Building a National Framework for the Establishment of Regulatory Science for Drug Development: Workshop Summary

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Building a National Framework for the Establishment of REGULATORY SCIENCE FOR DRUG DEVELOPMENT

Workshop Summary

Yeonwoo Lebovitz, Rebecca A. English, and
Anne B. Claiborne, *Rapporteurs*

Forum on Drug Discovery, Development, and Translation
Board on Health Sciences Policy

INSTITUTE OF MEDICINE
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"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 process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not endorse the final draft of the report before its release. The review of this report was overseen by **LESLIE Z. BENET,** University of California, San Francisco. Appointed by the National Research Council and the Institute of Medicine, he was

[1] Steven K. Galson was with Science Applications International Corporation until September 30, 2010.

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.

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Acronyms

AHRQ	Agency for Healthcare Research and Quality
AIDS	acquired immune deficiency syndrome
ARRA	American Recovery and Reinvestment Act of 2009
BC	Biomarkers Consortium
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CERTS	Centers for Education and Research on Therapeutics
COE	Centers of Excellence
COERS	Centers of Excellence in Regulatory Science Network
CPI	Critical Path Initiative
CTTI	Clinical Trials Transformative Initiative
DARPA	Defense Advanced Research Products Agency
FDA	Food and Drug Administration
FDAAA	FDA Amendments Act of 2007
FDAMA	FDA Modernization Act of 1997
FNIH	Foundation for the National Institutes of Health
GAO	Government Accountability Office

HHS	Department of Health and Human Services
HIV	human immunodeficiency virus
ICT-21	Information Communication Technology for the 21st Century
IIRIS	Incubator for Innovation in Regulatory and Information Science
IND	Investigative New Drug Application
IOM	Institute of Medicine
IOTF	NCI–FDA Interagency Oncology Task Force
IT	information technology
NCI	National Cancer Institute
NDA	New Drug Application
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
OMOP	Observational Medical Outcomes Partnership
OODP	Office of Oncology Drug Products
PDUFA	Prescription Drug User Fee Act
PhRMA	Pharmaceutical Research and Manufacturers of America
SAE	serious adverse event

Preface

Regulatory agencies worldwide are tasked with a difficult mandate to provide large populations with efficient access to drugs that are both safe and effective. They must also balance this task while adapting to new technologies in medicine and information technology. These demands are further complicated by the increasing globalization of drug development and regulatory relationships. These challenges, along with problems with contaminated supplies, serious adverse events, and other compounding issues that accompany changes in administration, contribute to the overburdening of a regulatory system whose resources have not increased along with its demands. We urgently need to ensure that our regulatory bodies have the autonomy, resources, and scientific support needed to function effectively to promote public health and safety.

The U.S. Food and Drug Administration (FDA) is a science-based agency responsible for regulating 80 percent of Americans' consumable goods and a quarter of the U.S. economy. It is imperative that every one of FDA's regulatory decisions be based on the best scientific evidence. Unfortunately, this has not always been possible due to several factors, including—but not limited to—inadequate human capital, leadership support, and funding. Above all, a weakening science base at the agency has threatened its ability to support its core regulatory functions and decisions. FDA needs to resolve this gap between scientific and regulatory decision making to ensure continuity of its duties in an environment of heightened public scrutiny on drug safety and rapid scientific advancements.

The public increasingly recognizes the importance of regulatory science. The notion of basing regulatory decisions on the best scientific knowledge

available is not new, but never before have funds been deliberately appropriated for the accomplishment of this task. FDA's 2011 budget proposal includes $25 million specifically allocated to the building of a regulatory science infrastructure at the agency. In anticipation of this event and as an acknowledgment of the "reform-ready" political atmosphere, the Institute of Medicine's Forum on Drug Discovery, Development, and Translation held a public workshop with the following goals in mind:

- Establish a clear definition of regulatory science, and engage the public and the policy community in a discussion of its challenges and opportunities.
- Increase awareness of inadequate funding for regulatory science and the impact on the development of new therapies on patients.
- Articulate priorities and strategies for building or rebuilding the infrastructure for regulatory science.

The one-day workshop featured leaders from government, such as Representative Rosa DeLauro (D-CT); Department of Health and Human Services Deputy Secretary, William Corr; and FDA Commissioner, Margaret Hamburg. Speakers from academia, industry, and patient advocacy groups provided a variety of perspectives and illuminated examples of the urgent need of a regulatory science infrastructure. Leaders in emerging technologies, such as genomics, biostatistics, and information technology—whose fields of study are influenced daily by regulatory decisions—deliberated on potential consequences arising from the failure to establish a robust scientific base at the agency level. In addition, moderated panels considered mechanisms for building a regulatory science infrastructure at FDA, analyzed existing implementation models, and posed strategies for engaging the public and policy makers.

This was a timely workshop that provided a valuable opportunity to bring together a diverse group for thoughtful discussion about improving drug development and strengthening regulatory science. I would like to thank all of the individuals—speakers, moderators, and panelists—who contributed to and participated in the workshop. In particular, I would like to thank a small team of participants in the workshop who spent many hours in advance of the workshop discussing the merits of Centers of Excellence in Regulatory Science and the critical characteristics of these centers including: K. Ahlport, M. Anderson, L. Benet, R. Califf, G. FitzGerald, S. Kim, J. Kramer, R. Nerem, D. Nordenberg, M. Osterholm, K. Schneeman, J. Shoemaker, E. Sigal, N. Sung, and J. Tobias. I would also like to thank the members of the Forum and Forum staff for their dedication and commitment to developing and executing this workshop.

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

1

Introduction[1]

The U.S. Food and Drug Administration (FDA) today has a broad range of responsibilities, regulating fully 25 percent of the American economy, including 80 percent of the nation's food supply and all drugs, devices, dietary supplements, animal drugs, cosmetics, biologics, and tobacco products. These responsibilities go far beyond those mandated in the agency's originating legislation—the *1906 Pure Food and Drugs Act*[2] and the *1938 Federal Food, Drug, and Cosmetics Act*.[3] The agency was initially established to prevent the entry of adulterated products into the public market; it was from its inception grounded in principles of scientific study in support of its core mission of regulating consumable goods. That mission remains today; however, the agency has assumed a far more scientifically complex and international reach, with centers located around the world. In the face of rapid advances in medicine and biomedical science, the FDA faces pressure to keep pace with new technologies and develop the expertise necessary to regulate those technologies as they emerge. At the same time, however, stagnant funding levels and

[1] While the Drug Forum conceived the idea for this workshop, this summary was prepared by the rapporteurs as a factual summary of the presentations and discussions that took place at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the Drug Forum or the National Academies, and should not be construed as reflecting any group consensus.

[2] *Pure Food and Drug Act of 1906* (34 U.S. Stat. 768).

[3] *Federal Food, Drug, and Cosmetic Act* (FDCA) (52 U.S. Stat. 1040).

staff turnover have increasingly hampered the agency's ability to fulfill its regulatory mission.

As discussed in this introduction, there has been much discussion regarding the urgency of evolving FDA to a robust and autonomous agency that has capacity to bridge gaps in knowledge and resources so that safe, effective drugs can be delivered to patients. Only recently, however, have funds been requested specifically for the task of fortifying the science base behind FDA's regulatory actions (FDA, 2010a).

WORKSHOP PURPOSE AND OBJECTIVES

In its 2007 report *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (IOM, 2007), the Institute of Medicine (IOM) identified the need for an improved science base for drug evaluation within FDA, including both internal resources and extramural funding for collaboration with academia. In that same year, the FDA Science Board,[4] at the request of Congress, reported on the agency's need for an enhanced science base, including infrastructure development, multisector collaboration, and an expanded workforce capable of addressing the rapidly evolving science of drug discovery and development. In 2008, the IOM Forum on Drug Discovery, Development, and Translation held a public workshop to explore the science of drug regulation, focusing on the gap between leading-edge technologies of drug development and FDA's capacity to adapt its process of regulatory evaluation to these technologies (IOM, 2008). Together, the results of these efforts suggest a widening gap between scientific developments in areas relevant to FDA's mission and its ability to address these innovations, as well as a lack of understanding among the public, policy makers, and the agency of what is required to fill this gap.

To address these concerns, the IOM Drug Forum convened a public workshop on February 26, 2010, to examine the state of the science of drug regulation and consider approaches for enhancing the scientific basis of regulatory decision making. The workshop provided an opportunity to explore the concept of regulatory science, examine how it can be used to improve regulatory decision making, and consider alterna-

[4] The FDA Science Board is an advisory committee with the following mission: "The Board shall provide advice primarily to the Commissioner and other appropriate officials on specific complex and technical issues as well as, emerging issues within the scientific community, in industry and academia. Additionally, the Board will provide advice to the Agency on keeping pace with technical and scientific evolutions in the fields of regulatory science, or formulating an appropriate research agendas; upgrading its scientific and research facilities to keep pace with these changes. It will also provide the means for critical review of Agency sponsored intramural and extramural scientific research programs" (FDA, 2010b).

tive mechanisms and institutional frameworks for its development and application.

Among the participants were experts in the science of drug regulation, as well as stakeholders in drug development and regulatory processes, including representatives of patient groups, academia, government, and industry. According to Gail H. Cassell, Vice President of Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly, and Drug Forum Co-Chair, the workshop had the following objectives:

- Establish a clear definition of regulatory science, and engage the public and the policy community in a discussion of its challenges and opportunities.
- Increase awareness of inadequate funding for regulatory science and the impact on the development of new therapies on patients.
- Articulate priorities and strategies for building or rebuilding the infrastructure for regulatory science.

A range of approaches and innovative mechanisms were considered, including fostering the scientific discipline of regulatory science, promoting closer collaboration between regulatory and academic researchers, and developing a solid infrastructure to support regulatory science. Among the specific models discussed were regulatory science centers of excellence, innovative federal grant-making mechanisms, and medical education and professional development programs.

ORGANIZATION OF THIS REPORT

This report summarizes the presentations and discussions at the workshop, highlighting key themes and concepts for enhancing regulatory science:

- Chapter 2 defines the concept of regulatory science in the context of FDA.
- Chapter 3 explicates the need for regulatory science in today's drug development environment, including areas in which regulatory science could track emerging technologies. It also examines potential negative consequences of deficiencies in regulatory science.
- Chapter 4 describes barriers to establishing a regulatory science infrastructure.
- Chapter 5 explores a collaborative model for promoting regulatory science and considers examples of past successes in similar fields.
- Chapter 6 examines ways to energize the public policy community to support the development of regulatory science.

- Chapter 7 elaborates on the desired outcomes of successful implementation of regulatory science.
- Chapter 8 summarizes next steps for enhancing regulatory science offered during the workshop.

2

Defining Regulatory Science

The concept of regulatory science is not a new one. The FDA Science Board's 2007 *Science and Mission at Risk* report (FDA Science Board, 2007) describes regulatory science as a science-based decision-making process needed to fulfill the responsibilities of a public health agency: "FDA must have the scientific staff and resources to undertake the regulatory research that will provide a basis to: (1) improve capacity for safety and efficacy evaluations and monitoring of candidate and licensed products, (2) modernize current regulatory pathways, and (3) develop new regulatory pathways where there are currently none." According to the report, this capacity is important because "decisions made in regulation development, pre-market approvals, legal actions and related public health emergencies must be based on understanding of contemporary and emerging science within the context of the risk analysis paradigm" (FDA Science Board, 2007, p. 14).

While a number of descriptions of regulatory science have been put forth, no formal definition exists. Some alternative definitions of regulatory science are presented in Box 2-1. The following general definition was submitted to the IOM Drug Forum for discussion at this workshop by Carl Peck, Professor of Bioengineering and Therapeutic Sciences at the University of California, San Francisco, Center for Drug Development Science, and former Director of FDA's CDER (1988–1993) (Peck, 2010, p. 1):

> Regulatory science is a broad term concerning drug and other product regulations, regulatory standards, law and procedures across many disciplines. It is a systemized body of knowledge (practiced by FDA and

BOX 2-1
Some Definitions of Regulatory Science

While no official definition of regulatory science has been promulgated by any U.S. regulatory agency or standards-setting body, the following definitions highlight a common theme: drawing science and policy together for the benefit of public health and safety:

- "…the science and tools we use to assess and evaluate a product's safety." Margaret Hamburg, FDA Commissioner (FDA, 2009)
- "The development and use of new tools, standards and approaches to more efficiently develop products and to more effectively evaluate product safety, efficacy and quality." Announcement of NIH–FDA Collaboration to Fast-Track Innovations to the Public (FDA, 2010c)
- "The acquisition and analysis of data sufficient to inform decision making pertinent to the approval of safe and effective therapeutics, devices and cosmetics and ensuring the safety and nutritional value of the food supply." Garret FitzGerald, University of Pennsylvania School of Medicine (FitzGerald, 2010)
- "Regulatory science is a unique application of science, at all levels, to the societal decision process." Alan Moghissi, President, Institute for Regulatory Science (*The Scientist*, 2009)
- "Regulatory Science relates the regulatory and legal requirements of biomedical product development to the scientific research needed to ensure the safety and efficacy of those products." Academic website for the University of Southern California School of Pharmacy (USC, 2010)

similar regulatory agencies world-wide) comprising public protection-oriented medical product regulations, policy and decisions using scientific methods employing empirical and causal evidence utilized in the evaluation and approval of all the products that FDA regulates.

Thus the role of regulatory science is inherent in FDA's functioning as a scientific agency. It plays a critical role in all aspects of the agency's mission, including:

- review and assessment of laboratory data;
- review and assessment of animal and human clinical data;
- methods development;
- facilities inspection; and
- development of technical and scientific standards for preclinical

assessment, product development, postmarket surveillance, manufacturing, packaging standards, food safety standards, and food processing technologies.

Garret FitzGerald, Professor of Translational Medicine and Therapeutics, University of Pennsylvania School of Medicine, offered the following guidelines for determining what the term does *not* denote:

- a new set of regulations;
- an approach to speeding up the approval process; or
- an attempt to establish cutting-edge biomedical science at FDA.

Nevertheless, regulatory science can aid in the above areas by boosting scientific capacity. It is not a cure-all for the shortfalls in drug regulation, yet is critical to FDA's accomplishment of its complex goals. Box 2-2 summarizes FDA Commissioner, Margaret Hamburg's talk on regulatory science, which encapsulates these intricacies. Workshop participants suggested that, because it lies beyond the traditional domain of biomedical science, the practice of making regulatory decisions on the basis of the best science possible is an emerging area of meta-science.

Jeffrey Drazen, Editor-in-Chief of the *New England Journal of Medicine* and Co-Chair of the Drug Forum, described regulatory science as "a science that has been evolving and is continuing to evolve, but it's not as hard a science as we would like." Thus, enhancement of the regulatory science discipline today represents a concerted attempt to systemize and standardize daily regulatory processes and bolster regulatory decision-making capabilities with a sound scientific base. The following chapter explores why such efforts are necessary.

BOX 2-2
Excerpts from the Commissioner's Speech

FDA Commissioner, Margaret Hamburg, provided an overview of regulatory science priorities at the agency. Commissioner Hamburg referred to regulatory science as "vital to enhance the quality and integrity of FDA's regulatory decisions."

The Commissioner's speech defined the need for and application of regulatory science; discussed collaborative efforts to advance regulatory science; and described models and initiatives that, if adequately funded, could significantly advance the field of regulatory science. The Commissioner emphasized that "[o]utreach and collaboration are central to regulatory science efforts. When successful, these collaborative efforts will help predict which discoveries will succeed or fail as actual products, thereby reducing product development costs and getting better products to patients faster." She remarked that FDA should actively participate in research and development by partnering with academia, industry, and other government agencies.

The following excerpts represent topical highlights from the Commissioner's presentation at the workshop:

- **Definition and Application of Regulatory Science**

  "[Regulatory] science that underlies the development and utilization of new tools, standards, and approaches for the assessment of medical product efficacy, safety, and quality, is the critical bridge between basic scientific research discoveries and new marketed medical products. Regulatory science comprises an array of disciplines and approaches. Regulatory science not only takes place in laboratories, but it also may involve clinical, epidemiological, and statistical tools and information-gathering systems.

  "Unlike work performed by specific sponsors, regulatory science is important for multiple products and stakeholders. The knowledge generated from such studies informs a whole class of potential products rather than a single product. It informs, in some instances, whole new ways of thinking about the potential of science."

- **Regulatory Science's Potential for Supplementing Biomedical Innovation**

  "…[A]n important regulatory science problem might be how to characterize the immune response that alters or blocks the effect of recombinantly produced proteins or antibodies used to treat many diseases, like cancer or rheumatoid arthritis. The knowledge generated from such studies would inform a whole class of potential products, a whole class of recombinant proteins, rather than a single product. So you go from what is an important and interesting question in science to something that actually makes the difference in the ability to move that science into the marketplace.

"…[R]egulatory science is essentially a goldmine that we must continue to excavate. For example, promising research is under way using stem cells to restore brain function lost in patients with Parkinson's Disease. But before these treatments can reach patients, we must develop scientifically valid standards and manufacturing processes for stem cell therapies so they can be produced reliably and safely.

"Regulatory science may help us bring promising platforms and multiuse technologies online. Some could be adapted to aid in our preparedness against some of the most important biological threats that we face as a global community, from pandemics, such as H1N1, to the emerging threat of bioweapons. These efforts should incorporate a systems biology approach, where data and knowledge is shared across multiple pathogens and used to translate basic discoveries into clinical application.

"[The lifecycle approach to drug development] is a very important new and growing emphasis within FDA. It is an area where I think we can and will bring important advances in regulatory science to bear, improving our understanding of pharmacoepidemiology as we address postmarketing surveillance, better use of bioinformatics in this regard, and, importantly, developing the science of comparative safety trials, which I think is an important gap in the work that we do."

- **Regulatory Science Initiatives at FDA**

"…[C]ollaboration between NIH and FDA scientists led to a new method, using gene biomarkers, to assess 'stemness'—that is, the extent of differentiation in several lines of stem cells. These methods are a first step in setting standards for ensuring that undifferentiated stem cells do not contaminate the final, more differentiated stem cells that are administered to patients.

"…[I]n 1997, the FDA, along with representatives from pharmaceutical companies and academia, came together to create the structure for the development of clinical data standards that could be used across the pharmaceutical industry without bias towards any one company or organization. These standards allowed for better and more efficient data analysis and faster approval of important medications.

"FDA has led several collaborative efforts with our European counterparts to identify and qualify novel biomarkers for assessing drug-induced kidney toxicity. These biomarkers, originally detected in microarrays, have led to a noninvasive strategy for detecting kidney toxicity in animal models and are more sensitive and specific than the test traditionally used, and … allow us to make assessments early on to prevent the investments of time and money in what may prove to be scientific dead-ends."

- **Areas of Need for Enhancing Regulatory Science at FDA**

"Our regulatory scientists must be able to understand therapies that are being developed using the most recent scientific advances, they must have

continued

BOX 2-2 Continued

the right tools to evaluate these therapies, and they must be a partner with the greater scientific community as they work to bring these therapies to people.

"[FDA must foster] a culture where multiple perspectives and opinions are sought and brought to bear on complex regulatory science problems. FDA must support and enhance its workforce, from clinical and scientific reviewers to lab and expert manufacturing, scientists, and inspectors, so that we can ably and effectively engage in the broader biomedical research and development enterprise, and so that we can effectively undertake our vital regulatory oversight and review work."

- **Partnerships to Build and Sustain a Regulatory Science Infrastructure**

"[On February 24, 2010,] we announced a first-of-its-kind collaboration between NIH and FDA. We have established a joint leadership council to enable our agencies to work together to improve regulatory science, beginning with what I think is a small but very important program of grants to advance important research in regulatory science. It's … an important first step[] to strengthen regulatory science as an organized research endeavor and as a catalyst to advance science at FDA more broadly. Moreover, as Secretary Sebelius noted at the announcement, collaboration between NIH and FDA, including support for regulatory science, will go a long way towards fostering access to the safest and most effective therapies for the American people.

"With our Critical Path Initiative, FDA will continue to partner with academic groups, patient advocacy groups, and industry to bring innovation to fields such as genomics, imaging, and informatics, so they can be applied to gaps in drug and diagnostic development.

"…[T]hrough a competitive application process, and resources willing, FDA hopes to support the notion of centers of excellence in regulatory science… These centers would perform research independently and collaboratively with FDA scientists to address unmet scientific needs in regu-

latory science and try to bridge the gap between research, discovery, and innovation and the evaluation and development of new safe and effective products.

"…[S]cience is a global enterprise. There are enormous opportunities to collaborate with scientific colleagues around the world on matters of mutual concern, but also to engage with sister regulatory agencies to address the sharing of important information and strategies and to harmonize standards and approaches."

In looking forward, the Commissioner said, achieving an enhanced regulatory science at FDA and beyond will require not only a concrete, coordinated plan, but also resources. She reported that, for the first time in history, the President's fiscal year 2011 budget included a targeted initiative to advance regulatory science for public health. She reported that FDA "will support scientific excellence by recruiting, training, and retaining FDA scientists through meaningful career ladders, fellowship programs, scientific collaborations, exchanges, and other professional development activities."

In addition to the collaboration with NIH, the Commissioner announced, other interagency partnerships will be explored, such as with the National Institute of Standards and Technology (NIST) regarding areas of standards development and qualification, and with the Defense Advanced Research Products Agency (DARPA) to help provide regulatory input on novel products at the early development stage in its programs. She also noted that FDA will continue to engage outside advisory groups, such as the FDA Science Board, to gather information to help define regulatory science priority areas and foster and support the work necessary to address them.

In closing, the Commissioner stated, "I think we really have the opportunity to lay out an important set of ideas and actions and also to help … shape this emerging field of regulatory science as a discipline. We are living in a century where the advances in biology are astounding and ripe for action. With our collective effort, these advances can be transformed into therapies that will alleviate suffering and products that will enhance our quality of life."

3

The Urgent Need for Regulatory Science

While the world of drug discovery and development has undergone revolutionary change, shifting from cellular to molecular and gene-based approaches, FDA's evaluation methods have remained largely unchanged over the last half century.

FDA Science Board, 2007

CHALLENGES FACED BY FDA

Congresswoman Rosa DeLauro, keynote speaker for the workshop, explained that the focus on regulatory science is a natural outcome of the drug safety issues that have surfaced in recent years. As the government investigates the origins and causes of these issues, such as contaminated heparin supplies and postmarket adverse events, one area of focus is the extent to which breaches are forming along the drug development path. Specifically, DeLauro cited "most fundamentally, [the] sheer lack of resources at the agency's disposal." She also expressed concern that initiatives aimed at accelerating approval could omit safety steps in an effort to speed up patients' access to new therapies. In addition, observed DeLauro, in 2009 the Government Accountability Office (GAO) released a report (GAO, 2009) alerting FDA to a loophole whereby Class III medical devices (e.g., pacemakers) were being approved without certain essential safety measures and in noncompliance with the premarket safety steps mandated by the *Safe Medical Devices Act of 1990*.[1]

According to DeLauro, despite progress made at FDA since 2007 and the enactment of the *Food and Drug Administration Amendments Act of 2007*, the ad hoc nature of the problems faced by the agency, such as continually emerging safety recalls, forces the agency to act reactively to issues as they arise instead of assuming a leadership role and proactively address-

[1] *Safe Medical Devices Act of 1990*, Public Law 101-629, 101st Cong. (November 28, 1990).

BOX 3-1
Potential Contributions of Regulatory Science to Cancer Therapy

Ellen Sigal, Chair and Founder, Friends of Cancer Research, suggested key areas in cancer care that stand to benefit from increased regulatory science capacity at FDA:

- improved clinical trial design, reflecting consideration of cancer as a set of multiple diseases;
- validation of biomarkers to better match clinical trial treatments with appropriate patient populations;
- availability of standardized metrics—beyond toxicity—for quality of life/symptom management;
- evaluation of combination therapies;
- advanced study of chemoprevention; and
- additional stem cell research.

ing regulatory needs. DeLauro suggested that this characterization of the agency reflects a common public sentiment.

Although FDA has unique opportunities to improve the public health through its access to a diversified workforce and a wealth of data, accomplishing this goal is a daunting task. According to Drazen, a key challenge is that the agency is often forced to "take limited data … based on small numbers of people's response to a given therapeutic approach—and determine what will happen when this therapy is unleashed to very large numbers of people."

Another challenge faced by FDA is the rapid emergence of new technologies. A theme among the speakers was that the agency currently is not supported sufficiently to deal with the masses of data that come from large investments in such areas as genomics and health information technology. At the same time, emerging technologies cannot meet the demand for new therapies without coordinated effort from regulatory bodies. The presentations summarized below focused on specific areas of emerging technology and the scientific gaps caused by the lack of strong regulatory science. Box 3-1 lists some ways in which regulatory science could contribute to the development of therapies in the specific area of cancer treatment.

THE NEED FOR REGULATORY SCIENCE IN PREDICTING OR ADDRESSING RARE ADVERSE REACTIONS[2]

The current safety-focused environment can serve to hinder innovation, as drug companies often are averse to risking investment in the development of new drugs not yet proven safe. The hope is that regulatory science can mitigate this problem by improving risk detection and creating rewards for discovery.

To illustrate this point, Watkins referred to a recent case involving FDA's review of a New Drug Application (NDA). In this case, FDA supported the NDA sponsor's conclusion about the drug's effectiveness; however, 2 of the 4,000 patients treated in Phase III clinical trials developed elevations in liver chemistry. In light of this finding of possible liver toxicity in the 2 patients, the sponsor was required to conduct a new safety study that involved treating 20,000 patients with the drug or a comparator for a full year.

Given the current model of drug development, in which the drug sponsor is responsible for the bulk of clinical testing, requiring such follow-up based on limited experience will reduce the drug's patent life by approximately 3 years. Together, moreover, the cost of conducting the trials and the lost profits from the drug's shortened patent life will cost the company millions of dollars, which will ultimately be passed on to the consumer.

The core issue in Watkins' example is the lack of understanding of idiosyncratic reactions, or serious adverse events (SAEs), in rare individuals for drugs that are otherwise proven safe. These idiosyncratic reactions are time-consuming and costly to address through the current regulatory system, and can result in the failure of effective drugs with the potential to reach previously untreated patients. Initiatives have been undertaken to improve the scientific knowledge surrounding these idiosyncratic reactions, such as the Serious Adverse Events Consortium[3] and the National Institutes of Health (NIH)-funded Drug-Induced Liver Injury Network.[4] Another such initiative, the Hamner Institute's study of inbred mice panels, is described in Box 3-2. Nonetheless, the problem persists, as there has

[2] This section is based on the presentation of Paul Watkins, Verne S. Caviness Distinguished Professor of Medicine, University of North Carolina at Chapel Hill, and Director, Hamner Institute for Drug Safety Sciences.

[3] The Serious Adverse Events Consortium, funded by pharmaceutical companies, examines gene banks of patients with common SAEs in an attempt to find genetic causes.

[4] The Drug-Induced Liver Injury Network is supported by NIH/the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK). It analyzes genetic material, such as blood, urine, and biopsy samples, from a registry of volunteer patients who can be contacted and offered future involvement in other studies.

BOX 3-2
Hamner Institute's Study of Inbred Mice Panels

In an attempt to identify mechanisms of idiosyncratic toxicities, the Hamner Institute created panels of inbred, genetically engineered mice to recreate the genetic heterogeneity found in patient populations. By injecting a single high dose of acetaminophen into 36 different inbred mice strains, the institute was able to show the effect of the injection among various genetic strains (see Figure 3-1 below). Following analysis, specific genetic variants pointed to high susceptibility to acetaminophen—resulting in severe liver damage—whereas other genetic variants showed no effects from the injection.

This work led to the discovery of a new risk factor called CD44, which was then shown to be an indicator for mild acetaminophen liver toxicity in healthy human volunteers. CD44 is present on the surface of white blood cells, and is also found on liver progenitor cells and may play a role in repair.

Following its success with inbred mice panels, the Hamner Institute is now partnering with the pharmaceutical industry to study proprietary drugs that have shown success in animal safety and preclinical studies but failed at various stages of the drug's life cycle due to severe toxicities. According to Watkins, such studies utilize academia's existing resources and access patient populations not available to FDA.

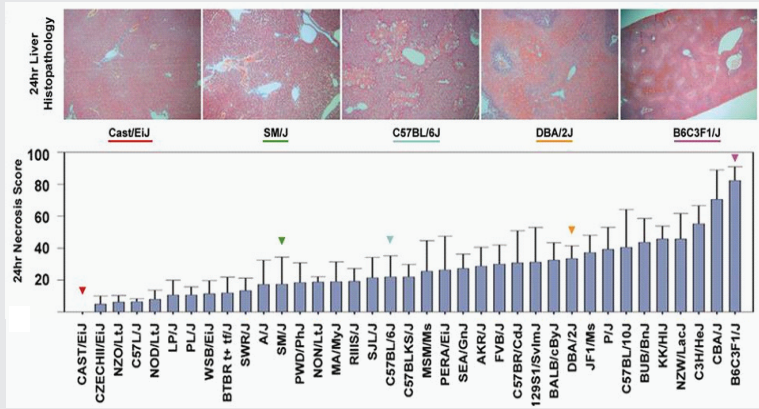

FIGURE 3-1 Graphic presentation of the effect of acetaminophen on various mouse gene strains. The grey bars indicate high liver injury.
SOURCE: Harrill et al., 2009.

been a general inability to access these resources for designing better trials or preventing drug failures in the clinical stages of drug development.

Watkins suggested that a regulatory science infrastructure that would partner the discovery science of academia with the regulatory efforts of FDA could mitigate the challenge to drug development posed by rare SAEs. While academic studies may generate a great deal of data, the ultimate value of the data in improving the public health will come from a regulatory agency's ability to synthesize that information into a usable and useful form.

THE NEED FOR REGULATORY SCIENCE IN GENOMICS[5]

In the past 10 years, the field of genomics has made great strides in better understanding of the genetic mapping of organisms. These advances have opened up new possibilities for personalized medicine and the discovery of new drugs. Despite increased funding for research and an extensive literature on the human genome and genomics, however, there is a dearth of new medicines on the market. Treatments with genetic-based side effects are still used widely, and little remains known about how to translate advances in genomics into reliable diagnostics or guidance for practitioners and patients. Roses suggested that regulatory science can help fill these gaps by:

- enhancing product development by minimizing the likelihood of imperfect data; and
- making it possible to analyze and interpret data in regulatory submissions taking into account all products of the genome, all genomes, integrative biology, constructive pharmacology, and translational analyses.

There is a great deal of new science in the genomics arena, and FDA must move quickly to adjust its review processes and determinations accordingly. Roses referred to his own experience in discovery of the translocase of outer mitochondrial membrane 40 homolog (TOMM40) gene that was found to greatly increase precise prediction in the estimation of age of late-onset Alzheimer's Disease for carriers of the ε4 allele of the apolipoprotein E (APOE) gene, which is considered the most highly replicated genetic factor for risk and age of the disease (Roses et al., 2009). He cited the subsequent process to gain approval from FDA for conducting a clinical trial as one of success because the agency utilized its capac-

[5] This section is based on the presentation of Allen Roses, Director, Deane Drug Discovery Institute, Duke University.

ity for regulatory science to nimbly analyze the scientific data and reach a decision. In particular, Roses highlighted the key factors of success in his experience.

Roses urged for the future establishment of regulatory science for the following reasons:

- FDA review teams have access to the specific scientific expertise required to produce sound judgments on the safety and efficacy of the products they review; and
- FDA reviewers of pharmacogenetics and outcome studies are able to balance retrospective and prospective data, benefits and risks, agnostic and hypothesis-driven approaches, clinical validity and epidemiological strengths, and validation and replication.

A regulatory science infrastructure is necessary to address these complex issues and develop consistent standards tailored to the science of genomics, said Roses.

Roses noted that it will be necessary to develop genetic diagnostics with clearly defined clinical parameters as well as reproducible methodologies, informed by an overarching concern for the safety and efficacy of products. Since every individual inherits a single strand of DNA from each parent, regulatory bodies must look to individuals' genetics to develop predictive data, rather than to the genome-wide association studies that are commonly discussed in the existing literature, according to Roses. An analogy is the approach taken by the typical physician to make an accurate treatment prediction by tailoring the analysis to the specific patient instead of considering some percentage of the clinical population that suffers an adverse event.

Influenza vaccines and human immunodeficiency virus (HIV) mutation are two examples of the successful use of regulatory science at FDA. In the case of influenza vaccines, phylogenetic mapping previously conducted by academic laboratories had prepared FDA for the incoming data, and the agency was quickly able to acquire the necessary expertise to perform due diligence in an efficient regulatory support process.

Regulatory science at FDA, warned Roses, may not be the same as that at NIH: "[Genomics] is very different from finding adverse events. This is about making drugs. This is about discovering which ones work, with fewer people, so you can do trials that are faster and safer." Therefore, Roses said, FDA's regulatory science in genomics must be able to balance efficacy determination with the identification of safety issues arising from adverse events.

Conversely, the use of genomic information can enhance the development of the discipline of regulatory science by showing how best to design

clinical trials and evaluate targeted therapies and assays for use in such therapies. Genomics could also help identify optimal analytic approaches for determining genomic characteristics in response to therapy and aid in the development of more efficient strategies for evaluating combination regimens aimed at molecular targets.

THE NEED FOR REGULATORY SCIENCE IN STATISTICAL DESIGN AND ANALYSIS[6]

Pressing issues in biostatistics stem from the lack of a regulatory science infrastructure in the field. Ellenberg called on her experience as head of the Office of Biostatistics and Epidemiology in FDA's Center for Biologics Evaluation and Research (CBER) to emphasize the importance of on-the-job regulatory training that can be attained only by working at the agency for a period of time. To fully understand statistical problems in a regulatory setting, said Ellenberg, one must be an FDA statistician, an industry statistician who interacts frequently with FDA, or an academic statistician who has served on FDA advisory committees or consulted frequently for industry. Unfortunately, noted Ellenberg, most statisticians—including epidemiologists, computational biologists, and informaticians—do not seek FDA reviewer positions.

Ellenberg suggested further that, despite expectations for improved quantitative approaches, they will not eliminate the need for sufficiently large populations for safety assessment, adequate duration of follow-up for documentation of sustained efficacy and long-term safety, or long-term data to validate the use of surrogate endpoints. Due to the constant tension between efficiency in getting products to market and the adequacy of safety assessments in regulatory decision making, systematic approaches are needed to transform statistical data into educated action quickly and effectively. Ellenberg described a number of possible innovations in such approaches and associated areas of need.

Bayesian Methods

Adoption of Bayesian methods—a form of meta-analysis using evidence to update beliefs—is one way to build a regulatory science capability at FDA. Ellenberg described FDA staff as taking their responsibilities very seriously, being well versed in potential biases and distortions of traditional analytical approaches, and concerned with potential biases and distortions in newer or less familiar designs and analytical approaches.

[6] This section is based on the presentation of Susan Ellenberg, Associate Dean and Professor of Biostatistics, University of Pennsylvania School of Medicine.

The latter concern can often lead to extreme caution in accepting new approaches, such as Bayesian methods, which in turn may impede the agency's fulfillment of its responsibilities in the long run.

Postmarket Safety Surveillance

Ellenberg remarked that postmarket safety surveillance is the topic with "the greatest likelihood of getting onto the front page of a newspaper." It is a crucial area for regulatory decision making and a new area for quantitative methodology. Ellenberg urged the use of incentives, such as grants, to draw more statisticians to focus on postmarket surveillance methodology. In addition, she emphasized the importance of involvement by both premarket and postmarket FDA scientists in monitoring spontaneous data, particularly because the Sentinel Initiative is likely to generate a great deal of data in the future; conducting and evaluating meta-analyses of completed trials and improving understanding of such analyses; and designing and analyzing postmarket observational studies and clinical trials.

Assessment of Multiple Related Outcomes

The current regulatory approach to a new product is to require that a sponsor identify a single primary endpoint to avoid concerns about multiple comparisons of its products and the possibility of false-positive errors. However, drugs often have multiple benefits, which are likely to be highly correlated. Ellenberg described the sponsor's frustration in being forced to "arbitrarily choose one outcome for submission to FDA." Because existing statistical methods, including global methods,[7] do not account for multiple comparisons, new regulatory methods that can calibrate the extent of correlation among the outcome variables are needed.

Adaptive Designs

The hope for adaptive designs is to telescope clinical trials into smaller, more efficient versions of themselves. Although many new approaches to adaptive designs have surfaced in the past 10 years, and some adaptation has already been built into traditional trials, many questions remain about how the adaptive designs will work:

[7] Global methods combine multiple outcomes into a multidimensional variable that, Ellenberg noted, does not accord well with a regulatory setting.

- How much can efficiency be increased by these designs?
- How reliable are these designs?
- Will the designs introduce more biases?
- Will increasing the efficiency of answering questions about efficacy compromise safety, and in effect lead to the wrong answers more rapidly?

These are legitimate concerns that FDA will need to evaluate fully and systematically, as the agency is uniquely situated with access to a large body of diversified data and knowledge, noted Ellenberg. As a regulatory and public health agency, FDA has an opportunity to ensure that increased efficiencies in trial design can be achieved without compromising safety.

Comparative Effectiveness Research

Ellenberg acknowledged that both the value of comparisons of widely used treatments and the complexities of interpreting results in comparative effectiveness studies have long been appreciated at FDA. This is the case because the results of comparative effectiveness research are ultimately derived in the context of FDA's supplemental applications and label changes. Thus, Ellenberg believes, the involvement of regulatory scientists in studying and developing an optimal design for comparative effectiveness research is critical.

Other Areas

Ellenberg cited a number of other areas in emerging statistical technologies that warrant a standardized, science-based system of regulatory decision making:

- developing regulatory pathways for biosimilars;[8]
- improving Phase I trial designs beyond cancer trials;
- developing pediatric indications for drugs already studied in adults;
- developing therapies for rare diseases;
- identifying optimal dosage levels in Phase II and III studies; and
- identifying safety signals during the translation phase from animal to first-in-human studies.

[8] Biosimilars are generic versions of biologic drugs, also known as follow-on biologics.

FDA statisticians, observed Ellenberg, have little discretionary time for methodological research. Conversely, research statisticians may not be informed of the regulatory constraints or pitfalls commonly known to regulatory scientists. Therefore, some approaches recommended by research scientists in published journals go unnoticed by agency scientists.

To make progress, said Ellenberg, two components are necessary: first, FDA statisticians who are adept at using newly developed approaches must be empowered to judge whether methods should be applied based on their appropriate scientific value; second, research statisticians must be knowledgeable about the regulatory environment so the advances created by their research will be relevant to, and take into account, issues faced by FDA. A regulatory science infrastructure can provide the mechanism to fill the gap between these two bodies of knowledge that otherwise delays innovation.

4

Barriers to Enhanced Regulatory Science

Progress toward meeting a need for an enhanced regulatory science is impeded by a number of barriers, which are reviewed in this chapter. Many of these barriers are identified in the FDA Science Board report (FDA Science Board, 2007); others relate to deficiencies in information technology (IT), a prerequisite and a foundation for promoting and enhancing regulatory science at FDA, or broader barriers that can be characterized as more systemic in nature.

FINDINGS OF THE FDA SCIENCE BOARD

Cassell summarized the findings of the FDA Science Board report regarding barriers to enhanced regulatory science at FDA. While noting the tremendous advances that FDA has made toward standardizing regulatory science prior to and since the publication of the report, Cassell provided the following overview to describe the need for continual support for the agency.

Gap Between Scope of Responsibilities and Funding Levels

The FDA Science Board calculated that in 2006, the agency regulated $1 trillion in consumer products and oversaw 300,000 sites in 100 different countries (Figure 4-1) with an appropriated budget of just $1.6 million. As of October 2009, FDA reported a total of 11,516 employees and is estimated to regulate $2 trillion across 150 countries worldwide (FDA,

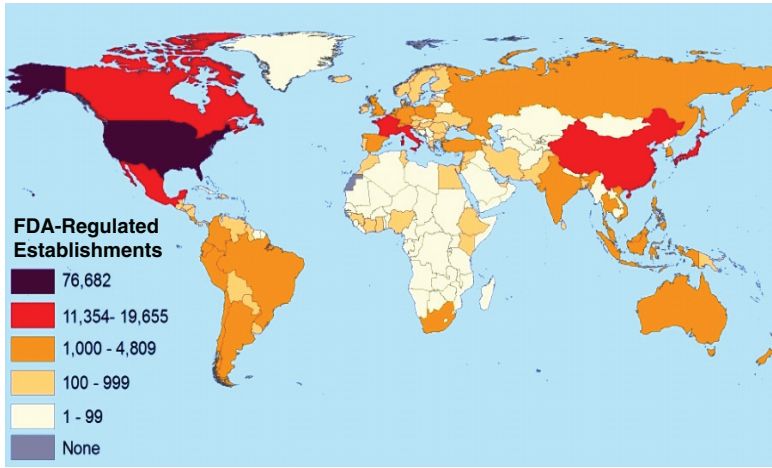

FIGURE 4-1 Breadth of FDA responsibilities by number of establishments as of 2007.
SOURCE: FDA, 2007.

2010e, 2010f). According to FDA, "[i]n the past five years, the number of FDA agreements with its regulatory counterparts throughout the world more than doubled and it continues to grow. FDA has over 100 formal agreements with its counterparts in 29 countries, 18 with the European Commission or its European Union members, and two with the World Health Organization." In addition, FDA established an office in China as of 2008, and has planned locations in India, Europe, Latin America, and the Middle East (FDA, 2010f). While user fees, such as those allowed by the *Prescription Drug User Fee Act*, can help support product review, user fees are restrictive, present conflict-of-interest issues, and are viewed with suspicion by the public, according to Cassell.

Since the FDA Science Board report was published, FDA has received limited increases in funding, yet its budget still pales in comparison with the funds allocated to similarly sized agencies. For example, FDA shared a similar budget and workforce as the Centers for Disease Control and Prevention (CDC) approximately 25 years ago (Grossman, 2010). As of 2009, however, CDC's total budget is more than three times the size of FDA's, and CDC holds approximately 4,000 more employees (CDC, 2009).

While money is not the sole problem, said Cassell, having sufficient funds is necessary to begin addressing other issues. The agency still needs a sustainable source of funding to gain autonomy and to ensure continuity of its operations.

Workforce Resource Constraints

FDA faces two related issues regarding its workforce: professional development and retention rates. As a science-based agency, FDA is staffed by many of the nation's best scientists. Because of budgetary and workload issues, however, FDA staff often cannot find time to attend professional workshops and miss opportunities to supplement their knowledge base. FDA also experiences twice the turnover rate among its scientific workforce of other federal agencies; as a result, remaining staff members are stretched thin and overburdened. Cassell added that, in 2006, although it had been given 100 more unfunded mandates since 1981, the agency had fewer full-time employees in 2006 than in 1981.

A large recruitment effort has been under way at FDA to resolve these workforce issues. Programs such as the Commissioner's Fellowship Program and scholars' sabbaticals have been created to recruit and train new talent. In 2008, the agency hired 1,200 new employees, 800 of whom filled newly created positions.

Harry Greenberg, Joseph D. Grant Professor of Medicine and Microbiology and Immunology and the Senior Associate Dean for Research at Stanford University School of Medicine, also stressed the importance of enhancing human capital at FDA. Greenberg suggested that trainees could be an important mechanism for improving collaborations within the FDA and between FDA and academia. FDA fellowship programs could be enhanced to allow postdoctoral students to be shared by FDA and academia. Such an arrangement could promote interaction between entities and simultaneously build a pipeline of young talent accustomed to drawing upon the wide-ranging expertise of academic and applying it to FDA's unique science needs.

Deficient Scientific Base

Cassell observed that, although three of the six FDA centers contain the term "research" in their titles, compounding daily responsibilities limit agency staff opportunities to conduct research. The FDA Science Board recommended that the agency establish a Chief Scientific Officer to establish strong scientific leadership, and the agency has implemented this recommendation. Given the scope and magnitude of the need for an adequate and robust science base at FDA, Cassell suggested, however, that the need must be addressed more systemically and comprehensively than is within the capacity of a single office.

Deficiencies in Information Technology[1]

Many workshop speakers argued that the greatest barrier to strengthening regulatory science is FDA's limited ability to adopt and utilize IT. IT is essential as a means to organize FDA's massive quantities of new and existing information so the agency can make science-based regulatory decisions. Kim cited three distinct but interdependent components of IT that are necessary to support regulatory science, all of which suffer due to IT deficiencies:

- **IT infrastructure**—Similar to other infrastructures, such as roads and bridges, IT infrastructure comprises the basic physical and organizational elements needed for the operation of a system. Examples include data centers, networks, computer servers, storage systems, and the organization of an operations panel.
- **Informatics**—Informatics, also known as information science, encompasses the practice of information processing and the engineering of information systems, including the structure, algorithms, behavior, and interactions of systems that store, process, access, and communicate information. In the context of the biomedical sciences, genomics and bioinformatics are examples of informatics sciences, involving the establishment of methods for handling vast quantities of data.
- **Scientific computing**—Scientific computing consists of the construction of mathematical models and numerical solution techniques and the use of computers to solve scientific problems. In silico[2] studies fall in this category.

Kim acknowledged the interdependency and overlap among skill sets and experts in these three areas, but warned that misunderstanding or conflation of the three could lead to misspent funds or underinvestment by stakeholders who view spending on IT infrastructure, informatics, and scientific computing as redundant. He also suggested that, as other organizations and enterprises move forward with advances in IT, FDA will face pressure to conduct its regulatory work at a pace commensurate with the growing demands on the agency. For example, an increasingly data- and informatics-savvy public will have rising expectations of FDA with respect to safety issues, as well as drug supply chains, postmarket surveillance, and adverse event reporting.

[1] This section is based on the presentation of Sangtae Kim, Executive Director, Morgridge Institute for Research, University of Wisconsin.

[2] In silico refers to a process similar to biological experimentation in *in vivo* or *in vitro* studies, but using computer simulations.

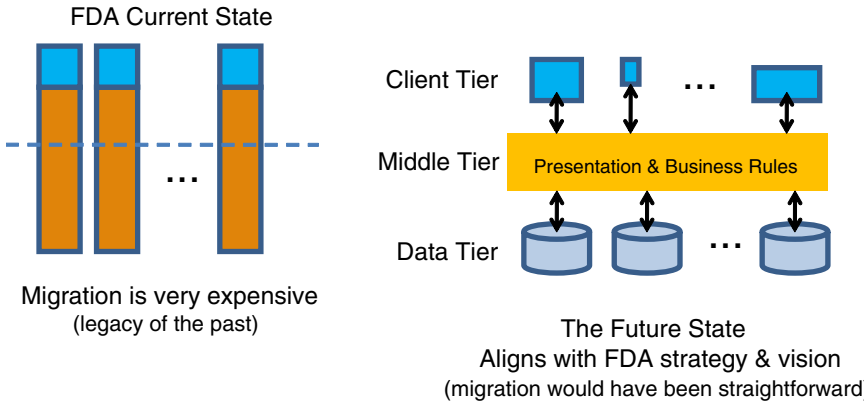

FIGURE 4-2 Flow of data in an Incubator for Innovation in Regulatory and Information Science (IIRIS)/Centers of Excellence (COE) model.
SOURCE: Kim, 2010.

Kim also addressed the question of the timing of investment in IT. He noted that delays in rebuilding infrastructure such as roads and bridges can actually result in lower costs due to improved technology and building materials. In contrast, building or rebuilding an IT infrastructure can become significantly more expensive and time-consuming as investments are delayed. For an information-based organization such as FDA, staff members frequently develop workarounds in the absence of an adequate IT infrastructure. The result is often increased costs and project time to recover lost data and rebuild lost connections into a larger workable foundation.

Kim suggested that, in moving forward, FDA may want to consider adopting the best practices of large enterprises of using data tiers and client tiers, which can be adjusted to the type of user access to information. Figure 4-2 illustrates how the middle tier serves to function as the link between the data layer and the user. Kim referred to an intramural collaboration concept introduced in the FDA Science Board Report, called the Incubator for Innovation and Regulatory Information Science (IIRIS)[3] model, which would function as a data sharing mechanism. In addition, if the agency in the future were to adopt a hub (Incubator for Innovation in Regulatory and Information Science [IIRIS]/Centers of Excellence

[3] In Kim's presentation, the IIRIS model was used interchangeably with the Centers of Excellence (COE) model.

BOX 4-1
The IIRIS Model

"[It] would be under the direction of the Chief Scientific Officer and would invest in the recruitment of talented cross-disciplinary scientists to serve as liaisons with groups across the Agency involved in the 'new science' programs. The IIRIS team would not do the scientific work, but rather would be the project managers to nurture and track program progress. IIRIS would also be responsible for the creation of the proper computation, technical and biological infrastructures (e.g., measurement, visualization and computational facilities), and work closely with the Director of External Collaborations and Training to create strategic partnerships with academia, industry and governmental laboratories to deliver the competency necessary in science, technology, commerce and policy to support industry innovation and the delivery of safe and efficacious products to the marketplace."

SOURCE: FDA Science Board, 2007, p. 28.

[COE]) model,[4] this data-sharing mechanism would lend itself easily to a collaborative model whereby shared networks of data and information create a whole that is greater than the sum of its parts (see also Chapter 5) (FDA Science Board, 2007, p. 28).

Box 4-1 presents Kim's description of the IIRIS model to the FDA Science Board.

IT plays a critical role in organizing data for a regulatory science infrastructure. It is also an area of rapid growth and complexity. In the open discussion following his presentation, Kim concluded that dedicated personnel will be needed at FDA for each of the three components of IT listed above. Clear communication by IT experts to the public and stakeholders will be needed as well. Kim noted that, although FDA was excluded from the $1.2 billion granted by the *American Recovery and Reinvestment Act of 2009* for the electronic medical records initiative, the agency is now receiving major IT investment from the *Information Communication Technology for the 21st Century (ICT-21)*[5] initiative.

[4] See Chapter 5 for a detailed discussion of the COE model.

[5] More information on ICT-21 is available at: https://www.fbo.gov/spg/HHS/FDA/DCASC/FDA-SOL-08-00600/listing.html (accessed September 24, 2010).

SYSTEMIC BARRIERS

Philip A. Pizzo, Dean, School of Medicine, Stanford University, and Chair of the Council of Deans, Association of American Medical Colleges, cited several broader obstacles to the development and promotion of regulatory science, which are encountered not only at FDA but also in academic medical centers. They include attrition of scientific talent due to a lack of financial incentives, driving (and restriction) of research based solely on funding sources and not on science, and reluctance to collaborate because of burdensome legal requirements. According to Pizzo, these more systemic barriers are symptomatic of problems found in the current drug development models.

Greenberg also observed an aversion to regulation found in academic medical settings. He said the nature of academia does not lend itself to a regulatory mindset, and thus, cultural differences will pose an additional challenge to effective collaboration between academic medical centers and FDA.

5

Potential Models for Building a Regulatory Science Infrastructure

A theme among the speakers was that collaboration is necessary to building a strong regulatory science infrastructure.

At the heart of the matter, said FitzGerald, is that the current drug development system is no longer sustainable. The traditional, vertically integrated large drug development model represents a siloed approach characterized by limitations of both finance and human capital. Moving a drug to market is already very costly, but the costs increase exponentially when one takes into account failed drugs and the increasing public and political pressure to lower prescription drug prices. The limitations of the siloed approach argue for a paradigm shift toward a modular, disaggregated model that encourages collaboration and distributes risk among the various stakeholders (see Figure 5-1).

Robust regulatory science at FDA will be essential to maintain purpose and focus within the agency and external respect for its scientific mission. FitzGerald suggested that FDA devise new ways to encourage and reward innovation, enhance risk detection to conserve value, and leverage the resources of the academic sector to refine its decision making as drug development grows more disaggregated and globalized. During a panel discussion led by Peter Honig, Head, Global Regulatory Affairs, AstraZeneca, and former Director of the Office of Drug Safety at the Center for Drug Evaluation and Research (CDER), participants considered potential models for building and strengthening regulatory science.

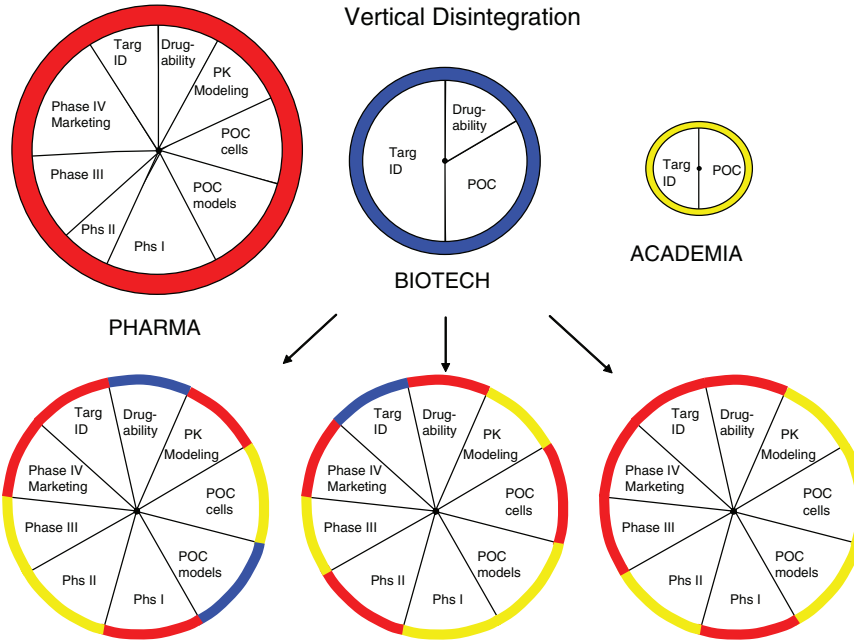

FIGURE 5-1 Visualization of how the current drug development model is growing disaggregated with the involvement of various sectors to reduce risk in innovation.
SOURCE: Skarke and FitzGerald, 2010.

COLLABORATIVE MODELS

According to FDA Commissioner Margaret Hamburg, FDA has been engaged in regulatory science for years, leading to several accomplishments. For example, as noted in Box 2-2, collaboration between FDA and NIH led to a new method of using gene biomarkers to assess the differentiation in stem cell lines; this was an initial step that will ultimately lead to setting standards for use in patients and for ensuring that undifferentiated lines do not contaminate the final product. In 1997, FDA collaborated with academia and industry to create clinical data standards that could be used universally. In the field of drug-induced kidney toxicity, the agency led joint efforts with European health agencies to identify and qualify novel biomarkers for drug assessment. This partnership led to a more sensitive and noninvasive strategy for detecting kidney toxicity in animal models, enabling regulatory bodies to perform assessments early in drug development to help prevent investments in scientific dead-ends.

Judith Kramer, Executive Director, Clinical Trials Transformative

Initiative (CTTI), Duke University, cited the Centers for Education and Research on Therapeutics (CERTs) as a model of collaboration. CERTs came about following the *FDA Modernization Act of 1997*[1] and were funded by the Agency for Healthcare Research and Quality (AHRQ). The program formed 60 interdependent centers across the country to provide expertise in therapeutics and to serve as a resource for patients, providers, and agencies, with the goal of optimizing therapeutics in practice. Kramer said that a unique aspect of the CERTs model is the leadership of a steering committee tasked with shaping the initiative and creating synergism across the collaborative efforts of the centers. This differs from the traditional model of funding individual, siloed, centers to conduct independent projects. Kramer indicated that the CERTs model allows the regulatory agency (e.g., AHRQ, FDA), which is required to apply the latest science in its decision-making authority, to collaboratively draw upon the expertise of various centers and meet the needs of both entities through evaluative science. Although the CERTs project was ultimately underfunded, the concept led to the Sentinel Initiative at FDA—a national, active, surveillance system to monitor drug safety.

The Critical Path Initiative (CPI)[2] is a similar collaborative effort, aimed at developing strategies to guide innovative medical products through FDA's regulatory system. CTTI, one of the programs stemming from the CPI, was formed through a memorandum of understanding between FDA and Duke University. The program joins industry, academia, patients, health care providers, investigators, and regulatory law firms as partners in pursuit of the common goal of improving the clinical research enterprise. Involvement of FDA in these collaborations, said Kramer, significantly increases the prospects for producing practicable solutions.

The Biomarkers Consortium (BC) is another collaboration to come out of FDA's CPI. Mark McClellan, Director of the Engelberg Center for Healthcare Reform at Brookings Institution, cited BC as an example of a successful public-private partnership, which was first undertaken by FDA, NIH, and the industry trade group—Pharmaceutical Research and Manufacturers of America (PhRMA)—in late 2006 to boost the science behind identification of high-impact biological markers for use in drug development, translational research, preventive and predictive medicine, and clinical practice guidelines. BC now consists of 60 partners from the government, industry, and non-profit sectors, and is managed by the

[1] *FDA Modernization Act of 1997*, Public Law 105-115, 105th Cong. (November 21, 1997).

[2] More information on FDA's Critical Path Initiative is available at: http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm (accessed September 24, 2010).

Foundation for the National Institutes of Health (FNIH). BC's research, including FDA's unique access to and analysis of Phase II data from pharmaceutical companies, has since identified adiponectin, a hormone in fat cells, as a predictive biomarker for type 2 diabetes and superior to the existing standard biomarker, hemoglobin A1C (Wagner et al., 2009).

Two additional collaborative models—in this case, in oncology—were described by Ellen Sigal, Chair and Founder, Friends of Cancer Research. These models are summarized in Box 5-1.

BOX 5-1
Collaborative Models in Oncology

Two existing partnerships bring government together with other sectors to promote cancer research and explore potential methods and solutions in cancer prevention, treatment, and patient issues:

- **National Cancer Institute's (NCI) Clinical Trials Cooperative Group Program**—This program was founded in 1955 to increase chemotherapy studies through a partnership among NCI, cancer researchers, academic centers, and community physicians. Today, the program involves 3,100 institutions across North America and Europe that conduct group clinical trials and study combination therapies in cancer treatment. There are currently 12 clinical trials being conducted by independent institutions with varied structures and research emphases, such as pediatrics, radiation therapy, and gynecologic oncology. The institutions share data and develop and conduct large-scale trials in multi-institutional settings. The diversity and large scale of the cooperative groups offer unique opportunities to study toxicology in approved drugs and to pursue possible additional indications (NCI, 2010).
- **NCI–FDA Interagency Oncology Task Force (IOTF)**—IOTF is a joint fellowship training program between NCI and FDA intended to foster the sharing of cancer-related scientific data and regulatory knowledge from bench to bedside. Training is conducted through staff exchanges. A sabbatical program for FDA staff at academic research centers is being developed. Thus far, the program has succeeded in supplying valuable input for the development of chemoprevention biomarkers, creating a cancer bioinformatics infrastructure, and exploratory investigative New Drug Applications (IOTF, 2010).

These cancer-specific collaborative programs can serve as useful case studies for building regulatory science. Evaluation of their successes can be helpful in devising ways to enhance FDA's regulatory science infrastructure.

SOURCE: Sigal, 2010.

THE CENTERS OF EXCELLENCE MODEL

Establishing a regulatory science infrastructure is a major undertaking that cannot be accomplished by any single group. Workshop participants discussed whether a COE model could be applied to address the barriers to building a regulatory science infrastructure at FDA, as reviewed in Chapter 4. A COE model at its most basic level consists of a network comprising one intramural center, with connections to extramural centers that can then be linked to other networks and/or centers.

Dale Nordenberg, Director, Novasano Health and Science, and former Associate Director, CDC, identified the COE model as a mechanism that could simultaneously support FDA's regulatory activities, encourage partnerships for research in innovation, and help educate outside groups on regulatory processes. This model could rapidly link the agency with needed expertise—whether internal or external—to enable it to keep pace with emerging science and globalization (see attributes listed in Figure 5-2). The COE model would be funded by FDA and centered in academic institutions. As an FDA-led and community-enhanced initiative, advisory boards from the COE (i.e., academic institutions) and/or the Science Advisory Board within FDA would inform the scientific direction of the

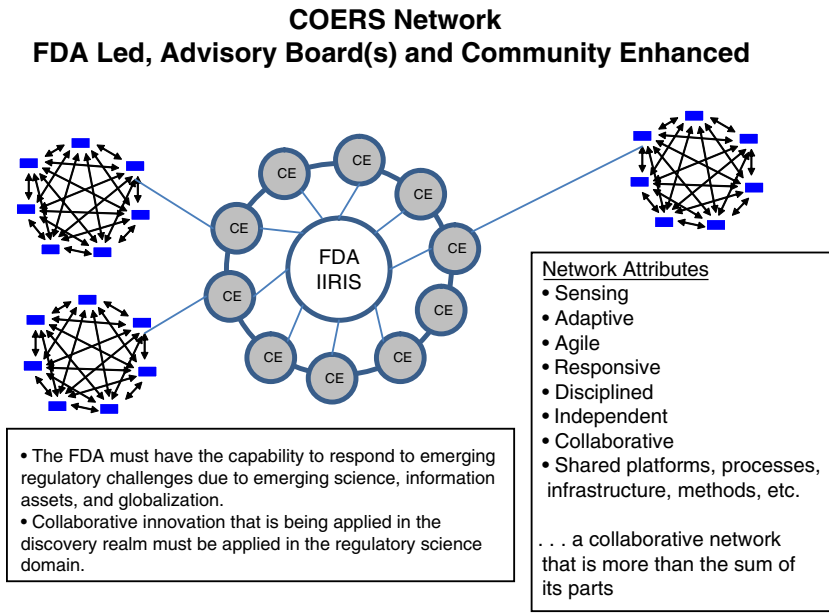

FIGURE 5-2 Centers of Excellence in Regulatory Science Network.
SOURCE: Nordenberg, 2010.

collaboration. Ultimately, the extramural COE and FDA's intramural center would function as a network with a shared infrastructure.

As an open innovation model, centers would not function in silos but rather as a network to draw out the broad expertise necessary to conduct regulatory science. With the understanding that a single system cannot fully meet FDA's broad needs, the COE model creates a network of networks to safeguard FDA's ability to access scientific expertise. Ultimately, this model would:

- **Enhance FDA's regulatory activities**—Nordenberg characterized FDA as an applied organization, meaning that the agency delivers services to broad groups of stakeholders. Should FDA not have access to the requisite expertise or be unable to provide the necessary number of experts, the COE structure would enable the agency to reach out to a support network on an ad hoc basis to fill the gaps. FDA would benefit from such consultations in both regulatory review and policy determination (e.g., development of guidance documents).
- **Advance research in innovation**—A COE model would make available to FDA experts from all scientific sectors, permitting strategic development of research and innovation plans. The model would establish a natural leadership role for FDA with its regulatory authority and scientific base. Figure 5-2 portrays such a model—the Centers of Excellence in Regulatory Science Network (COERS)—whose hub is FDA IIRIS, as discussed in Chapter 4.
- **Help FDA educate about regulatory processes**—A useful result of relationships formed in the COE model is mutual education and understanding. By better understanding FDA's regulatory processes, sponsors could more efficiently meet the safety requirements imposed by the agency. The agency could also utilize these connections to develop fellowship programs and construct curricula collaboratively.

Nordenberg also stressed that clear outcome measures will be necessary for evaluating, assessing, and ultimately documenting the impact of this collaborative model. A COE model for FDA's regulatory science framework, said Nordenberg, could be used for clinical trials, safety surveillance, and comparative effectiveness research. "The structure and operational model for the COE is an important enabler of innovation, outcomes, and ultimately public health impact," concluded Nordenberg.

Moving Toward a COE Structure

It was suggested during the workshop that some centers already in place today can serve as models of the open collaborations being sought in COE. For instance, CERTs (as described earlier in Chapter 5) were highlighted as a unique model for leveraging the resources of a network of centers to assist regulatory agencies. As opposed to funding individual centers to conduct independent research, the CERTs model presents a unique structure in which a steering committee provides leadership and guides the efforts of the centers, creating synergies through the network that are ultimately to the benefit of regulatory science and decision making.

Moving toward a successful COE model will largely rely on the human capital available and able to be activated in the name of regulatory science. Margaret Anderson, Executive Director of FasterCures, discussed strengthening human capital through the engagement of a broad population with different perspectives. For example, the unique communication of online communities such as Facebook and PatientsLikeMe provide an opportunity to harness the energy, engagement, and informatics expertise of a new generation.

Examples of successful implementation of the COE model also exist. The Observational Medical Outcomes Partnership (OMOP) is a public–private partnership designed to help improve monitoring of the safety of drugs (OMOP, 2010). Its membership consists of all stakeholders in drug safety, including FDA, NIH, and industry. The collaboration is focusing on detection of safety signals. OMOP is also building artificial and synthetic data sets and running simulations to test new methods. Likewise, disease-based organizations, such as the Cystic Fibrosis Foundation, are driving collaborative science and conducting their own research within their networks, aided by readily available patient population data. According to Nordenberg, FDA and its collaborative partners could study these and other examples to anticipate and develop solutions to potential barriers to the successful establishment and operation of a collaborative COE model.

The COE model is not without obstacles, said Ellenberg. FDA review staff are subject to stringent conflict-of-interest rules that could discourage collaboration. The current environment includes particular scrutiny of relationships with industry and suspicion of potential bias arising from collaboration. To implement a collaboration model, it will be necessary to merge differing approaches to confidentiality of information, as academic culture tends toward open sharing of scientific discoveries, while the economics of successful drug development mandate that scientific discoveries be treated as proprietary and confidential, said Ellenberg. A delicate balance should be struck between collaboration and confidentiality, with confidentiality being maintained in all linked COE.

6

Challenges in Engaging the Public Policy Community

Over the course of the workshop, several participants stressed the importance of a rapid response to the need for an enhanced regulatory science discipline and infrastructure at FDA. Speakers credited the recent interest in regulatory science to new leadership at the health agencies and a President who is focused on revitalizing science. In early 2010, President Barack Obama requested funding in FDA's fiscal year 2011 budget specifically to support the advancement of regulatory science.[1] William Corr, Deputy Secretary, Department of Health and Human Services (HHS), noted in his presentation, "It is not a huge amount. It's $25 million, and in the HHS budget, sometimes $25 million seems small. But it is a great beginning." Hamburg agreed with the importance of expanding regulatory science to open up possibilities for new diagnostics and safer and more effective treatments: "It's essential," she said, "that we have a regulatory agency that is scientifically robust and trusted by policy makers and the American people."

Proper support for scientific capacity and sustainable resources can provide the autonomy FDA needs to pursue its mission free of the influence of political tides or funding mandates, said Hamburg.

1 "Investing in FDA's Scientific Infrastructure: The Budget includes $25 million for advancing regulatory science at FDA. This initiative builds on the President's commitment to harness the power of science for America's benefit and includes $15 million for nanotechnology-related research, which holds great promise for advances in medical products and cosmetics. The additional resources will also enable FDA to update review standards and provide regulatory pathways for new technologies, such as biosimilars" (HHS, 2010).

Speakers from the patient community, such as Ellen Sigal of Friends of Cancer Research and Margaret Anderson of FasterCures, highlighted the importance of public policy advocates as the ultimate catalysts for political reform. The final workshop session examined ways to interact with the public policy community, gain its support, and mitigate the unique challenges faced in the process.

CHALLENGES IN ENGAGING THE PUBLIC POLICY COMMUNITY

Steven Grossman, founder of Alliance for a Stronger FDA, highlighted three principal challenges that hinder engagement of the public policy community in support for enhanced regulatory science at FDA: funding, policy development, and communication.

- **Funding**—Fully 80 percent of FDA's budget goes to personnel costs. Grossman expressed concern that—despite the increase in FDA's appropriated budget for 2011—the agency faces an unprecedented need for scientific research combined with increased expectations. Given the fixed expenses required to run the agency, little funding will remain for new initiatives.
- **Policy development**—In policy development, there is often a demand for fast results; however, building a regulatory science infrastructure will require a significant investment of resources and time. Strong leadership and a clearly articulated implementation process must be communicated to policy makers at the outset to prevent a loss of support, said Grossman. He also suggested that the move to build a regulatory science infrastructure at FDA should remain independent of user fees and other potential funding sources that could be perceived as posing a conflict of interest.
- **Communication**—A common theme underlying public policy challenges is the importance of communication and education. FDA will need to build an understanding of regulatory science among the public and policy makers, remarked Grossman, as well as those directly partnering with the agency.

PUBLIC OPINION POLL DATA ON FDA

Mary Woolley, President, Research!America, presented the results of a survey conducted by her organization (Research!America, 2010) as context for the actions needed to energize the public policy community to support the development of a regulatory science infrastructure at FDA. Woolley noted that public sentiment is dynamic and is driven by emotion,

the media, and high-profile leadership initiatives, among other influences. Figure 6-1, for example, illustrates shifts over the last 6 years in public sentiment on the most important health issues. Woolley predicted that concern about obesity will continue to increase as a result of First Lady Michelle Obama's "Let's Move" campaign, aimed at reducing childhood obesity (White House, 2010).

FDA is currently on the public radar, particularly due to recent food and drug recalls. As Figure 6-2 indicates, the majority of those surveyed selected "somewhat confident" when asked about their confidence in current systems for monitoring the effectiveness and safety of new medicines and medical devices. Figure 6-3 shows that respondents cited "protecting public safety" as FDA's most important role. A subsequent survey question in the same series showed respondents were evenly divided when

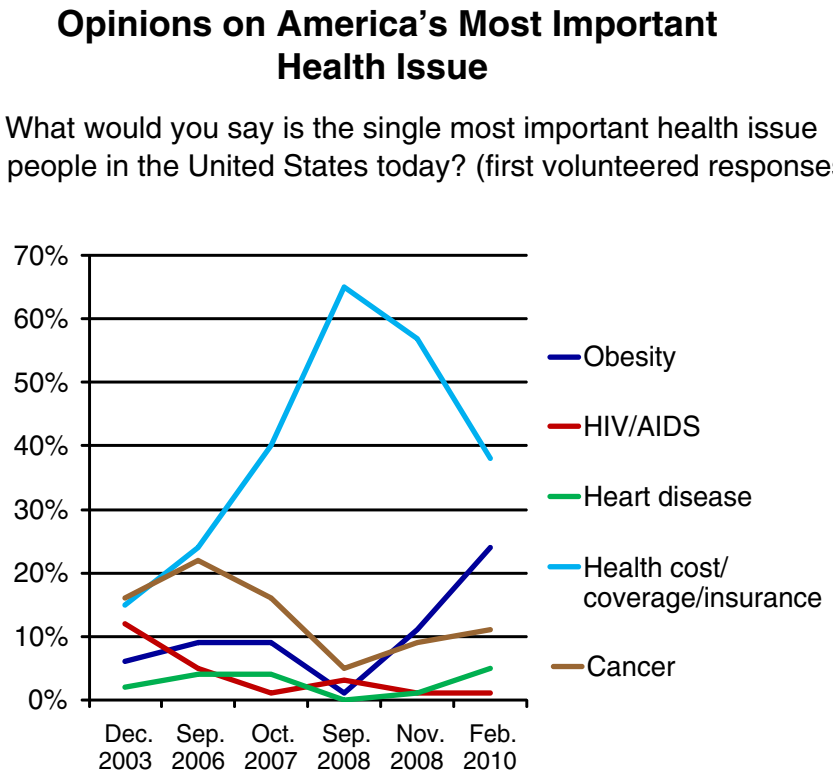

FIGURE 6-1 Shifting opinions on America's most important health issue, December 2003–February 2010.
SOURCE: National Public Opinion Polls, 2003–2010, Charlton Research Company for Research!America.

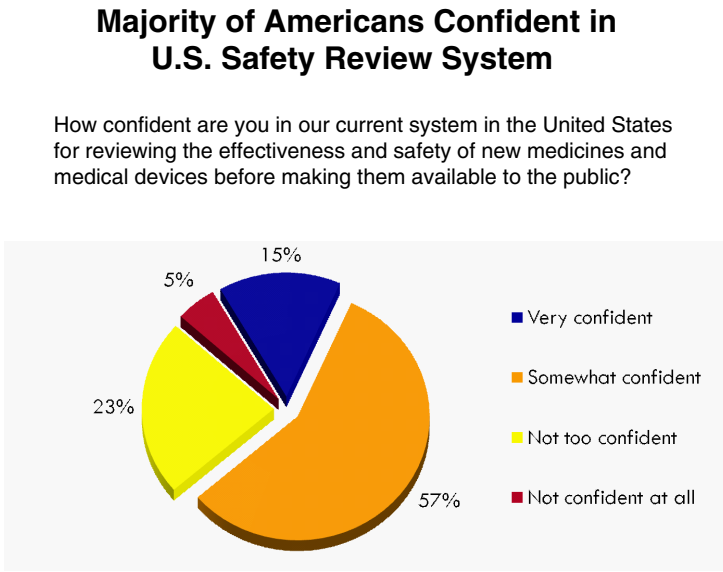

FIGURE 6-2 Americans' level of confidence in systems for monitoring the effectiveness and safety of new medicines and medical devices.
SOURCE: National Public Opinion Polls, 2003–2010, Charlton Research Company for Research!America.

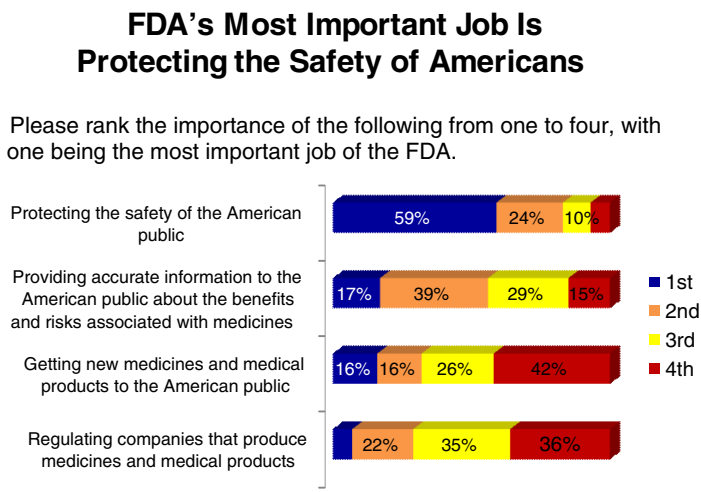

FIGURE 6-3 Americans' views on FDA's most important role.
SOURCE: National Public Opinion Polls, 2003–2010, Charlton Research Company for Research!America.

asked whether the FDA should speed up the approval process at the risk of compromising safety (Research!America, 2010). This latter opinion poll reflects the dichotomy in the public's understanding of the regulatory processes required to deliver the results expected from FDA. Some of the speakers identified improved communication and public outreach as a means to help mitigate this knowledge gap. Workshop participants also expressed desire for detailed surveys that focus specifically on drug development in order to understand the roots of the public's attitudes toward benefits and risks of FDA-regulated products.

THE POWER OF PATIENT ADVOCACY

Perhaps the most effective way to reach policy makers is through those they are supposed to represent: the public and patients. Newly tested positive for HIV in the mid-1980s, Michael Manganiello, Partner, HCM Strategists, and a patient advocate, recalled his initial layperson's view of FDA: "I knew about as much about FDA as I did about quantum physics, which was nothing, except I quickly became aware that FDA was the place that was standing in the way of me getting better drugs." Manganiello said he revised his opinion after learning that many more barriers stood in his way: lack of political will, lack of resources, and lack of support from the American people.

Today, the movement that followed to bring awareness to the HIV/AIDS epidemic is touted as a major success—in rallying public and government support, intensifying scientific innovations, and producing therapeutics. Manganiello credits the grassroots movement of patient groups as the driving force behind this success. Patient groups have grown much more sophisticated since then and generally can exercise considerable political influence over the allocation of scientific resources and expertise.

Patient advocacy groups and disease-based foundations have the potential to aid in the building of regulatory science through media-savvy communication and access to patient populations. They also appreciate the importance of involving FDA to produce results, as well as the challenges that face regulatory agencies. Thus, patient advocates can prove to be valuable partners in future regulatory science initiatives at FDA. Box 6-1 presents an example of the impact of patient advocacy, in this case with respect to cancer therapeutics.

BOX 6-1
The Impact of Patient Advocacy for Cancer Therapeutics at FDA

Until recently, patient communities were concerned principally with improving research capacity at NIH in their efforts to advance cancer care, according to Ellen Sigal. The role of FDA, on the other hand, remained unclear and thus ignored. The cancer research community has since come to understand the critical functions of FDA in the emergence of new therapeutics for cancer. The community also observed that more could be done to promote cancer care at FDA—beginning with the elevation of oncology to a new office within the agency infrastructure.

In July 2005, the cancer community, including professional groups, cancer centers, scientists, the American Society of Clinical Oncology, and the American College of Radiology, succeeded in bringing about the agency's Office of Oncology Drug Products (OODP). OODP uniquely encompasses both small-molecule drugs and biologics within one office in an effort to consolidate oncology regulations and improve consistency in review standards and policies, and serves as a small-scale example of flourishing regulatory science.

In going forward, Sigal observed that OOPD could further advance regulatory science by enhancing collaboration among the different FDA centers, increasing interactions with other health-related federal agencies, expanding external advisory capacity, and harmonizing with international regulatory bodies.

SOURCE: Sigal, 2009.

7

Envisioning Successful Regulatory Science at FDA[1]

Emphasizing the neglected state of regulatory science at FDA, Goodman noted that science is critical to the agency's mission to promote and protect the public health and safety, as well as to the integrity of its decision making. Improvements in the practice of regulatory science must occur at all levels, including population, epidemiology, clinical, manufacturing, and behavioral science. Understanding a molecule or a nanoparticle is not useful unless the information can benefit people.

Pharmaceutical companies perform excellent scientific assessments of their products, said Goodman, but they are limited by the costs and risks associated with innovation. Therefore, a major function of FDA is to engage in a science-based manner both internally and with industry, academia, patients, and other agencies throughout the product development and evaluation processes.

KEY AREAS OF SCIENTIFIC EMPHASIS

As FDA's Chief Scientist whose office has primary responsibility for overseeing the scientific capacity of FDA, Goodman shared his vision of a successful regulatory science infrastructure within the agency. He described ideal circumstances in which product development, treatments for rare diseases, regenerative medicine, predictive medicine, and infor-

[1] This section is based on the presentation of Jesse Goodman, Chief Scientist and Deputy Commissioner for Science and Public Health, FDA.

mation technology would be made scientifically robust through agency-wide adoption of a regulatory science discipline.

Goodman outlined the following areas of scientific emphasis and the vision of success for each:

- **Transform product development**—Given calls for a paradigm shift in drug development, Goodman predicted that the process will be radically different upon successful implementation of regulatory science at FDA. He described the ideal process as agile and adaptive to new information, with the ability to consolidate clinical and biological information and identify population subgroups that can uniquely benefit from new drugs, with the ultimate goal of delivering products to patients efficiently and safely. Personalized medicine, diagnostics, biomarkers, innovative clinical trial designs, and combination interventions can all benefit from this change.
- **Identify unmet public health needs**—The ability to respond rapidly to a pandemic with prepared countermeasures is crucial to the safety and security of the nation and to the national and global public health. Sound science, technology, and methods are essential for the development of products to respond to global diseases, emerging infectious disease threats, and bioterrorism; vaccines; and diagnostics. An ideal regulatory system will be able to identify innovative products with the potential to address unmet medical needs and provide countermeasures for public health and stability.
- **Focus on regenerative medicine**—Stem cells, engineered tissues, and combination products are areas of rapidly emerging technology; however, FDA's intervention will be necessary to bridge the gap between innovation and the market. Despite limited resources, stated Goodman, FDA recognizes the importance of regenerative medicine and has made an effort to interact with the development community and NIH to consider standards and models in this area. The hope is that such medicines will be successfully developed to treat serious diseases, replace damaged organs and tissues, and create new treatments for diabetes and cardiac and neurogenerative diseases.
- **Modernize predictive science**—As with regenerative medicine, FDA has the potential to improve predictive science and translate advances in life science and engineering into practice. With a sound science base and the right resources, the agency can modernize *in vitro* toxicology and product characterization, rapidly detect pathogens and contaminants in food and medical products, and assess environmental and chemical hazards.

- **Use informatics to enhance outcomes**—Goodman envisioned informatics being used to enhance safety and health outcomes and transform health care. The application of informatics in a regulatory science infrastructure would include monitoring safety using vast amounts of clinical, health care, and biological data. In partnership with the health care sector and community settings, the knowledge derived through informatics could result in optimized outcomes, clinical trials, and patient safety and ultimately speed up product development.

Finally, Goodman suggested that methods for resolving scientific disputes internally and externally are needed to match the rapid pace of research. There is never a single scientific truth. FDA will need to foster the creation of a culture that allows for diverse opinions to take advantage of all available scientific evidence in regulatory decision making.

8

Considering Next Steps

As noted by both Hamburg and Goodman, a wealth of scientific and regulatory knowledge already exists at FDA. There have been a number of examples of successful use of regulatory science and collaborative models at the agency level. Likewise, several recent initiatives—the *Food and Drug Administration Amendments Act*, the creation of the Office of the Chief Scientist, increased funding and recruitment, and enhanced FDA–NIH interaction—represent efforts to move in the direction of scientific regulatory decision making.

On February 24, 2010, HHS Secretary Katherine Sebelius announced a new partnership between FDA and NIH to spur the development, evaluation, and approval of new medical products. The partnership focuses particularly on strengthening regulatory science research. The FDA–NIH collaboration represents the type of partnership advocated by workshop speakers. As HHS Deputy Secretary Corr stated:

> NIH is the world's leader in biomedical research and FDA is the gold standard across the world in the evaluation and approval of drug products and other medical products. Secretary Sebelius and I are confident that, with the two dedicated leaders we have in Peggy Hamburg, one of the nation's foremost advocates for public health, and in Francis Collins, one of the nation's most distinguished scientists, they will lead us into a new era in which we can promote and protect public health by realizing the promise of science.

The primary goal of the FDA–NIH Collaboration Initiative is to improve and harmonize the functions of two interrelated disciplines,

regulatory and translational science, through the expertise available in FDA and NIH for efficiently and effectively guiding biomedical discoveries into safe therapies for the public. It will be led by a newly established Joint FDA–NIH Leadership Council,[1] which will be charged with including regulatory considerations in biomedical research and vice versa. As a part of the Initiative, FDA and NIH issued a joint Request for Applications making available $6.75 million dollars for work in regulatory science over the course of three years.

"We now have a special opportunity—and responsibility—to harness advances in science and technology to support our efforts. We are working in collaboration with the best minds and research institutions available, so that we can better develop and utilize new tools, standards and approaches needed to properly assess the safety, effectiveness and quality of products currently in development or already on the market," said Hamburg at the announcement of the initiative (NIH, 2010).

IMMEDIATE NEXT STEPS FOR FDA

Goodman stated that FDA must proceed with the development of regulatory science regardless of external barriers. He outlined the following key implementation steps for first creating an internal support system for a regulatory science infrastructure at the agency:

- **Leadership to strengthen and support science and promote innovation at FDA**—Both the Commissioner's Office and leadership at FDA centers are supportive of promoting science and innovation. There is interest across the agency in multicenter working groups, scientific guidance, and sharing of resources. Goodman also announced the creation a new Office of Science and Innovation within the Office of the Chief Scientist to coordinate such efforts.
- **Excellence in professional development**—Professional development is essential to a scientific career and needs to be built in at the agency level. Goodman acknowledged that some FDA staff are unable to attend professional meetings because of either funding or time constraints. Given the success of staff colleges at each FDA center, Goodman encouraged the development of training programs at NIH and local universities, as well as online programs for staff.
- **Recruitment and retention of outstanding scientists**—Building regulatory science at FDA will require that the agency recruit and

[1] Available at http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm201654.htm (accessed September 24, 2010).

retain top talent. To reverse its high turnover rate the agency will need to continue and expand fellowship programs such as its present Commissioner's Fellowship Program[2] and other tools such as its scholar in-residence sabbatical programs.

BUILDING A FRAMEWORK: THEMES FROM THE WORKSHOP

Weak regulatory science is not a problem just for the FDA; it is a shared problem that requires a shared solution. Several workshop participants called for development of a common framework for enhancing regulatory science. A number of individual suggestions were made during the workshop about the initial steps toward building a national regulatory science infrastructure. They are compiled here as part of the factual summary of the workshop, and should not be construed as reflecting consensus or endorsement by the workshop, the Forum, or the National Academies. They are as follows:

- **Enable emerging technologies to strengthen regulatory science.** Massive amounts of new data are expected to come from emerging technologies in such areas as rare adverse events, genomics, and biostatistics. Each of these areas presents unique opportunities for regulatory science, as well as the potential for serious adverse consequences if the gaps between scientific and regulatory needs are not bridged.
- **A strategic plan is critical.** While many of the elements of regulatory science are already instilled in the functioning of FDA, a strategic approach will be necessary going forward. The blueprint should account for the numerous complexities that will be faced, should acknowledge the need for priority setting, and should involve all stakeholders.
- **Approach barriers to enhanced regulatory science one at a time.** By addressing issues of resources, sustainable funding, recruitment and retention of talent, incentives for the scientific workforce, and building and utilization of IT, the foundation for a regulatory science infrastructure can be laid.
- **Consider existing efforts to bolster regulatory science.** Centers of excellence models, public–private partnerships, and federal col-

[2] The Commissioner's Fellowship Program offers an opportunity for health professionals and scientists to receive training and experience at the FDA for a two-year period. More information is available at http://www.fda.gov/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/CommissionersFellowshipProgram/default.htm (accessed August 11, 2010).

laborative initiatives offer numerous lessons for developing a standard mechanism for regulatory science. Several successful models of collaborative networks already exist, such as the Tufts Center for the Study of Drug Development, DC-based UCSF Center for Drug Development Science, European Center for Pharmaceutical Medicines, European Innovative Medicines Initiative, and further analysis of these initiatives can be useful in developing an implementation plan for building regulatory science within FDA.

- **Leverage informatics and existing network capabilities.** Various industry sectors have devoted considerable resources to development of surveillance, which could be leveraged through cross-sector and cross-disciplinary partnerships.
- **Educate the public.** Public education is an important component to raise awareness and understanding about the complexity of clinical research and the drug development process, and about the need for a strong regulatory science to support drug development. There is a general lack of understanding, by not only the public but also by academia, about the roles of NIH and FDA, respectively, in supporting regulatory science for drug development. Patient advocacy voices are a key element in providing models and input for energizing the public about the need for enhanced regulatory science.
- **Actively engage public policy community.** The public policy community is a strong force for enacting reform and should be considered a partner in the efforts to boost regulatory science. As demonstrated by improvements in HIV/AIDS therapies and cancer care, an effort as substantial as the establishment of a regulatory science infrastructure cannot succeed without the understanding and support of the public policy community. FDA and other stakeholders will need to involve and communicate effectively with patient advocates, policy makers, and the public in its endeavors to move forward with this effort.
- **Secure sustainable support for regulatory science.** Although FDA's FY 2011 proposed budget includes an allotment for regulatory science activities, establishing a regulatory science infrastructure will not happen overnight and will require steady funding, workforce, and leadership for realization.

Many workshop participants acknowledged that simultaneously developing in-house expertise, taking advantage of available funding mechanisms, and coordinating with external experts will be a massive undertaking. Building a regulatory science infrastructure will require tremendous commitment, resources, and an agreed-upon blueprint to be successful.

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Appendix A

Agenda

Building a National Framework for the Establishment of Regulatory Science for Drug Development

February 26, 2010
National Academy of Sciences Building
Lecture Room
2100 C Street NW
Washington, DC

8:00–8:15 OPENING REMARKS

Drug Forum Co-Chairs:
Gail Cassell, *Eli Lilly and Company*
Jeffrey Drazen, *New England Journal of Medicine*

8:15–8:45 REGULATORY SCIENCE: OVERVIEW

Moderator: **Jeffrey Drazen**, *New England Journal of Medicine*

Garret FitzGerald, *Institute for the Translational Medicine and Therapeutics, University of Pennsylvania*

8:45–9:15 KEYNOTE SPEAKER

Congresswoman Rosa DeLauro (D-CT)

9:15–10:00 FDA INITIATIVES ON REGULATORY SCIENCE

Margaret Hamburg, *FDA Commissioner*

10:00–10:15 Break

10:15–11:30 Session I: OPPORTUNITIES FOR ENHANCING REGULATORY SCIENCE

Moderator: **Mark McClellan**, *The Brookings Institution*

The IOM and FDA Science Board Recommendations
Gail Cassell, *Eli Lilly and Company*

Academic Perspective
Philip Pizzo, *Stanford University School of Medicine, Council of Deans, Association of American Medical Colleges*

A Blueprint from the Patient's Perspective
Ellen Sigal, *Friends of Cancer Research*

11:30–11:45 Break and Working Lunch
Guests are asked to pick up lunch and return to their seats.

11:45–1:15 Session II: OPPORTUNITIES FOR ENHANCING REGULATORY SCIENCE (cont'd)

Moderator: **Barbara Alving**, *National Center for Research Resources, NIH*

Translational Approaches to Understand and Predict Rare Adverse Reactions to Drugs
Paul Watkins, *Hamner–University of North Carolina Institute for Drug Safety Sciences*

A Role for Regulatory Science in Emerging Technologies: Genomics
Allen Roses, *Deane Drug Discovery Institute, Duke University*

Opportunities in Statistical Design, Analysis, and Modeling
Susan Ellenberg, *University of Pennsylvania School of Medicine*

IT Infrastructure, Informatics and Scientific Computing in Regulatory Science
Sangtae Kim, *Morgridge Institute for Research*

1:15–2:15 **Panel I: A COMPARISON OF EXISTING AND POTENTIAL MECHANISMS FOR PROMOTING REGULATORY SCIENCE**

Moderator: **Peter Honig**, *FDA and Merck (ret.)*

Panelists:

- **Jesse Goodman**, *FDA*
- **Dale Nordenberg**, *Novasano Health and Science*
- **Judith Kramer**, *Clinical Trials Transformation Initiative, Duke University*
- **Margaret Anderson**, *FasterCures*
- **Harry Greenberg**, *Stanford University School of Medicine*

2:15–2:30 **Break**

2:30–3:15 **Panel II: ENERGIZING PUBLIC POLICY TO ADVANCE THE SCIENCE**

Moderator: **Janet Tobias**,[1] *Ikana Media*

Panelists:

- **Steven Grossman**, *HSP Group and Alliance for a Stronger FDA*
- **Michael Manganiello**, *HCM Strategists*
- **Mary Woolley**, *Research! America*

3:15–3:45 **HHS PERSPECTIVE**

Protecting the Public through Regulatory Science—A National Priority
William Corr, *HHS Deputy Secretary*

3:45–4:00 **SUMMARY AND NEXT STEPS**

Gail Cassell, *Eli Lilly and Company*

[1] Unable to attend the workshop due to weather.

Appendix B

Participant Biographies

Barbara Alving, M.D., M.A.C.P., is the Director of the National Center for Research Resources (NCRR), which funds the development of new technologies for basic and clinical research, supports training for researchers in the biomedical sciences, develops preclinical models, and provides health and biomedical education for the public. The NCRR is responsible for developing the new Clinical and Translational Science Award (CTSA) program that has evolved from the NIH Roadmap initiative to re-engineer clinical research. Dr. Alving received her M.D. cum laude from Georgetown University School of Medicine in Washington, DC. After an internship in internal medicine at Georgetown University Hospital, she completed a residency in internal medicine and a fellowship in hematology at the Johns Hopkins University Hospital in Baltimore, Maryland. Dr. Alving then became a research investigator in the Division of Blood and Blood Products at the FDA on the NIH campus. In 1980, she joined the Department of Hematology and Vascular Biology at the Walter Reed Army Institute of Research and became Chief of the Department in 1992. She left the Army at the rank of Colonel in 1996 to become the Director of the Medical Oncology/Hematology Section at the Washington Hospital Center in Washington, DC. In 1999, she joined the National Heart, Lung, and Blood Institute (NHLBI), serving as the Director of the extramural Division of Blood Diseases and Resources until becoming the Deputy Director of the Institute in September 2001. From September 2003 until February 1, 2005, she served as the Acting Director of the NHLBI. From October 2002 until January 2006, she served as the Director of the Wom-

en's Health Initiative, which is funded through the NHLBI. In March 2005, she became the Acting Director, NCRR and was named Director in April 2007. Dr. Alving is a Professor of Medicine at the Uniformed Services University of the Health Sciences in Bethesda, 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 previous member of the FDA Blood Products Advisory Committee. She is a co-inventor on two patents, has edited three books, and has published more than 100 papers in the area of thrombosis and hemostasis.

Margaret Anderson is Executive Director of FasterCures/The Center for Accelerating Medical Solutions, defining the organization's strategic priorities and positions on key issues, developing its programmatic portfolio, and managing its operations. Prior to her appointment, she was FasterCures' COO for 5 years. Ms. Anderson previously served as deputy director of the Academy for Educational Development and led programs and studies at the Society for Women's Health Research, the American Public Health Association and the Congressional Office of Technology Assessment. She serves on the boards of the Alliance for a Stronger FDA and the Council for American Medical Innovation. She holds a Bachelor's degree from the University of Maryland and a master's degree in science, technology and public policy from George Washington University's Elliott School of International Affairs.

Gail H. Cassell, Ph.D., 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 NIH during the decade of her leadership. She obtained her B.S. 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 Ph.D. 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, 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 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 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, 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.

William Corr, J.D., was unanimously confirmed on May 6, 2009, by the Senate as Deputy Secretary of the Department of Health and Human Services. As Deputy Secretary, he is responsible for the operations of the largest civilian department in the federal government. "Bill Corr's policy expertise and management experience will be invaluable as we work together to manage the Department and pass and implement comprehensive health reform," Secretary Sebelius said. "Bill knows our department inside and out, and I look forward to partnering with him in the years ahead." Mr. Corr most recently served as executive director of the Campaign for Tobacco-Free Kids. Previously, he served for 12 years as counsel to the U.S. House of Representatives' Subcommittee on Health and the Environment. Additionally, Mr. Corr served as Chief of Staff for the Department of Health and Human Services. Mr. Corr is a graduate of the University of Virginia and the Vanderbilt University School of Law.

Representative Rosa DeLauro has worked a lifetime for the people of Connecticut. She was first elected to Congress from Connecticut's Third District in 1990, and is currently serving her tenth term. Congresswoman DeLauro sits on the influential House Appropriations and Budget Committees. She serves as chairwoman of the Agriculture-FDA Appropriations Subcommittee and as a member of the Labor–Health and Human Services–Education and Financial Services Appropriations Subcommittees. In 1999, she was elected Assistant to the Democratic Leader by her colleagues, making her the second highest ranking Democratic woman in the House of Representatives. She was re-elected to this position in 2000. She has served as co-chair of the House Steering and Policy Committee since 2002. Congresswoman DeLauro was born and raised in New Haven's Wooster Square, where for years her grandmother owned and operated a pastry shop. Her father, Ted DeLauro, was a New Haven Alderman whose hard work earned him the nickname "Mayor of Wooster Square." DeLauro's mother, Luisa, was the longest-serving member of the New Haven Board of Aldermen, serving from 1965 to 1998. Since coming to Congress, DeLauro has built a solid reputation for constituent service and hard work. In 1998, 2000 and 2002, she was recognized as one of the House of Representative's top "Workhorses" by *Washingtonian* magazine, and was called a "hero for working families" by nationally syndicated columnist Tom Oliphant. DeLauro has helped Connecticut families get ahead by making economic improvement a top priority. The first bill she introduced as a Member of Congress was a middle-class tax cut. More recently, she has fought for targeted tax cuts such as a $500 per child tax credit, a tax cut for children's health care, and education tax cuts to give every Connecticut family the chance to send their kids to college. DeLauro has authored legislation that would guarantee men and women equal pay for equal work. From her seat on the Appropriations Committee, DeLauro has successfully secured millions in vital funds for Connecticut's defense industry. In addition, DeLauro has become a leader in the effort to protect and strengthen Social Security for today's seniors and future generations. During her tenure in Congress, DeLauro has taken a special interest in health care issues, leading the fight for affordable, quality health care. She has worked aggressively with a bipartisan group of legislators to lower the rising costs of prescription drugs. As a result of her efforts, the U.S. House passed legislation allowing the importation of drugs from countries like Canada in the 108th Congress. A survivor of ovarian cancer, DeLauro has been a leading voice for increasing critical cancer research. Her work led to passage of "Johanna's Law" in the 109th Congress—a law that will increase awareness of the gynecologic cancers. From her position on the Labor–Health and Human Services–Education Appropriations Subcommittee, DeLauro has fought to increase funding for breast and

cervical cancer screenings and research. DeLauro has also authored legislation to ensure longer hospital stays for women undergoing breast cancer surgery that enjoys bipartisan support. She led an effort to enact national legislation to address the public health crisis of underage drinking in our country. In the 109th Congress, "The STOP (Sober Truth on Preventing) Underage Drinking Act" became law. In February 2005, DeLauro was honored to be appointed ranking member of the House Appropriations Agriculture Subcommittee and charged with overseeing what she considers the core responsibilities of our federal government. Through the position, DeLauro has worked to provide funding for a safe food supply, a healthy agricultural economy, and for the FDA to regulate thousands of products we use every day. DeLauro has made reform of the FDA a top priority to strengthen oversight of food and drugs. With rising instances of food safety and food-borne illness a concern for many Americans, DeLauro co-founded the Congressional Food Safety Caucus to explore remedies to secure the food supply. As chairwoman of the Appropriations Agriculture Subcommittee in the 110th Congress, DeLauro worked to restore the oversight functions of the subcommittee by examining the nation's food safety system and ensuring that federal agencies such as the FDA and USDA prioritize science and the public interest. She worked to make bold investments in renewable energy technologies, expand rural development programs and support specialty crop initiatives that are important to Connecticut. DeLauro has spearheaded initiatives in Washington and Connecticut to meet the challenges facing parents and children. She has championed legislation that would make child care more affordable, and has worked to improve public education by reducing class size and modernizing public schools. In 1999, DeLauro established "Rosa's Readers," a program designed to increase interest in reading outside the formal classroom environment. During the first Rosa's Readers summer program, more than 400 first graders completed the challenge of reading twenty books over the summer and were rewarded at a pizza party with their family and friends. Since she first came to Congress in 1990, DeLauro has put every pay raise she has received toward the Ted DeLauro Scholarship, which she founded in memory of her late father. To date, $478,000 has helped 478 students further their education. In 2004, DeLauro also used the Congressional pay raise to initiate the Maria Baez Perez Scholarship, established in the name of a former staff person. Since that time, 38 area students have received $1,000 scholarships as well. Prior to her election to the House of Representatives, DeLauro served as Executive Director of EMILY'S List, a national organization dedicated to increasing the number of women in elected office. She served as Executive Director of Countdown '87, the national campaign that successfully stopped U.S. military aid to the Nicaraguan Contras. From 1981–1987, DeLauro served

as Chief of Staff to U.S. Senator Christopher Dodd. DeLauro is a graduate of Marymount College, where she received her B.A. with honors. She earned her master's in International Politics from Columbia University, and studied at the London School of Economics. DeLauro is married to Stanley Greenberg, President of Greenberg-Quinlan Research, Inc., a public issues research and polling firm.

Jeffrey M. Drazen, M.D., was born in Missouri. He attended Tufts University with a major in physics and Harvard Medical School, and served his medical internship at Peter Bent Brigham Hospital in Boston. Thereafter, he joined the Pulmonary Divisions of the Harvard hospitals. He served as Chief of Pulmonary Medicine at the Beth Israel Hospital, Chief of the combined Pulmonary Divisions of the Beth Israel and Brigham and Women's Hospitals, and finally as the Chief of Pulmonary Medicine at Brigham and Women's Hospital. Through his research, he defined the role of novel endogenous chemical agents in asthma. This led to four new licensed pharmaceuticals for asthma with more than 5 million people on treatment worldwide. In 2000, he assumed the post of Editor-in-Chief of the *New England Journal of Medicine.* During his tenure, the journal has published major papers advancing the science of medicine, including the first descriptions of SARS and papers modifying the treatment of cancer, heart disease and lung disease. The journal, which has more than a million readers every week, has the highest impact factor of any journal publishing original research.

Susan Ellenberg, Ph.D., is Professor of Biostatistics, Center for Clinical Epidemiology and Biostatistics, and Associate Dean for Clinical Research, University of Pennsylvania School of Medicine. Dr. Ellenberg's research has focused on practical problems and ethical issues in designing, conducting and analyzing data from clinical trials, including surrogate endpoints, data monitoring committees, clinical trial designs, adverse event monitoring, vaccine safety and special issues in cancer and AIDS trials. At Penn, in addition to her teaching and administrative duties, she serves as senior statistician for three multicenter clinical trials and directs the Biostatistics Core of the Penn Center for AIDS Research. In her role as Associate Dean for Clinical Research, she oversees the human subjects protections programs of the University of Pennsylvania School of Medicine. Prior to her appointment at Penn, Dr. Ellenberg held positions of increasing responsibility in the federal government. From 1993 to 2004 she served as Director, Office of Biostatistics and Epidemiology in the Center for Biologics Evaluation and Research (CBER) at the FDA; prior to that she served as the first Chief of the Biostatistics Research Branch in the Division of AIDS, National Institute of Allergy and Infectious Diseases

(1988–1993), and served in the Biometric Research Branch in the Cancer Therapy Evaluation Program, National Cancer Institute (1982–1988). During Dr. Ellenberg's tenure at FDA, she played a leading role in the development of international standards for design and analysis of clinical trials performed by the pharmaceutical industry, developed productive programs for postmarketing safety surveillance of biological products, and coordinated the development of policy for the establishment and operation of clinical trial data monitoring committees. Dr. Ellenberg is a Fellow of the American Statistical Association, the Society for Clinical Trials and the American Association for the Advancement of Science, and is an elected member of the International Statistical Institute. Her book, *Data Monitoring Committees in Clinical Trials: A Practical Perspective*, co-authored with Drs. Thomas Fleming and David DeMets, was named WileyEurope Statistics Book of the Year for 2002. Dr. Ellenberg received her undergraduate degree from Radcliffe College and her Ph.D. in Mathematical Statistics from the George Washington University.

Garret FitzGerald, M.D., is chair of Pharmacology and director of the Institute for Translational Medicine and therapeutics at the University of Pennsylvania School of Medicine. His work is focused on prostaglandins and their inhibitors and on the role of molecular clocks in cardiovascular biology and metabolism. He has previously served as chair of medicine and therapeutics at University College, Dublin, and director of Clinical Pharmacology at Vanderbilt. Besides the IOM Drug Forum, he serves on the Science Board of the FDA and the Peer Review Advisory Committee of the NIH.

Jesse Goodman, M.D., M.P.H., became Chief Scientist and Deputy Commissioner for Science and Public Health of the FDA in 2009. He has broad responsibility for and engagement in leadership and coordination of the agency's cross-cutting scientific and public health efforts. From 2003–2009, he was Director of FDA's Center for Biologics Evaluation and Research (CBER), which oversees medical and public health activities critical to U.S. and global preparedness concerning the development, evaluation, safety, quality, and availability of biologics. A graduate of Harvard, he received his M.D. from the Albert Einstein College of Medicine and did residency and fellowship training at the Hospital of the University of Pennsylvania and at UCLA (where he was also Chief Medical Resident). Prior to joining FDA, he was Professor of Medicine and Chief of Infectious Diseases at the University of Minnesota, where he directed the multihospital Infectious Diseases research, training, and clinical programs, and where his NIH-funded laboratory first isolated and characterized *Anaplasma phagocytophilum,* the infectious agent causing a new tick-borne disease, human

granulocytic ehrlichiosis. He has authored numerous scientific papers and edited the book *Tick-Borne Diseases of Humans* published by ASM Press in 2005. Dr. Goodman has been elected to the American Society for Clinical Investigation and to the Institute of Medicine of the National Academy of Sciences, where he is a longstanding member of the Forum on Emerging Threats. He is an active clinician and teacher who is board certified in internal medicine, oncology, and infectious diseases and is Staff Physician and Infectious Diseases Consultant at both the National Naval and Walter Reed Army Medical Centers, and is Adjunct Professor of Medicine at the University of Minnesota.

Harry Greenberg, M.D., received his B.A. in History from Dartmouth College in 1966. He received his M.D. from Columbia College of Physicians and Surgeons in 1970. He did his internal medicine house staff and GI fellowship training at Bellevue Hospital and Stanford University respectively. Dr. Greenberg spent 10 years at the NIH in the Laboratory of Infectious Disease as a tenured scientist before returning to Stanford in 1983. He is currently the Joseph D. Grant Professor of Medicine and Microbiology and Immunology and the Senior Associate Dean for Research at Stanford University School of Medicine. He is also a staff physician at the Palo Alto VA hospital. Dr Greenberg is a member of a variety of scholarly societies, governmental committees, and editorial boards. He is the past President of the American Society of Virology, a consultant for a variety of vaccine manufacturing companies and the director of Stanford's NIH-funded CTSA. He has been an active NIH-funded investigator for more than 30 years during which time his studies have focused primarily on viruses that infect the GI tract, liver, or respiratory tree. He has published more than 400 articles, chapters, and reviews. His work has spanned the spectrum from basic studies of viral:host cell interaction to translation work on the immune response to important pathogens in both animal models and humans to clinical trials of vaccine safety and efficacy. He has trained a large number of M.D. and Ph.D. postdoctoral students who are now in independent careers in science and academic medicine. He has also carried out a variety of other administrative roles at Stanford including being the Chief of the GI division of the Department of Medicine, the acting Chairperson of the Department of Medicine (twice) and the ACOS for research at the Palo Alto VA. During a 2-year leave of absence from Stanford, Dr. Greenberg was the Chief Scientific Officer at a biotechnology company called Aviron (now MedImmune Vaccines) where he played a key role in bringing the live attenuated influenza vaccine to licensure.

Steven Grossman, J.D., is the President of HPS Group, LLC, a public affairs consulting firm that specializes in health policy and FDA regula-

tory issues. His clients include patient and research advocacy groups, professional societies, and FDA-regulated companies. Mr. Grossman is also the author of the blog: FDA Matters, www.fdamatters.com. In 2007, he was a founder of Alliance for a Stronger FDA, the only multi-stakeholder group advocating on behalf of increased appropriations for FDA. He continues to serve as the group's Deputy Executive Director. Earlier in his career, Mr. Grossman was a Deputy Assistant Secretary for Health at DHHS and Health Staff Director and Counsel to the Senate Labor and Human Resources Committee. He was one of the chief Senate negotiators on the Orphan Drug Act and on the Patent Term Restoration and Drug Price Competition Act (Hatch-Waxman). He received his B.A. from Oberlin College and his J.D. from Georgetown University School of Law.

Margaret Hamburg, M.D., was confirmed on May 18, 2009, by a unanimous Senate voice vote to become the 21st Commissioner of Food and Drugs. The second woman to be nominated for that demanding position, Dr. Hamburg is exceptionally qualified for her new job by her training and experience as a medical doctor, scientist, and public health executive. Dr. Hamburg graduated from Harvard Medical School, and completed her residency in internal medicine at what is now New York Presbyterian Hospital–Weill Cornell Medical Center, one of the top-ten hospitals in the nation. She conducted research on neuroscience at Rockefeller University in New York, studied neuropharmacology at the National Institute of Mental Health on the NIH campus in Bethesda, Maryland, and later focused on AIDS research as Assistant Director of the National Institute of Allergy and Infectious Diseases. In 1990, Dr. Hamburg joined the New York City Department of Health and Mental Hygiene as Deputy Health Commissioner and within a year was promoted to Commissioner, a position she held until 1997. During her tenure she was widely praised for her initiatives, decisive leadership, and significant public health measures she carried out despite severe budget constraints and while holding academic positions at Columbia University School of Public Health and Cornell University Medical College. Dr. Hamburg's accomplishments as New York's top public health official included improved services for women and children, needle-exchange programs to reduce the spread of HIV (the AIDS virus), and initiation of the first public health bioterrorism defense program in the nation. Her most celebrated achievement, however, was curbing the spread of tuberculosis. In the 1990s, TB resurged as a major public health threat, largely because many patients did not complete the full course of the treatment and the disease became resistant to standard drugs. Dr. Hamburg confronted the problem by sending health care workers to patients' homes and taking other steps to make sure they completed the drug regimen. Thanks to this program, in a five-year span, the TB rate

in New York City fell by 46 percent overall, and 86 percent for the most drug-resistant strains. Dr. Hamburg's innovative approach has become a model for health departments world-wide. In 1994, Dr. Hamburg was elected to the membership in the IOM, one of the youngest persons to be so honored. Three years later, at the request of President Clinton, she accepted the position of Assistant Secretary for Policy and Evaluation in the U.S. Department of Health and Human Services (HHS). In 2001, Dr. Hamburg became Vice President for Biological Programs at the Nuclear Threat Initiative, a foundation dedicated to reducing the threat to public safety from nuclear, chemical, and biological weapons. In that position, she advocated broad reforms in public health infrastructure and policy, from local health departments to the national agency, in order to meet the dangers of modern bioterrorism as well as the threats of naturally occurring infectious diseases such as pandemic flu. Beginning in 2005, Dr. Hamburg served as the initiative's Senior Scientist. President Barack Obama nominated her for the FDA Commissioner on March 25, 2009. Upon Dr. Hamburg's confirmation by the U.S. Senate, HHS Secretary Kathleen Sebelius has praised her as "an inspiring public health leader with broad experience in infectious disease, bioterrorism, and health policy," and added that "Personally, I have been impressed by the calm and confidence Dr. Hamburg has shown in the face of a wide variety of challenges."

Peter K. Honig, M.D., M.P.H., is Head of Global Regulatory Affairs at AstraZeneca Pharmaceuticals. He was executive vice president for Worldwide Regulatory Affairs and Product Safety within Development at Merck Research Laboratories since March of 2002. In this role, he was responsible for Global Regulatory Affairs, Worldwide Product Safety and Quality Assurance, Preclinical Pharmacology/Toxicology as well as Worldwide OTC Development. He is former Director of the Office of Drug Safety in FDA's Center for Drug Evaluation and Research (CDER). He received his baccalaureate, medical, and public health degrees from Columbia University in New York. He has postgraduate training and is board certified in internal medicine and clinical pharmacology and is a Fellow of the American College of Physicians. Dr. Honig retains faculty appointments at the Uniformed Services University of the Health Sciences and Georgetown University Medical School. He recently served as President-Elect of the American Society of Clinical Pharmacology and Therapeutics and has previously served as a Vice President and Chair of its section on Pharmacoepidemiology, Drug Safety and Outcomes Research. He is the PhRMA representative to the International Conference on Harmonization (ICH) Steering Committee. Dr. Honig joined CDER as a medical officer in the Division of Oncology and Pulmonary Drug Products in 1993. He

also served as the FDA representative to the CERTs Steering Committee (Centers for Education and Research on Therapeutics), CDER liaison to the Harvard Clinical Investigators fellowship training program, CDER representative to the MedDRA Management Board, and the ICH E2B Expert Working Group.

Sangtae Kim, Ph.D., brings a unique combination of academic, industry, and government agency experience to bear on the problem of drug discovery and development. He came to the Morgridge Institute in 2008 from Purdue University, where he was the Donald W. Feddersen Distinguished Professor of Mechanical Engineering and Distinguished Professor of Chemical Engineering. During his six years in industry, Dr. Kim led research and development efforts at the pharmaceutical giants Eli Lilly and Pfizer. He also served the National Science Foundation as director of the division of shared cyberinfrastructure in 2004–2005, while on loan from Purdue University. In 2001, Dr. Kim was named a member of the National Academy of Engineering for his contributions to microhydrodynamics, protein dynamics, and drug discovery through the application of high-performance computing. After earning a master's degree from the California Institute of Technology, Dr. Kim received a doctorate in chemical and biological engineering from Princeton University in 1983. He joined the UW-Madison faculty in 1983 and served as chair of the Department of Chemical Engineering from 1995–1997. During that time, he also was granted a rare "courtesy appointment" in the Department of Computer Sciences.

Judith Kramer, M.D., has a broad background in both pharmacy and medicine, having worked in roles as practitioner, clinical researcher, scientific administrator, and policy advisor. Currently, she is Associate Professor of Medicine in the Division of General Internal Medicine at Duke University Medical Center, where she is involved full time in research-related activities. From 2000–2007, she was the principal investigator for Duke's Center for Education and Research on Therapeutics (CERTs), focused on cardiovascular disease. She continues as a co-investigator of the Duke CERTs and is currently chairperson of the FDA's Drug Safety and Risk Management (DSaRM) Advisory Committee. In 2008, Dr. Kramer was named Executive Director of the Clinical Trials Transformation Initiative, (CTTI), a public private partnership under FDA's Critical Path Program aimed at improving the quality and efficiency of randomized clinical trials. Dr. Kramer received her B.S. and M.S. in pharmacy and M.D. from the University of North Carolina at Chapel Hill and is board-certified in internal medicine. She did her residency in primary care internal medicine at Massachusetts General Hospital in Boston, and a senior residency in

internal medicine at UNC Chapel Hill. After 5 years in practice of internal medicine in rural North Carolina, Dr. Kramer worked for 10 years at Burroughs Wellcome Co. where she became VP of Medical, directing U.S. Clinical Research. She continued in the merged GlaxoWellcome as International Director of Cardiovascular/Critical Care Clinical Research before leaving to work at Duke in 1996. At Duke she served as Chief Medical Officer of the Duke Clinical Research Institute from 1997–2006, and regulatory consultant to the Duke Translational Medicine Institute from 2006–2008. From 1999–2001, Dr. Kramer also served as the Founding Director of the Master's Program in Clinical Research at Campbell University, in Research Triangle Park, North Carolina. Dr. Kramer's research interests have focused on finding safe and effective cardiovascular therapies, assuring persistent use of life-saving medications, and using new methods to study postmarketing safety of drugs and devices.

Michael Manganiello has more than 15 years of experience in patient advocacy and public health with a strong background in formulating policy, building coalitions, managing nonprofits, and organizing grassroots campaigns. Diagnosed as HIV positive in 1988, he was an early participant in NIH clinical trials that eventually led to treatments that have benefited many people today. In 1996, he helped establish the Christopher Reeve Foundation, a patient advocacy organization dedicated to curing spinal cord injury by funding innovative research and improving the quality of life for people living with paralysis through grants, information, and advocacy. At the Reeve Foundation, Mr. Manganiello authored and secured introduction of the Christopher Reeve Paralysis Act and raised $22.5 million for the Christopher and Dana Reeve Paralysis Resource Center. He was chair of the Paralysis Task Force, in collaboration with the Centers for Disease Control and Prevention and the Hope Network, which connects more than 50,000 advocates across the country. Mr. Manganiello is a founding member and president emeritus of the Coalition for the Advancement of Medical Research (CAMR), which unites more than 100 diverse organizations, universities, scientific societies, and foundations in a bipartisan call for breakthrough medical research. Mr. Manganiello and CAMR were instrumental in the U.S. Congress' passage of the Stem Cell Research Enhancement Acts in 2006 and 2007. He continues to serve on CAMR's board. Today, CAMR and its 25,000 grassroots members conduct education, outreach, and advocacy about stem cell research, somatic cell nuclear transfer, and other technologies. This alliance strengthens the voices of families who cope with life-threatening illnesses, such as cancer, diabetes, Parkinson's, and Alzheimer's, as well as spinal cord injuries and other conditions. Mr. Manganiello also served for three years on the NIH Director's Council of Public Representatives, a group that

advises the NIH director about policy issues in biomedical research from the public perspective. He currently serves on several boards and advisory panels, including the Whitman-Walker Clinic, the National Association for Biomedical Research, the Prevent Cancer Foundation, and the National Symposium on Health Care Reform through the Mayo Clinic. In 2008, Mr. Manganiello and his two partners, Terrell Halaska and Kristin Conklin, established HCM Strategists, a consulting firm specializing in health care and education based on the belief that sound public policy drives progress and the results ensure that good ideas spread boldly to effect change in our communities. Their goals of achieving policy change in a reasonable time frame takes a combination of high-level government experience, a network of strong relationships, and the ability to find a fresh, creative approach to addressing the issues. When you can enlighten all participants by capturing their attention, finding common ground, and building strong alliances, success is within reach. Mr. Manganiello has a master's degree in public administration from Columbia University and a bachelor's degree in political science from Villanova University.

Mark McClellan, M.D., Ph.D., is Director of the Engelberg Center for Healthcare Reform at Brookings Institution. Dr. McClellan is former Administrator for the Centers for Medicare and Medicaid Services (CMS) and former Commissioner of the FDA. 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 J*ournal 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 M.D. from the Harvard-MIT Division of Health Sciences and Technology in 1992, and his Ph.D. 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.

Dale Nordenberg, M.D., is a principal with Novasano Health and Science. He is a physician executive who leverages his experience as a pediatrician, medical epidemiologist, and informatician to deliver strategic, operational, and scientific services to clients in the healthcare and health information technology arena. Clients include both private and public sector institutions that are engaged in challenging activities such as new operational or business model development, novel information infrastructure development, collaborative/open innovation activities that are dependent on complex information supply chains, and the development of funding strategies. Client activities are both domestic and international. Recent projects include the development of a public–private partnership to build laboratory capacity for multidrug resistant TB across diverse international settings which he is currently leading, development of governance structures for the National Biosurveillance System for Human Health, development of a multi-institutional collaboration to revise FDA regulatory processes to more effectively establish laboratory data standards for national laboratory data exchange, and the evaluation of emerging diagnostics related to the gut microbiome from both the scientific and clinical perspectives. For the past few years, Dr. Nordenberg has been working as a healthcare consultant first with PricewaterhouseCoopers and then with Novasano. From 2002 through 2007, Dr. Nordenberg held various positions at CDC including Associate Director and Chief Information Officer (CIO), National Center for Infectious Diseases (NCID) and Senior Advisor for Strategic Planning, Office of the CIO, CDC. During this time, Dr. Nordenberg led the development of the CDC's agency-wide IT strategic plan (2008–2012) and he was responsible for informatics for the agency's infectious disease center where he initiated the implementation of a single laboratory platform for NCID's labs and launched the Public Health Laboratory Interoperability Project (PHLIP) in collaboration with the Association of Public Health Labs to create a standards-based national laboratory data sharing network. Dr. Nordenberg led and participated in many disease surveillance, outbreak response, and bioterrorism preparedness and response activities and associated informatics initiatives. He has worked extensively in the arena of pandemic influenza preparedness and response. He was detailed part time to the Office of the National Coordinator for Health Information Technology in 2004–2005 to cata-

lyze a national strategy for children's health information technology. Dr. Nordenberg has been a member of the Science and Technology Subcommittee of the Science Advisory Board of the FDA in 2007 and 2009, which was tasked with the evaluation of science and technology at the FDA. Prior to CDC, Dr. Nordenberg was a founding executive of a company that launched VeriSign affiliates in Latin America and Asia and prior to that he was faculty in the Emory School of Medicine where founded and directed the Office of Medical Informatics for the Emory University Children's Center. Dr. Nordenberg has served on the boards of numerous companies. Most recently he was a member of the board for Coventry Health Care of Georgia. Dr. Nordenberg is a board certified pediatrician. He received a B.S. in Microbiology from the University of Michigan, his M.D. from Northwestern University, and completed his training in pediatrics at McGill University, Montreal Children's Hospital. He completed his fellowship in epidemiology and public health in the Epidemic Intelligence Service Program at the CDC.

Philip A. Pizzo, M.D., became dean of the Stanford School of Medicine in April 2001. Before joining Stanford, he was the physician-in-chief of Children's Hospital in Boston and chair of the Department of Pediatrics at Harvard Medical School from 1996–2001. Dr. Pizzo is recognized for his contributions as a clinical investigator, especially in the treatment of children with cancer and HIV. Dr. Pizzo received his undergraduate degree from Fordham University and an M.D. from the University of Rochester School of Medicine. He completed an internship and residency at Children's Hospital Medical Center in Boston, a teaching fellowship at Harvard Medical School, and a clinical and research fellowship in pediatric oncology at the National Cancer Institute. Dr. Pizzo served as head of the institute's infectious disease section, chief of the NCI's pediatric department, and acting scientific director for NCI's Division of Clinical Sciences between 1973 and 1996. Dr. Pizzo devoted much of his distinguished medical career to the diagnosis, management, prevention, and treatment of childhood cancers and the infectious complications that occur in children whose immune systems are compromised by cancer and AIDS. Dr. Pizzo and his research team pioneered the development of new treatments for children with HIV infection, lengthening and improving the quality of life for children with this disease. His research soon led to important clues about how to treat HIV-positive children and adults, and how to manage life-threatening infections. He is the author of more than 500 scientific articles and 15 books. Dr. Pizzo has received several awards from the U.S. Public Health Service, including the Outstanding Service Medal in 1995. He was awarded the Ronald McDonald Charities "Award of Excellence" in 2009, has been cited in Best Doctors of America since 1995, and in 1990

was declared "Washingtonian of the Year" by *Washingtonian* magazine for helping to found the Children's Inn, a temporary home for children undergoing treatment at the NIH and their families. In 2004, he was the first person named to the Independent Citizens' Oversight Committee, which oversees the California Institute for Regenerative Medicine. He is a member of a number of prestigious organizations. He currently serves on the Council of the IOM of the National Academy of Sciences, is Chair of the Association of Academic Health Centers and Chair of the Council of Deans of the Association of American Medical Colleges. In 2009, he was elected to the Board of Trustees of the University of Rochester and Koc University in Istanbul, Turkey.

Allen D. Roses, M.D., was one of the first clinical neurologists to apply molecular genetic strategies to neurological diseases. His laboratory at Duke reported the chromosomal location for more than 15 diseases, including several muscular dystrophies and Lou Gehrig's disease. He led the team that identified apolipoprotein E4 [APOE4] as the major susceptibility gene for common late-onset Alzheimer's Disease (AD) in 1992. Dr. Roses was the Jefferson Pilot Professor of Neurobiology and Neurology and the Division Chief Neurology. Dr. Roses became Senior VP for Genetic Research at GlaxoSmithKline and a leader in applied pharmacogenetics. His teams completed the first efficacy pharmacogenetic clinical trial, identifying the responsive and non-responsive patients in a clinical trial of rosiglitazone for the treatment of AD. Dr. Roses' GSK teams also identified the first highly accurate predictive test for a drug allergy using genomic technology. A pioneer in the application of whole genome analyses for several common diseases, Dr. Roses returned to Duke to initiate the Deane Drug Discovery Institute. In 2009, he reported the identification of a polyT variable repeat in the TOMM40 gene in AD, based on the first phylogenetic demonstration of multiple independent mutations at the same locus for AD co-dominant inheritance. Dr. Roses established Zinfandel Pharmaceuticals, Inc. to design and sponsor a combination Alzheimer's Disease diagnostic validation and clinical trial to test delay of age of onset in a pharmacogenetic-assisted clinical trial of normal individuals stratified by variable TOMM40 polyT polymorphism and age at entry.

Ellen V. Sigal, Ph.D., is Chairperson and Founder of Friends of Cancer Research ("Friends"), a non-profit organization based in the Washington, DC metropolitan area. For more than 12 years, Friends has convened leading cancer advocates and researchers to create strategic consensus; educated policy makers and the general public about new research opportunities and existing obstacles; pioneered valuable public–private partner-

ships to maximize resources; and created an effective dialogue between researchers and regulators to minimize institutional barriers and ensure safety. Dr. Sigal is Vice Chair of the inaugural board of directors of the Reagan-Udall Foundation, a partnership designed to modernize medical product development, accelerate innovation, and enhance product safety in collaboration with the U.S. FDA. She serves on the NIH Foundation Board chairing its Public–Private Partnerships Committee, the American Association for Cancer Research Foundation Board, and on the board of several national cancer centers. Dr. Sigal was recently appointed to the Stand Up To Cancer (SU2C) Advocate Advisory Council, and she is one of two Council members nominated to the SU2C Scientific Advisory Committee. She served on the National Cancer Institute Board of Scientific Advisors from 2003–2009, and the NIH Director's Council of Public Representatives from 2003–2006. She was a Presidential Appointee to the National Cancer Advisory Board from 1992–1998 chairing its Budget and Planning Committee, which oversees the federal cancer budget.

Paul B. Watkins, M.D., is the Verne S. Caviness Distinguished Professor of Medicine, and also Professor of Pharmacology and Experimental Therapeutics, and Professor of Toxicology at the University of North Carolina in Chapel Hill (UNC-CH). He attended medical school at Cornell and completed his residency in internal medicine at New York Hospital–Cornell Medical Center. He received subspecialty training in hepatology at the Medical College of Virginia. He was on faculty at the University of Michigan from 1986–1999 when he moved to North Carolina. There he became the Director of the General Clinical Research Center and more recently director of the UNC Translational and Clinical Sciences (TraCS) Institute. In June of 2009, he became the director of a new Institute for Drug Safety Sciences, which represents a collaboration between UNC-CH and the Hamner Institutes. The Hamner Institutes is a not-for-profit organization based in Research Triangle Park. It was formerly called the Chemical Institute for Industrial Toxicology [CIIT] and has a three-decade history of leading research into the health effects of environmental chemicals. Dr. Watkins is an accomplished basic and translational investigator in the fields of drug metabolism and hepatotoxicity. He is the recipient of numerous honors and awards including the Therapeutic Frontiers Award from the American College of Pharmacy and election to the Association of American Physicians. He is one of the most frequently cited authors in the field of pharmacology according to www.ISIhighlycited.com. He serves as the chair of both the Steering and Genetics Committees for the national Drug Induced Liver Injury Network (DILIN) (U01DK065201).

Mary Woolley is the president of Research!America, the nation's largest not-for-profit alliance working to make research to improve health a higher national priority. Under her leadership, Research!America's publications and initiatives have been honored by leading communications and advocacy organizations. Dr. Woolley is an elected member of the IOM and serves on its Governing Council. She is a Fellow of the American Association for the Advancement of Science and serves on the National Academies Board on Life Sciences. She is a Founding Member of the Board of Associates of the Whitehead Institute for Biomedical Research. She has served as president of the Association of Independent Research Institutes, as editor of the *Journal of the Society of Research Administrators*, as a reviewer for the National Institutes of Health and National Science Foundation, and as a consultant to several research organizations. Dr. Woolley has a 30-year editorial and publication history on science advocacy and research-related topics. She is a sought-after speaker and is frequently interviewed by science, news, and policy journalists.