Dr. Galson began his Public Health Service (PHS) career as an epidemiological investigator at CDC after completing a residency in internal medicine at the Hospitals of the Medical College of Pennsylvania. He has held senior-level positions at the Environmental Protection Agency (EPA); the Department of Energy, where he was Chief Medical Officer; and the Department of Health and Human Services. Prior to his arrival at the FDA, he was Director of the EPA's Office of Science Coordination and Policy, and the Office of Prevention, Pesticides and Toxic Substances. Dr. Galson joined the FDA in April 2001 as CDER Deputy Director. He is the recipient of numerous PHS awards, including the Outstanding Service Medal for his leadership and management of CDER while serving as Acting Center Director from November 2001 to February 2002. He is also the recipient of three Secretary of Energy Gold Awards. Dr. Galson is a board member of the National Board of Medical Examiners and a regular peer reviewer for medical journals. He holds a BS from Stony Brook University, an MD from Mt. Sinai School of Medicine, and an MPH from the Harvard School of Public Health. He is board certified in preventive medicine and public health and occupational medicine.

Session 2: Integration of Pre- and Postmarket Review

HUGH TILSON, MD, DrPH (Washington University, St. Louis, Missouri, 1964, and Harvard School of Public Health, 1972), is a practicing epidemiologist and outcomes researcher whose career in public health and preventive medicine spans 40 years. Fifteen years of public service included duties as a U.S. Army Preventive Medicine Officer in Germany; consultant to the U.S. Office of Economic Opportunity, National Center for Health Services Research, and Veterans Health Administration; Local Public Health Officer and Human Services Director for Multnomah County (Portland), Oregon (National Association of County and City Health Officials [NACCHO] President, 1976); and State Public Health Director for North Carolina. During his 15 years working in the multinational pharmaceutical industry for the Wellcome Foundation, he is credited with introducing many epidemiological principles and innovations. Upon his retirement from GlaxoWellcome in 1996, he joined the clinical faculty of the University of North Carolina. He is an advisor to government and industry in health outcomes, drug safety, and evidence-based health policy, including, most recently, public health preparedness. He was a member of the working groups on drug safety of the Council for International Organisations for the Medical Sciences (CIOMS) from 1990 to 2001 and an advisor to the recent CIOMS VI and to the World Health

Organization's Collaborating Centres. In the United States, he chairs the National Steering Committee for the Centers for Education and Research on Therapeutics program for AHRQ, and serves as senior advisor and epidemiologist for the international Antiretrovirals in Pregnancy Registry. He was a member of the recently adjourned IOM Clinical Research Roundtable and served as a consultant to the IOM's landmark study *The Future of Drug Safety*, released in fall 2006. He recently chaired two IOM study committees—Safety of Therapeutic Devices in Children and Prevention of HIV for Injection Drug Users. Dr. Tilson has been designated a Lifetime National Associate of the IOM.

GARRET A. FITZGERALD, MD (Member, IOM Forum on Drug Discovery, Development, and Translation), is Professor of Medicine and Elmer Bobst Professor of Pharmacology, University of Pennsylvania, where he chairs the Department of Pharmacology and directs the Institute for Translational Medicine and Therapeutics. Previously, he was Professor and Chair of the Department of Medicine and Experimental Therapeutics, University College, Dublin, Ireland, as well as founding Director of the Center for Cardiovascular Science. Prior to that, he was William Stokes Professor of Experimental Therapeutics and Director of the Division of Clinical Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee. Dr. FitzGerald holds membership in a number of learned societies in the United States and the United Kingdom, and has received numerous honors. He has authored 257 original articles in the fields of cardiovascular medicine and pharmacology. His work has contributed to the adoption of low-dose aspirin for cardiac prophylaxis, and he was the first to predict a cardiovascular hazard from selective inhibition of COX-2. He also pioneered the emergence of isoprostanes as biomarkers of oxidant stress. More recently, his group defined the role of peripheral clocks in vascular function and metabolism.

ROBERT TEMPLE, MD, is Director of the Office of Medical Policy of CDER and Acting Director of the Office of Drug Evaluation I (ODE-I). Dr. Temple received his medical degree from the New York University School of Medicine in 1967. In 1972 he joined CDER as a review Medical Officer in the Division of Metabolic and Endocrine Drug Products. He later assumed the position of Director of the Division of Cardio-Renal Drug Products. In his position as Acting Director of ODE-1, he oversees that office's regulation of cardio-renal, neuropharmacological, and psychopharmacological drug products. He also oversees the Office of Medical Policy, which is responsible for the regulation of promotion through the Division of Drug Marketing, Advertising, and Communication. He has served in this capacity since the office's establishment in 1995.

ELLIS F. UNGER, MD, is Acting Deputy Director of CDER's Office of Surveillance and Epidemiology (OSE). He obtained his medical degree from the University of Cincinnati, and received postdoctoral training at the Medical College of Virginia (internal medicine) and The Johns Hopkins Hospital (clinical cardiology). Dr. Unger was a Senior Investigator in the Cardiology Branch of NIH's National Heart, Lung, and Blood Institute from 1983 to 1997, where he directed a research program in angiogenesis, developing new approaches for the treatment of coronary artery disease and peripheral vascular disease. From 1997 to 2003, he served as Medical Officer, Team Leader, and subsequently Branch Chief in the Office of Therapeutics Research and Review (OTRR) in the FDA's Center for Biologics Evaluation and Research. In 2003, Dr. Unger assumed the responsibilities of Deputy Director, Division of Cardiovascular and Renal Products, in CDER. He served as FDA representative to CIOMS Working Group VII, and presently represents the agency on the International Conference on Harmonization Expert Working Group on E2F, the Development Safety Update Report. Dr. Unger has authored, co-authored, and edited numerous scientific articles and is a co-holder of two patents.

TIMOTHY R. FRANSON, MD, is currently Vice President of Global Regulatory Affairs for Lilly Research Laboratories and Assistant Professor of Medicine at Indiana University School of Medicine. He received his undergraduate degree in pharmacy (with honors) at Drake University and his MD (James Scholar, with honors) at the University of Illinois; he completed internal medicine training at the University of Iowa, followed by a fellowship in infectious diseases and epidemiology at the Medical College of Wisconsin. He is board certified in internal medicine and infectious diseases. He was previously Assistant Professor of Medicine and Hospital Epidemiologist at the Medical College of Wisconsin, where he was an NIH-funded investigator and a member of the State of Wisconsin's Governors Task Force on AIDS. He joined Eli Lilly and Company in 1986, where he has served as Director of Anti-Infectives; Group Medical Director, Europe (based in the United Kingdom); Executive Director of Health Economics Research and Decision Sciences; Executive Director of North American Regulatory Affairs; and from 1997 to 2003, Vice President of Clinical Research and Regulatory Affairs-U.S. In 2002 he received the Lilly Chairman's Ovation Award. Dr. Franson has authored more than 50 articles and a text in the fields of infectious disease, epidemiology, pharmacoeconomics, and antibiotic utilization. He has served as Chair of the Clinical Steering Committee and as a member of the Regulatory Affairs Coordinating Committee of the Pharmaceutical Research and Manufacturers' Association (PhRMA), previously chaired PhRMA's GMP Steering Committee, and now chairs its FDA Committee Staff Work Group. He

was co-chair of the joint FDA–industry working group addressing clinical aspects of the FDA Modernization Act of 1997, including renewal of the Prescription Drug User Fee Act (PDUFA); he co-chaired the industry–FDA committee for PDUFA-III renewal and has testified as an industry representative at several congressional hearings. Dr. Franson also co-chaired an FDA–industry safety interventions working group, was a member of the American Association of Medical Colleges PhRMA Clinical Trials Forum, and is a member of the Regulatory Advisory Board for the Centre for Medicines Research International. He previously served on the Board of Directors of the National Patient Safety Foundation (2001–2006) and on the Editorial Advisory Board for the FDA's Advertising and Promotional Manual. He is now chair of the Board of Directors of the Villages of Indiana child welfare services and a member of the Indiana State Museum Foundation, as well as the Board of Trustees of Xavier University of Louisiana; he also serves on the American Association of Colleges of Pharmacy Professional Education Advisory Council. He is a fellow of the Infectious Diseases Society of America and the American College of Physicians, served on the European Working Party for Antimicrobial Trial Guidelines, and was principal respondent for industry at the FDA Advisory Committee review of the FDA/Infectious Diseases Society of America (IDSA) Antimicrobial Trial Guidelines project.

Session 3: Enhancing Postmarket Safety Monitoring

GERALD DAL PAN, MD, MHS, is Director of OSE in CDER. He previously was Director of CDER's Division of Surveillance, Research, and Communication Support, Office of Drug Safety (now OSE), a position he held from 2003 to 2005. Dr. Dal Pan joined the agency in 2000 and spent 3 years as a medical reviewer in the Division of Anesthetic Critical Care and Addiction Drug Products before assuming his position in the Office of Drug Safety. Prior to joining CDER, Dr. Dal Pan directed clinical research, including clinical trial design and interpretation of clinical data, for Guilford Pharmaceuticals and HHI, LLC, Clinical Research and Statistical Services. He also served on the faculty of The Johns Hopkins University School of Medicine, where he conducted clinical research in addition to teaching medical students. He continues there as a part-time Assistant Professor in the Department of Neurology.

MARK B. MCCLELLAN, MD, PhD, is former Administrator for the Centers for Medicare and Medicaid Services (CMS) and former Commissioner of food and drugs. He has had a highly distinguished tenure of public service. In the George W. Bush administration, he served as a member of the President's Council of Economic Advisers and Senior Director for

Health Care Policy at the White House (2001–2002), FDA commissioner (2002–2004), and CMS Administrator. In these positions, he developed and implemented major reforms in health policy. In the Clinton administration, Dr. McClellan was Deputy Assistant Secretary of the Treasury for Economic Policy from 1998 to 1999, supervising economic analysis and policy development on a range of domestic policy issues. He subsequently directed Stanford's Program on Health Outcomes Research, and was a Research Associate of the National Bureau of Economic Research and a visiting scholar at the American Enterprise Institute. Additionally, he was Associate Editor of the *Journal of Health Economics* and co–principal investigator of the Health and Retirement Study, a longitudinal study of the health and economic well-being of older Americans. A graduate of the University of Texas at Austin, he earned his MPA from Harvard's Kennedy School of Government in 1991, his MD from the Harvard-MIT Division of Health Sciences and Technology in 1992, and his PhD in economics from MIT in 1993. He completed his residency training in internal medicine at Brigham and Women's Hospital, Boston. Dr. McClellan has been board certified in internal medicine and has been a practicing internist during his academic career. His academic research has been concerned with the effectiveness of medical treatments in improving health, the economic and policy factors influencing medical treatment decisions and health outcomes, the impact of new technologies on public health and medical expenditures, and the relationship between health status and economic well-being. He has twice received the Kenneth J. Arrow Award for Outstanding Research in Health Economics.

RICHARD PLATT, MD, MSc, is Professor and Chair of the Department of Ambulatory Care and Prevention, Harvard Medical School. He is an internist trained in infectious diseases and epidemiology. He is a member of the Association of American Medical Colleges Advisory Panel on Research and the IOM Roundtable on Evidenced Based Medicine, and currently chairs the FDA's Drug Safety and Risk Management Advisory Committee. He has chaired the Executive Committee of the HMO Research Network, was co-chair of the Board of Scientific Counselors of CDC's Center for Infectious Diseases, and chaired the NIH study section Epidemiology and Disease Control 2 and the CDC Office of Health Care Partnerships Steering Committee. His research focuses on developing multi-institution automated record linkage systems for use in pharmacoepidemiology and population-based surveillance, reporting, and control of both hospital- and community-acquired infections, including bioterrorism events. He is principal investigator of the CDC-sponsored Center of Excellence in Public Health Informatics (www.phiconnect.org) and the AHRQ-sponsored HMO Research Network Center for Education and

Research in Therapeutics (www.certs.hhs.gov), and co–principal investigator of the Modeling Infectious Disease Agent Study (http://www.nigms.nih.gov/Initiatives/MIDAS) and the CDC-sponsored Eastern Massachusetts Prevention Epicenter.

BARBARA M. ALVING, MD, is Acting Director of NIH's National Center for Research Resources (NCRR). NCRR provides funding for general clinical research centers, biomedical technology, preclinical models, and other resources to enhance the research environment of biomedical investigators engaged in health-related research. Dr. Alving earned her medical degree (cum laude) from Georgetown University School of Medicine, where she also completed an internship in internal medicine. She received her residency training in internal medicine at The Johns Hopkins University Hospital, followed by a fellowship in hematology. She then became a research investigator in the FDA's Division of Blood and Blood Products. In 1980 she joined the Department of Hematology at the Walter Reed Army Institute of Research, where she became Chief in 1992. She left the Army at the rank of colonel in 1996 to become Director of the Medical Oncology/Hematology Section at Washington Hospital Center in Washington, DC. In 1999 she joined the National Heart, Lung, and Blood Institute (NHLBI), serving as Director of the extramural Division of Blood Diseases and Resources until becoming Deputy Director in September 2001. From September 2003 to February 1, 2005, she served as Acting Director of NHLBI. She became Acting Director of NCRR in March 2005. Dr. Alving is Professor of Medicine at the Uniformed Services University of the Health Sciences in Bethesda, Maryland; a Master in the American College of Physicians; a former member of the Subcommittee on Hematology of the American Board of Internal Medicine; and a former member of the FDA's Blood Products Advisory Committee. She is a coinventor on two patents, has edited three books, and has published more than 100 papers in the areas of thrombosis and hemostasis.

ALEXANDER M. WALKER, MD, DrPH, is Senior Vice President for Epidemiology in the i3 Drug Safety group at Ingenix. He is Adjunct Professor of Epidemiology at Harvard School of Public Health, where he was formerly Professor and Chair of the Department of Epidemiology. His research encompasses the safety of drugs, devices, vaccines, and medical procedures. Current studies address postmarketing safety for recently approved drugs, the natural history of disease as context for Phase III clinical trials, the impact of drug labeling and warnings on prescribing behavior, and determinants of drug uptake and discontinuation. His additional areas of research and expertise include health effects of chemicals used in the workplace and statistical methods in epidemiology.

Dr. Walker received his MD from Harvard Medical School in 1974 and his doctorate in public health in epidemiology from the Harvard School of Public Health in 1981. He is associate editor of *Pharmacoepidemiology and Drug Safety* and is on the Board of Directors of the International Society for Pharmacoepidemiology, which he also served as President in 1995 to 1996. He was a statistical consultant for the *New England Journal of Medicine* from 1992 through 1996 and a contributing editor of *The Lancet* from 1999 through 2001. Dr. Walker has written or contributed to more than 250 peer-reviewed articles on drug safety, epidemiology, and occupational health, and is the author of a book of essays entitled *Observation and Inference: An Introduction to the Methods of Epidemiology*.

RONALD L. KRALL, MD (Member, IOM Forum on Drug Discovery, Development, and Translation), is Senior Vice President and Chief Medical Officer for GlaxoSmithKline (GSK). He is responsible for all matters of human safety for all GSK compounds used in development and medicinal and vaccine products, and for pharmaceutical regulatory affairs and GxP compliance. Dr. Krall joined GSK in 2003. Previously, he held positions at AstraZeneca Pharmaceuticals, Abbott Laboratories, and Lorex Pharmaceuticals. He earned his bachelor's degree in mathematics from Swarthmore College and his MD from the University of Pittsburgh, trained as a Staff Associate at the NIH Epilepsy Branch, and completed his training in neurology and clinical pharmacology at the University of Rochester. He is board certified in neurology, and is a former member of the Board of Directors of the National Sleep Foundation, a member of the Board of Directors of the Delaware Valley Science Fairs, a member of the University of Pennsylvania Center for Bioethics Advisory Board, and a past Trustee of the American Academy of Pharmaceutical Physicians.

Session 4: Conducting Confirmatory Drug Safety and Efficacy Studies

JANET WOODCOCK, MD (Member, IOM Forum on Drug Discovery, Development, and Translation), is Deputy Commissioner for Operations and Chief Medical Officer, FDA. She is responsible for overseeing agency operations and cross-cutting regulatory and scientific processes. Dr. Woodcock served as CDER Director from 1994 to 2005. She previously served in other positions at the FDA, including Director, Office of Therapeutics Research and Review, and Acting Deputy Director, Center for Biologics Evaluation and Research. Dr. Woodcock received her MD from Northwestern Medical School, and completed further training and held teaching appointments at the Pennsylvania State University and the University of California, San Francisco. She joined the FDA in 1986.

ROBERT CALIFF, MD (Member, IOM Forum on Drug Discovery, Development, and Translation), is currently Vice Chancellor for Clinical Research, Director of the Duke Translational Medicine Institute, and Professor of Medicine in the Division of Cardiology at the Duke University Medical Center in Durham, North Carolina. For 10 years he was Director of the Duke Clinical Research Institute (DCRI), the largest academic research organization in the world. He is editor-in-chief of *Elsevier's American Heart Journal*. He has been an author or co-author of more than 650 peer-reviewed journal articles and is a contributing editor for www.theheart.org. Dr. Califf led DCRI for many of the best-known clinical trials in cardiovascular disease. In cooperation with his colleagues from the Duke Databank for Cardiovascular Disease, he has written extensively about the clinical and economic outcomes of chronic heart disease. He is considered an international leader in the fields of health outcomes, quality of care, and medical economics. He has served on the FDA's Cardiorenal Advisory Panel and the IOM's Pharmaceutical Roundtable. He served on the IOM committees that recommended Medicare coverage of clinical trials and the banning of Ephedra, and he is currently serving on the IOM's Committee on Identifying and Preventing Medication Errors. He is Director of the coordinating center for the Centers for Education and Research on Therapeutics, a public–private partnership among AHRQ, the FDA, academia, the medical-products industry, and consumer groups. Dr. Califf graduated from Duke University (summa cum laude) in 1973 and from Duke University Medical School in 1978. He performed his internship and residency at the University of California, San Francisco, and his fellowship in cardiology at Duke University. He is board certified in internal medicine and cardiology and is a fellow of the American College of Cardiology.

DEBORAH A. ZARIN, MD, is Director, ClinicalTrials.gov, and Assistant Director for Clinical Research Projects, Lister Hill National Center for Biomedical Communications, National Library of Medicine. In this capacity, she oversees the development and operation of an international registry of clinical trials. Previously, she served as Director, Technology Assessment Program, AHRQ, and Director, Practice Guidelines Program, American Psychiatric Association. In these positions, she conducted systematic reviews and related analyses to support the development of clinical and policy recommendations. Dr. Zarin's academic interests are in the area of evidence-based clinical and policy decision making. She graduated from Stanford University and received her doctorate in medicine from Harvard Medical School. She completed a clinical decision-making fellowship and is board certified in general psychiatry, as well as in child and adolescent psychiatry.

GRETCHEN DIECK, PhD, is Senior Vice President, Safety and Risk Management, Pfizer Inc., where she is responsible for providing risk management support and compliance functions across the product portfolio. Included in these responsibilities are case processing and risk management functions related to epidemiology and medical safety evaluation, as well as safety and risk management–related analysis and documentation. Dr. Dieck has been at Pfizer for more than 20 years, having started as a staff epidemiologist in 1986. She was a founding board member of the International Society for Pharmacoepidemiology and is a member of the International Conference on Harmonization (ICH) Risk Communication Working Group. In addition, she is past Chair of the Pharmacovigilance and Epidemiology Technical Group of PhRMA and heads the Risk Management Working Group of PhRMA's Pharmaceuticals Innovation Steering Committee. Dr. Dieck represented PhRMA during PDUFA III discussions, and both co-leads the PostMarket Safety Group and serves on the Steering Committee for PDUFA IV. She received an AB in biological sciences from Smith College; she received an MPhil and PhD in epidemiology and also completed a postdoctoral fellowship in cardiovascular disease epidemiology at Yale University.

Session 5: Enhancing Postmarket Regulation and Enforcement

CHRISTOPHER H. SCHROEDER, MDiv, JD (Member, IOM Drug Safety Committee), is Charles S. Murphy Professor of Law and Professor of Public Policy Studies and Director of the Program in Public Law at Duke University. He served as Deputy Assistant Attorney General in the Office of Legal Counsel, U.S. Department of Justice, and in 1996–1997 was Acting Assistant Attorney General in charge of that office. Previously, he worked for the Senate Judiciary Committee, serving as its Chief Counsel in 1992–1993. Dr. Schroeder's scholarship includes work on constitutional law, Congress, risk regulation and theory, and tort. Current projects include a book on democratic theory and executive power. He co-authors a leading environmental law casebook, *Environmental Regulation: Law, Science and Policy* (5th Edition, 2006) with Robert Percival, Alan Miller, and James Leape. He also serves as Vice President of the Center for Progressive Reform, a network of scholars who write about and adovcate progressive approaches to environmental, health, and safety policy. Along with Rena Steinzor, he is co-editor of the center's book *The New Progressive Agenda for Public Health and the Environment* (2005) (www.progressivereform.org). His work with O'Melveny & Myers focuses on appellate litigation.

PETER BARTON HUTT, JD, LLM, is Senior Counsel in the Washington, DC, law firm of Covington & Burling LLP, specializing in food and

drug law. He graduated from Yale College and Harvard Law School and obtained a master of laws degree in food and drug law from New York University Law School. Mr. Hutt served as Chief Counsel for the FDA between 1971 and 1975. He is co-author of the casebook used to teach food and drug law throughout the country, and has published more than 175 book chapters and articles on food and drug law and health policy. Since 1994 he has taught a full course on this subject each year during winter term at Harvard Law School, and in 1998 he taught this course during spring term at Stanford Law School. Mr. Hutt has been a member of the IOM since it was founded in 1971. He serves on academic, philanthropic, and venture capital advisory boards and the boards of startup biotechnology companies. He is a member of the FDA's Science Board Working Group, which reviews the agency's science needs to perform its regulatory mission. He is a member of the Board of Directors of the AERAS Global TB Vaccine Foundation, and he recently served on the Panel on the Administrative Restructuring of the National Institutes of Health and the Working Group to Review Regulatory Activities within the Division of AIDS of the National Institute of Allergy and Infectious Diseases. Mr. Hutt was named by *Washingtonian* magazine as one of Washington's 50 best lawyers and one of Washington's 100 most influential people; by the *National Law Journal* as one of the 40 best health care lawyers in the United States; and by *European Counsels* as the best FDA regulatory specialist in Washington, DC. In June 2003, *Business Week* referred to him as the "unofficial dean of Washington food and drug lawyers." In naming Mr. Hutt in September 2005 as one of the 11 best food and drug lawyers, the *Legal Times* also referred to him as "the dean of the food-and-drug bar." In April 2005, Mr. Hutt was presented the FDA Distinguished Alumni Award by FDA Commissioner Crawford. In May 2005, the Foundation for Biomedical Research gave him the Lifetime Achievement Award for research advocacy.

EVE E. SLATER, MD, FACC, is a graduate of Vassar College and of Columbia University's College of Physicians and Surgeons. She completed her internship and residency at the Massachusetts General Hospital (MGH) and is board certified in both internal medicine and cardiology. In 1976 Dr. Slater became the first woman Chief Resident in Medicine at MGH, and from 1977 through 1982 she served as Chief of the hospital's Hypertension Unit and was Assistant Professor of Medicine at Harvard Medical School. She joined Merck Research Laboratories (MRL) in 1983 and became Head of Regulatory Affairs in 1988, Vice President of Clinical and Regulatory Development in 1990, and Senior Vice President in 1994. In 2001 she was named Senior Vice President of MRL External Policy and Vice President, Corporate Public Affairs. Dr. Slater supervised

worldwide regulatory activities for all Merck medicines and vaccines, which included responsibility for FDA and international agency liaison, worldwide New Drug Application (NDA) submissions, product labeling, quality assurance, and pharmacovigilance. She served on the International Conference on Harmonization Subcommittee on the Structure and Content of Clinical Studies Reports (Chair), and on both the Regulations Advisory (Chair) and Policy Boards for the UK Centre for Medicines Research. She was named by President George W. Bush as Assistant Secretary for Health, Department of Health and Human Services, in September 2001 and received Senate confirmation to this position in January 2002, becoming the first woman to hold the position. She served HHS Secretary Tommy Thompson as Chief Health Policy Advisor, with special emphasis on translational medicine, including electronic systems (eHealth) and innovation, biosecurity, protection of human subjects, women's health, elder care, and HIV/AIDS. She resigned in 2003, and is currently serving as Director of Vertex Pharmaceuticals, Cambridge, Massachusetts; Phase Forward, Waltham, Massachusetts; VaxGen, Brisbane, California; and Theravance, South San Francisco, California. She is Commissioner of the Urban Indian Health Commission and a member of the Scientific Advisory Committee for the Global Alliance for TB Drug Development and the FDA Science Board Working Group.

MARY K. PENDERGAST, JD, LLM, is President of Pendergast Consulting, a legal and regulatory consulting firm founded in 2003. Previously she was Executive Vice President, Government Affairs, at Elan Corporation (1998–2003) and Deputy Commissioner and Senior Advisor to the Commissioner at the FDA (1990–1998). Ms. Pendergast also served as Associate Chief Counsel for Enforcement at the FDA from 1979 to 1990 and as Attorney, Office of the General Counsel, Department of Health and Human Services, from 1977 to 1979. At the FDA, she was responsible for the agency's efforts to regulate emerging areas such as biotechnology, cellular and tissue-based therapies, genetic testing, xeno-transplantation, and acute-care research. She also served as the FDA's "crisis manager," handling sensitive and precedent-setting situations, and led the agency's efforts to assist the Newly Independent States after the breakup of the Soviet Union. Ms. Pendergast has testified on many occasions before the U.S. Congress and has spoken to numerous international organizations, foreign governments, and scientific and academic institutions. She is on the Board of Directors of Nuvelo, Inc. and Child Trends, a research organization focused on children. She received her LLM, JD, and BA degrees from Yale Law School, the University of Iowa College of Law, and Northwestern University, respectively.

MARLENE E. HAFFNER, MD, MPH, recently joined Amgen as Executive Director, Global Regulatory Intelligence and Policy. Previously she was for 20 years Director of the Office of Orphan Products Development at the FDA. She received her MD from The George Washington University School of Medicine, with further training in internal medicine, hematology, and dermatology. She received her MPH from The Johns Hopkins University School of Hygiene and Public Health. A career public health administrator and educator, she has a passion for addressing issues of the underserved, including the development of therapeutics for grievous illness and patients' access to therapy for their illnesses.

Session 6: Drug Safety Regulation: Looking to the Future

MYRL WEINBERG, CAE, is President of the National Health Council, an umbrella organization that has served as the place where "the health community meets" for 85 years. The council's 115 members are national organizations that are committed to quality health care, and its core constituency of more than 50 leading voluntary health agencies represents approximately 100 million people with chronic diseases and/or disabilities. Ms. Weinberg has a long history of board and committee service, including serving as a member of the American Heath Information Community's Consumer Empowerment Workgroup, the IOM's Health Sciences Policy Board, the AcademyHealth Coalition for Heath Services Research Board, the Center for Information and Study on Clinical Research Participation Advisory Board, the Roche International Genetics Science and Ethics Advisory Committee, and the IOM's Committee on Clinical Trial Registries, and as a founding member of the Association for the Accreditation of Human Research Protection Programs and Chair-Elect of the Governing Board of the International Alliance of Patients' Organization. Ms. Weinberg also served on the congressionally mandated IOM committee created to assess how research priorities are established at NIH and on the National Research Council/IOM Committee on the Organizational Structure of NIH.