FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

CHALLENGES FOR THE FDA

THE FUTURE OF DRUG SAFETY

Workshop Summary

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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Leslie Pray and Sally Robinson, *Rapporteurs*

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Board on Health Sciences Policy

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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.

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Catherine Bonuccelli, AstraZeneca Pharmaceuticals
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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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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.