Strengthening a Workforce for Innovative Regulatory Science in Therapeutics Development: Workshop Summary

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STRENGTHENING A WORKFORCE FOR INNOVATIVE REGULATORY SCIENCE IN THERAPEUTICS DEVELOPMENT

Workshop Summary

Steve Olson and Anne B. Claiborne, *Rapporteurs*

Forum on Drug Discovery, Development, and Translation

Board on Health Sciences Policy

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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:

William W. Chin, Harvard Medical School
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Michael Manganiello, HCM Strategists, LLC
Brian L. Strom, University of Pennsylvania School of Medicine

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by **Hugh Tilson,** University of North Carolina at Chapel Hill. Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authors and the institution.

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Acronyms

CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDSS	Centre for Drug Safety Science
CERSI	Center for Excellence in Regulatory Science and Innovation
CF	cystic fibrosis
CFP	Commissioner's Fellowship Program
CRO	contract research organization
CTP	Center for Tobacco Products
CTSA	Clinical and Translational Science Awards
ECPM	European Center of Pharmaceutical Medicine
EMA	European Medicines Agency
EU	European Union
FDA	U.S. Food and Drug Administration
HRA	Health Research Alliance
IMI	Innovative Medicines Initiative
IND	Investigational New Drug
IOM	Institute of Medicine
IOTF	Interagency Oncology Task Force
IRB	Institutional Review Board

MCM	medical countermeasure
MIT	Massachusetts Institute of Technology
NCATS	National Center for Advancing Translational Sciences
NCI	National Cancer Institute
NDA	new drug application
NEWDIGS	New Drug Development Paradigms
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
PDP	product development partnership
PharmaTrain	Pharmaceutical Medicine Training Programme
RAPS	Regulatory Affairs Professional Society
RFA	Request for Application
TB	tuberculosis
UCSF	University of California, San Francisco
UNC	University of North Carolina at Chapel Hill
USC	University of Southern California

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Introduction[1]

The Food and Drug Administration (FDA) has defined *regulatory science* as the "science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products" (FDA, 2010). The development and application of regulatory science calls for a well-trained, scientifically engaged, and motivated workforce. FDA faces challenges in retaining these scientists and providing them with opportunities for professional development. Stretched thin by resource constraints and a workload of constantly increasing complexity, FDA scientists are hard pressed to interact with other scientists and enhance their scientific knowledge base. Moreover, in the private sector, including industry and academia, the advancement of the science of innovation in drug discovery and development has not always been clearly defined, well coordinated, or connected to the needs of the regulatory agency. A number of gaps in the regulatory science discipline and infrastructure have been identified, including workforce and resource constraints not only within FDA but also in the extramural community; cultural differences and systemic barriers to collaboration and exchange among the agency, academia, and industry; and deficiencies in the net-

[1] The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop.

work and infrastructure necessary to forge the collaboration and communication needed to advance regulatory science.[2]

In February 2010, the Forum on Drug Discovery, Development, and Translation within the Board on Health Sciences Policy of the Institute of Medicine (IOM) held a workshop, "Building a National Framework for the Establishment of Regulatory Science," that examined the state of the science of drug regulation and considered approaches for enhancing the scientific basis of regulatory decision making (IOM, 2011).

As a follow-on to that workshop, and building on pronouncements from and developments to advance regulatory science at FDA in the interim months, the Forum convened a workshop on September 20-21, 2011, entitled "Strengthening a Workforce for Innovative Regulatory Science in Therapeutics Development." This workshop provided a format for establishing a specific agenda to implement the vision and principles relating to a regulatory science workforce and infrastructure as articulated in the 2010 workshop on regulatory science. The broad objectives of the workshop were (1) to consider opportunities and needs for advancing innovation in the discipline of regulatory science for therapeutics development through an interdisciplinary regulatory science workforce and (2) to examine specific strategies for developing a discipline of innovative regulatory science through development of a robust workforce within academia and industry and at FDA.

Specific objectives included the following:

- Define and discuss the current regulatory science workforce, with particular attention to the disciplines involved, professional training opportunities, and gaps in the essential components of this workforce.
- Consider workforce development needs in areas identified as key components of a robust discipline of innovative regulatory science in therapeutics development.
- Examine the application and advantages of collaborative (multisector and multidisciplinary) approaches for strengthening the national regulatory science workforce.
- Explore the resources and stakeholder engagement needed, not only within FDA and other federal agencies but throughout the extramural sector, to build the discipline and establish career paths in regulatory science for therapeutics development.

[2] The Fiscal Year (FY) 2011 President's Budget for FDA programs requested $25 million to support Advancing Regulatory Science for Public Health, and ultimately $17.4 million was appropriated by Congress for FY 2011 to support regulatory science at FDA.

In her introductory remarks, the co-chair of the planning committee, Elaine Gallin, Principal, QE Philanthropic Advisors, remarked that, as the Forum offers a neutral venue where stakeholders in drug development can meet to discuss issues of mutual interest and concern, the Forum and this workshop format can enhance the needed collaboration among government, academia, industry, foundations, and patient groups that is critical in enhancing regulatory science.

The other co-chair of the planning committee, Barry Coller, Vice President for Medical Affairs, Physician-in-Chief, and David Rockefeller Professor, The Rockefeller University, observed that while everyone has a sense that regulatory science is important, everyone also has a slightly different sense of *why* it is important. Coller emphasized that the focus of the workshop was on innovative regulatory science in therapeutics development, which calls for an interdisciplinary workforce to develop those innovative skills and methodologies. By bringing together stakeholders from all the sectors interested in regulatory science, the workshop provided an opportunity to compare diverse perspectives and find areas of agreement.

SCOPE OF THE WORKSHOP AND ORGANIZATION OF THE SUMMARY

Over the course of the workshop many participants offered their individual definitions of the concept of regulatory science in therapeutics development and elaborated on how regulatory science relates to drug development more generally. Although the scope of the workshop was focused on regulatory science in therapeutics development, a number of workshop discussants offered viewpoints or illustrations that were relevant to regulatory science more generally (e.g., application of regulatory science to regulation of tobacco products; post-approval safety monitoring of therapeutics). These perspectives were sought to the extent they could illuminate and elaborate on fundamental principles and components undergirding the development and practice of innovative regulatory science and its application to therapeutics development. This report summarizes the presentations and discussions of the workshop, highlighting key themes and identified needs in the development of an innovative regulatory science workforce for therapeutic development.

- Chapter 2 provides perspectives from FDA, the National Institutes of Health (NIH), industry, academia, and the patient on the importance of innovative regulatory science with a primary focus on its role to support and advance drug development and how to strengthen that science.

- Chapter 3 examines definitions of innovative regulatory science for therapeutics development and lists certain "core competencies" considered part of the multidisciplinary pursuit of regulatory science. This chapter addresses difficulties and discordance in defining regulatory science as identified by many workshop participants.
- Chapter 4 looks at how education and training could be structured to achieve the development of a regulatory science workforce that encompasses the needed competencies.
- Chapter 5 samples potential regulatory science career paths inside and outside academia.
- Chapter 6 considers international dimensions and needs for a regulatory science workforce to achieve innovation on a global scale.
- Chapter 7 reviews new collaborative models to strengthen and support regulatory science research and practice and provides participant summaries of the workshop discussions and suggestions for moving the field forward.

2

The Importance of Innovative Regulatory Science

Key Messages

- Collaboration among federal agencies offers a particularly productive venue for developing a regulatory science workforce.
- Creating a supportive academic environment and training a new generation of researchers who are skilled in such areas as clinical pharmacology can contribute greatly to the development of regulatory science as an accepted discipline.
- Regulatory science is more than just developing new methods for understanding and assessing risk; it also includes consideration of cultural and societal issues relating to how individual patients and society view the tradeoff between reward and risk.

Different stakeholders in the therapeutics development enterprise may have somewhat different perspectives on regulatory science. In the opening session of the workshop, representatives of the four key "locuses" of the development and practice of innovative regulatory science for therapeutics development (FDA, NIH, the pharmaceutical industry, and academia) described these perspectives. All four emphasized the importance of developing regulatory science as an academic discipline to address the multiple challenges they face. At the same time, different perspectives create opportunities for productive collaboration, though

as some participants cautioned, also potentially create opportunities for misunderstandings.

Vicki Seyfert-Margolis, Senior Advisor for Science Innovation and Policy, Office of the Commissioner, FDA, presented FDA's rationale for regulatory science and the strategic plan the agency has developed to pursue this science. Story Landis, Director, National Institute of Neurological Disorders and Stroke (NINDS), NIH, described some of the collaboration ongoing between FDA and NIH. Andrew Dahlem, Vice President and Chief Operating Officer, Lilly Research Laboratories, Eli Lilly & Co., summarized some of the challenges and needs facing industry in a radically changed drug development environment. Ralph Snyderman, Chancellor Emeritus, Duke University, discussed therapeutics development in the broader context of personalized medicine. Ellen Sigal, Chair and Founder, Friends of Cancer Research, provided a patient perspective on the importance of regulatory science and moderated a panel discussion among the keynote speakers.

PERSPECTIVE FROM THE FOOD AND DRUG ADMINISTRATION[1]

Addressing the Product Development Ecosystem

Seyfert-Margolis noted that FDA can bring data, insight, and knowledge to the therapeutics development ecosystem. In the months preceding the workshop, FDA had been examining the medical products ecosystem to determine how the agency can facilitate innovation. The agency's innovation initiative will include regulatory science as a key component.[2] According to Seyfert-Margolis, a major finding from this review was that all of the various players in this arena are experiencing new stresses and challenges. The scientific and global market environments are moving away from the traditional blockbuster drug development model. In aca-

[1] This section is based on the presentation by Vicki Seyfert-Margolis, Senior Advisor for Science Innovation and Policy, Office of the Commissioner, FDA.

[2] FDA released a report on innovation, *Driving Biomedical Innovation: Initiatives to Improve Products for Patients*, on October 5, 2011. The report defines the "medical product ecosystem" in the following context:

> Translating a new idea from a discovery into a medical product is a complex process involving an entire ecosystem consisting of academia, industry, small businesses, payors, physicians, government agencies, and patient and consumer groups. Each member of the ecosystem has an important role to play in bringing a new medical product to market, and each piece of the ecosystem is currently under stress, putting America at risk of losing its competitive edge as the leader in scientific innovation.

For more information, see http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm274333.htm (accessed November 28, 2011).

demia, the demands of tenure and recognition do not always align well with the team-oriented imperatives of clinical research and development. At the same time, academics confront difficulties in moving their ideas into the clinic given the challenges of securing funding.

A number of interesting models are emerging to deal with these challenges, said Seyfert-Margolis. Some of these models are being supported directly by academic institutions, while others involve venture philanthropy. Small business plays an important role in the product development ecosystem, but small businesses today are often undercapitalized and are struggling with the complexities of the therapeutic product development cycle. FDA has been engaged in discussions with companies along the size spectrum—from small biotechnology to large pharmaceuticals—to provide advice on how to move ideas forward successfully. Seyfert-Margolis noted that the calculus of risks and benefits is an important discussion to have as a scientific community and as a society and needs to be taken into account in consideration of potential new regulatory pathways such as conditional or progressive approval strategies.

Physicians and patients have their own concerns regarding new technologies and therapeutics. Society's tolerance for risk is low, Seyfert-Margolis observed, so it is important to communicate information and concepts about risks and rewards more effectively to patients and physicians. Payers are focusing on the concepts of evidence- and value-based medicine to align their reimbursement structures with the actual real-world performance of drugs, which is usually less than that seen in clinical trials. Once in the real world, the risk equation shifts as comorbidities and other influences on drug performance become apparent.

The Rationale for Regulatory Science

According to Seyfert-Margolis, there are four major reasons why regulatory science is needed.

First, major investments and advances in basic sciences are not fully translating into products to benefit patients. In part, this is because of the so-called "valley of death" (Figure 2-1). The valley of death refers to the gap in funding between, on the one hand, NIH, state, and foundation grants that support discovery, preclinical development, and the earliest stages of clinical development and, on the other hand, pharmaceutical company involvement that supports the later stages of clinical development and commercialization. This funding gap has a critical, negative impact on the translation of discoveries into medical products and new medicines. Seyfert-Margolis emphasized that regulatory science can play an important role in helping to bridge this gap.

Second, product development is increasingly costly and uncertain

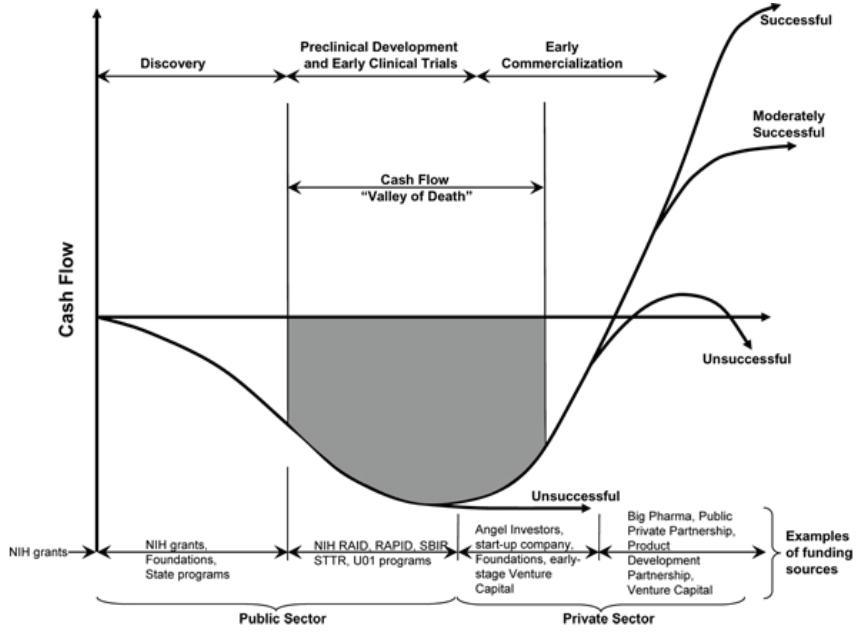

FIGURE 2-1 Many discoveries fail to traverse the "valley of death" from discovery to commercial product.
NOTE: RAID, Rapid Access to Interventional Development; RAPID, Rapid Access to Preventive Intervention Development; SBIR, Small Business Innovative Research; STTR, Small Business Technology Transfer; U01, Cooperative Agreement Research Project Awards.
SOURCE: Seyfert-Margolis, 2011. Presentation at IOM workshop on Strengthening a Workforce for Innovative Regulatory Science in Therapeutics Development.

while success rates remain low. For example, according to Seyfert-Margolis, the need for cost containment has driven clinical trials to other countries; now, approximately 50 percent of the clinical trials data included in regulatory submissions to FDA is generated in India or China. These populations differ from the average U.S. population in terms of nutrition, genetics, environment, lifestyle considerations, and other factors. As a result, data from those populations may not fully translate into the average U.S. population, said Seyfert-Margolis, while noting that this issue needs further study. FDA believes that uncertainties associated with differences among populations lie more in the scientific than in the policy realm, pointing to the need for regulatory science.

Third, development and evaluation tools and approaches have not kept pace with and have not incorporated emerging technologies. Examples include the new fields of nanotechnology, where tools to evaluate

the safety and toxicity of nanoscale products and genetically engineered foods are lacking. Shortcomings in scientific capacity in this area also affect the ability of FDA to educate and communicate with the public about the risks and benefits of new technologies.

Fourth, without regulatory science the economic health of the biotechnology and medical products industry is at risk. This is of particular concern given the importance to the U.S. economy of maintaining and building on the nation's leadership role in this important technological sector.

FDA now has several programs in place, including a formal partnership with NIH, to advance regulatory science. For the first time in its history, FDA has a budgetary line item for regulatory science and has issued direct funding solicitations for projects in reproductive toxicology and biomarker research and qualification.

The FDA Strategic Plan for Regulatory Science

FDA has issued a strategic plan for regulatory science that was crafted with input from all of its centers yet takes an agency-wide, rather than center-specific, perspective (FDA, 2011). The strategic plan's vision statement says that "FDA will advance regulatory science to speed innovation, improve regulatory decision-making, and get safe and effective products to people in need. Twenty-first-century regulatory science will be a driving force as FDA works with diverse partners to protect and promote the health of our nation and the global community."

The strategic plan lays out eight priority areas:

1. Modernize toxicology to enhance product safety.
2. Stimulate innovation in clinical evaluation and personalized medicine.
3. Support new approaches to improve product manufacturing and quality.
4. Ensure FDA readiness to evaluate emerging technologies.
5. Harness diverse data through information sciences to improve health outcomes.
6. Enable a prevention-focused food safety system.
7. Facilitate development of medical countermeasures (MCMs) to protect U.S. and global health and security.
8. Strengthen social and behavioral science to help consumers and professionals make informed decisions.

Seyfert-Margolis briefly described FDA's intentions in each of these eight areas (see Box 2-1).

BOX 2-1[a]
FDA Strategic Plan for Regulatory Science

Modernize toxicology to enhance product safety. FDA plans to develop better models of human adverse response, identify and evaluate biomarkers and end points that can be used in nonclinical and clinical evaluations, and use and develop computational methods and *in silico* modeling.

Stimulate innovation in clinical evaluation and personalized medicine. FDA seeks to develop and refine clinical trial designs, end points, and analysis methods; leverage existing and future clinical trial data; identify and qualify biomarkers and study end points; increase the accuracy and consistency, and reduce interplatform variability, of analytical methods to measure biomarkers; and develop a "virtual physiologic patient."

Support new approaches to improve product manufacturing and quality. FDA plans to enable development and evaluation of novel and improved manufacturing methods, develop new analytical methods, and reduce the risk of microbial contamination of products.

Ensure FDA readiness to evaluate emerging technologies. FDA will stimulate development of innovative medical products while concurrently developing novel assessment tools and methodologies, develop assessment tools for novel therapies, assure safe and effective medical innovation, and coordinate regulatory science for emerging technology product areas.

Harness diverse data through information sciences to improve health outcomes. FDA plans to enhance information technology infrastructure development and data mining; develop and apply simulation models for product life cycles, risk assessment, and other regulatory science uses; analyze large-scale clinical and preclinical data sets; incorporate knowledge from FDA regulatory files into a database integrating a broad array of data types; and develop new data sources and innovative analytical methods and approaches.

Enable a prevention-focused food safety system. The agency will establish and implement centralized planning and performance measurement processes, improve information sharing internally and externally, maintain mission-critical science capabilities, and cultivate expert institutional knowledge.

Facilitate development of MCMs to protect U.S. and global health and security. FDA will develop, characterize, and qualify animal models for MCM development; modernize tools to evaluate MCM product safety, efficacy, and quality; develop and qualify biomarkers of diseases or conditions; and enhance emergency communication.

Strengthen social and behavioral science to help consumers and professionals make informed decisions. FDA seeks to know its audience, reach that audience, ensure audience understanding, and evaluate the effectiveness of communication about regulated products.

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[a] Based on the presentation by Vicki Seyfert-Margolis, Senior Advisor for Science Innovation and Policy, Office of the Commissioner, FDA, which drew directly from FDA's recent strategic plan for regulatory science (FDA, 2011).

Seyfert-Margolis also noted that applications were under review for a new National Capitol Region Center for Excellence in Regulatory Science and Innovation (CERSI). The goal of the new center is "to advance the field of regulatory science (including laboratory, population, behavioral, and manufacturing sciences) and the Critical Path Initiative toward more effective and efficient product development and evaluation. CERSI efforts will focus on promoting innovation in support of the development and evaluation of safe and effective products through training, applied collaborative science, professional development and scientific exchanges."[3]

PERSPECTIVE FROM THE NATIONAL INSTITUTES OF HEALTH[4]

Landis illustrated the promise of regulatory science through the case example of advancements over the past 15 years in the development of human embryonic stem cells and new techniques allowing dedifferentiation and differentiation, with extraordinary potential for application to regenerative medicine. She commented that there is a need for regulatory science in thinking about how to understand, regulate, and enable clinical trials using human embryonic stem cells. She noted that FDA has embraced this innovative technology and enabled it to move forward, with three clinical trials currently being conducted in the United States.

Landis also described an innovative new initiative in which NIH is partnering with FDA and the Defense Advanced Research Projects Agency (DARPA) to develop embryonic stem cells as microphysiological systems—organs on a chip—that could be used instead of laboratory animals to screen for safe and effective drugs. This partnership has received 5 years of funding worth $140 million, a substantial investment that addresses goals of modernizing toxicology and adopting new innovative technologies.

[3] According to the CERSI Request for Application (RFA), the CERSIs should be academic, M.D. and Ph.D. degree–granting institutions with both strong life science and clinical medical science activities. FDA also specified that they should be located within a 50-mile radius of FDA's Silver Spring, Maryland, campus to facilitate and enable training, research, scientific exchanges, and other collaboration among CERSI institution staff, students, and trainees and FDA staff scientists. See http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-11-033.html (accessed November 28, 2011). The CERSI awards, totaling $2 million, were announced on October 26, 2011. The centers, which will be located at the University of Maryland and Georgetown University, will focus on strengthening science and training needed to modernize and improve the ways drugs and medical devices are reviewed and evaluated. See http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm277267.htm (accessed November 28, 2011).

[4] This section is based on the presentation by Story Landis, Director, NINDS, NIH. Landis also serves as one of the co-chairs of NIH's regulatory science initiative and is a member of the NIH-FDA Joint Leadership Council.

NIH-FDA Collaborative Efforts and Regulatory Science Funded Projects

Landis noted that the NIH and FDA have a history of innovations in therapeutics development, for example, the creation of the exploratory Investigational New Drug (IND) application. The exploratory IND came about through a partnership between the National Cancer Institute (NCI) and FDA and aimed to address the fact that the behavior of anticancer agents seen in animal models does not translate well into humans by developing innovative strategies to screen possible therapeutic candidates for cancer in humans. The exploratory IND is designed to inform decision making on target selection and dose. It assesses pharmacokinetics, biodistribution, and drug engagement with the appropriate target using very small doses of drug and with no therapeutic intent.

The formation of the NIH-FDA Joint Leadership Council in 2010 greatly enhanced the partnership between NIH and FDA, Landis noted. The council has six working groups that review proposals for collaboration in areas that include regulatory science, training, and education. In addition, the leadership council created cooperative research grants to advance translational regulatory science, and four projects totaling approximately $9 million over 3 years have been funded under this initiative:

- Creating an organ on a chip that functions as a heart-lung micromachine model to test the safety and efficacy of drugs
- Designing innovative, adaptive clinical trials for evaluating drugs and devices used in the emergency care of patients with acute neurological illness or injury
- Developing an understanding of how nanoparticles interact with the complement system and developing a model that can predict which nanoparticles might activate the complement cascade
- Developing a novel strategy to predict ocular irritancy

NCATS and NIH Training Initiatives

The NIH-proposed National Center for Advancing Translational Sciences (NCATS), if appropriated and stood up, would assume responsibility for the agency's regulatory science initiatives, in a shift from the distributed function currently residing in NINDS and the National Institute of Diabetes and Digestive and Kidney Diseases.[5] The vision and mission of NCATS have evolved over the year that the proposed new center

[5] NCATS was formally established by Congress in the FY 2012 Omnibus Appropriations Bill, signed into law on December 23, 2011 (after the date of the workshop). The new center has a budget of $575 million.

has been in the planning stages; although there may have initially been a notion that NCATS was envisioned as the "center for cures," as the mission has been clarified, the center will be focused on "the science of how you do translation better." The center will be charged with advancing the discipline of translational science to catalyze the development and testing of novel diagnostics and therapeutics across a broad range of diseases and conditions. In this pursuit the proposed NCATS will approach the drug development pipeline as a "scientific problem ripe for intervention, experimentation, and process engineering, looking for bottlenecks and creating solutions." NCATS will also have a training function in translational science, including clinical pharmacology.

Landis noted that NIH currently carries out a training function through the institutes and centers. The broad training environment created by NIH-funded programs operated by the institutes and centers represents a real opportunity for producing scientists and physician-scientists who can think about regulatory science, she said. She cited three examples of training programs of relevance to regulatory science:

- Pre- and postdoctoral fellows programs that often feed trainees into positions at FDA
- Programs in the National Institute for General Medical Sciences for physician-scientists, together with institute-specific initiatives targeted at physician-scientists
- The Clinical and Translational Science Awards (CTSAs) (currently residing within the National Center for Research Resources; slated to move to the new NCATS)

PERSPECTIVE FROM THE PHARMACEUTICAL INDUSTRY[6]

Views about the division of labor among NIH, academia, and industry in drug discovery and development have changed dramatically over the past 20 years, observed Dahlem. Historically, NIH has had responsibility for basic research, academia discovered potential new targets, and industry looked for the commercial potential of those targets, with FDA providing regulatory oversight of new drug applications (NDAs). In a shift, today, Dahlem said, NIH has become increasingly interested in drug discovery and development, while researchers in academia have joined their industry colleagues in searching for new drugs rather than limiting their pursuits to basic discovery.

[6] This section is based on the presentation by Andrew Dahlem, Vice President and Chief Operating Officer, Lilly Research Laboratories, Eli Lilly & Co.

Challenges Faced by Industry

Dahlem noted that drug development expenditures have increased while approvals have decreased. The number of drugs that will go off patent is increasing, which will cause companies to become even more cost-conscious in the coming years. This will affect not only industry hiring (and contribute to the shedding of jobs) but also the amount of money industry will provide to academia to support research. This evolving framework provides a backdrop for thinking about the workforce needs and capacity.

Industry is acting to reduce the failure rate of drugs in the development pipeline, said Dahlem. For example, in 1988, nearly 40 percent of Lilly's drugs failed because of pharmacokinetic problems; today that number has been reduced to about 3 percent through advancements in science. Now, the most common reason for a drug to fail in clinical trials is that data from animal models are not good enough predictors of success in humans.

Dahlem also noted that, in any exercise to define and ascertain how to develop a workforce, one must keep in mind that, from any student's perspective, a training program must provide opportunities that allow trainees to generate sufficient income to repay debts assumed during education and training.

Dahlem provided several observations about industry needs for the regulatory science process. First, industry needs timely and predictable reviews of NDAs, which could be achieved through enhanced collaboration among industry, academia, and FDA. Second, Dahlem called for unbiased third-party assessments of benefits and risks, especially when drug candidates move from the preclinical setting to human clinical trials. Such a mechanism could address real and perceived biases that may color industry assessment of risk and benefit. Third, harmonization of global regulatory expectations is also a critical need, as industry files for regulatory approvals around the world. Fourth, industry needs researchers and regulators who are trained to make both science- and judgment-based decisions. This is a particular concern today because of the increasing number of experienced regulators and researchers—individuals who have seen multiple iterations of problems and issues and who understand not just the rules but potential exceptions to those rules that they have uncovered over the course of their careers—who are retiring or leaving the industry because of consolidations and mergers. Dahlem emphasized that there is a critical need to capture the experiences of these individuals and to convey, perhaps using information technology–based tools, their experiences to new generations of researchers and regulators. Fifth, there is a huge need to better educate the public about risks and benefits to reduce public misperceptions about medications and vaccines.

Dahlem also listed specific scientific challenges that could be addressed through collaborative regulatory science initiatives:

- Scientists who are trained to understand the preclinical-to-clinical transition. In particular, he said, funding needs to be restored for training scientists in the classical disciplines of whole-animal pharmacology and physiology.
- Toxicology advances to provide better predictions of human clinical outcomes. This will involve better selection of animal models to ensure human safety, new methods to provide better correlations between whole-animal studies and human disease outcomes, and improved *in silico* modeling.
- In the clinical area, industry needs better clinical trial designs as well as an improved understanding of clinical trial data, particularly of the placebo effect. The biological origins of phenotypic responses need to be better understood, as do the effects of drugs in special populations.

PERSPECTIVE FROM ACADEMIA[7]

The magnitude of change that has occurred in medicine over the past century is staggering, Snyderman observed. The first major transformation occurred when science brought to medicine the understanding that at least some diseases could be defined as being caused by specific agents such as particular types of bacteria. This mechanism-based understanding of disease led to what he called the "find and fix it" philosophy that currently guides medicine. Today, the application of genomics, proteomics, metabolomics, systems biology, informatics, and micro- and nanoprocessing is creating a "predict it and personalize it" philosophy, one guided by understanding the complexity of both health and disease.

Also transformational has been the growing understanding that all diseases develop over time. Some develop rapidly, but the major chronic diseases typically develop over a long period of time. For those diseases, intervention typically occurs late, when the underlying pathology makes reversibility difficult and therapy expensive. Today, new technologies are seeking to enable earlier interventions, before primary symptoms develop. For example, genomics provides an understanding of baseline risks through the interaction of biology with the environment. This new knowledge will lead to new products that will require a new way of looking at regulation. FDA's strategic plan for regulatory

[7] This section is based on the presentation by Ralph Snyderman, Chancellor Emeritus, Duke University.

science is timely because it seeks to develop the regulatory science that will be needed to deal with these new technologies and products, noted Snyderman.

Snyderman reinforced the observation that, whereas 20 years ago academic medical centers were focused largely on basic discovery work, today scientists at these institutions participate in the entire range of drug discovery and development activities. Moving forward, he said, these activities will include regulatory science and the development of new tools for measuring the safety and efficacy of not only drugs but also the accompanying diagnostics that are being developed.

Snyderman analogized the development of a discipline of regulatory science to efforts to advance translational research and the conduct of clinical trials within academic medical centers. There is now a need to approach the regulatory sciences in a concerted, organized way, to define the discipline and competencies associated with its conduct, and to define it as an innovative science that is a valid career path for young scientists.

Snyderman listed the following as necessary elements in the fostering of the regulatory scientist-investigator:

- Recognition and role models within the academic institution
- Training and research training programs
- Appropriate tenure tracks
- Research infrastructure where scientists reside
- Means of support, including federal funding
- Respect of their colleagues—regulatory science being viewed as "worthwhile"

Snyderman made the following recommendations for the development and advancement of regulatory science:

- Recognize it as a discipline
- Define the discipline
- Define the qualifications
- Define educational needs
- Create academic homes and promotion/tenure tracks

PATIENT PERSPECTIVE[8]

Sigal reminded the workshop participants that the ultimate responsibility of regulatory science is to meet the needs of the patient. Among

[8] This section is based on remarks given by Ellen Sigal, Chair and Founder, Friends of Cancer Research.

the questions patients ask are the following: Will this new drug work for me? What are my risks? Sigal also noted that, until recently, FDA was not perceived to be a science-based agency. It had the burden of approving drugs and diagnostics, but it did not have the ability to do the science needed to guide decision making for the benefit of patients, which was instead assumed to be the province of NIH.

Sigal remarked that a greater sense of urgency is needed to reinforce that regulatory science is crucial to delivering therapies for patients. She remarked that the agency has not had sufficient resources to accomplish the science needs and added that the resources that are needed to advance regulatory science include not just a budget line item but also a supportive scientific ecosystem to continue the collaborative advancements, notwithstanding a heavily resource-constrained environment.

PRINCIPLES AND THEMES

In a panel discussion, the keynote speakers and audience members identified what they saw as the key needs for strengthening regulatory science. The discussion included individual observations about the principal barriers as well as the most promising opportunities. This section provides an integrated summary of their remarks and discussions with workshop participants during the panel and should not be construed as reflecting consensus or endorsement by the workshop participants, the planning committee, the Forum, or the National Academies:

- Among the biggest barriers to advancement of the science is a shortage of experienced regulatory scientists and the lack of experience among the scientists now being trained.
- A key element of the practice of regulatory science is an understanding of societal and personal tolerance for risk and how society and individuals experience the benefits of new drugs and technologies. Participants called for a more developed approach to benefit-risk assessment that takes patient perspectives into account.
- It is important for FDA scientists to be able to participate as scientists in academic settings or at NIH. It also is important that academic and NIH scientists be allowed and encouraged to work at FDA.
- Having an academic culture that views regulatory science as an inherently collaborative enterprise and that recognizes the need for development of people in academia to contribute to the science would contribute greatly to development of the workforce.
- Safe harbors could support and protect collaborations not only among the federal government and academia but also including the pharmaceutical industry and patients.

- Although progress has been made in providing opportunities for continuing formal interactions between industry and FDA during the drug development process, more work is needed to be done to enhance and increase access to resources at FDA, including increased informal interactions with FDA scientists and staff.
- Some participants called for definition as to what each sector (academia, industry, the agencies) needs to do to improve and enhance the support and practice of regulatory science.
- A next-level, precise definition of regulatory science—and the components of its practice—would spur academic medical centers to create programs in this area. This exercise would include identification of specific regulatory science competencies and definition of collaborative mechanisms established to connect academic training programs to relevant programs at NIH and FDA.

3

Defining a Discipline of Regulatory Science and Core Competencies for Its Workforce

Key Messages

- Regulatory science encompasses a wide range of subjects, including not only disciplines traditionally associated with regulation, such as statistics and clinical research, but also disciplines outside the biomedical sciences such as economics, risk communication, and sociology.
- Regulatory science could be a methodological means of determining the impact and value of the rules, principles, and laws governing FDA-regulated research.
- A strong relationship between regulatory science and translational science could provide a path to creating a well-rounded discipline.
- Defining a regulatory science workforce includes defining, and making promising scientists aware of, regulatory science as an attractive, respected career option.

The discussions in the next session of the workshop recognized and were built from the premise that developing a discipline of regulatory science calls for defining what is meant by regulatory science and then building a workforce equipped with a set of core competencies to fit that definition.

In a dialogue, Barry Coller, The Rockefeller University, and Rob Califf, Professor of Medicine, Vice Chancellor for Clinical and Translational Research, Duke University Medical Center, described regulatory science

as seen through the lens of translational science. In a panel discussion, panelists provided observations about the core competencies needed for an effective regulatory science workforce and offered perspectives on the role of regulatory science in their respective sectors and agencies.

DEFINING REGULATORY SCIENCE THROUGH THE LENS OF TRANSLATIONAL SCIENCE[1]

A Regulatory Science Taxonomy

In Coller's view, regulatory science is a subset of translational science. He provided the following definitions as a basis for the discussion:

- **Translational science** is the application of the scientific method to address a health need.
- **Regulatory science** is the application of the scientific method to improve the development, review, and oversight of new drugs, biologics, and devices that require regulatory approval prior to dissemination.

Translational science traditionally has been broken down into four phases:

- T1: Discovery to candidate health application
- T2: Health application to evidence-based practice guidelines
- T3: Practice guidelines to health practice
- T4: Practice to population health impact

The taxonomy of regulatory science can be aligned with the translational science taxonomy through four analogous phases, as follows:

- RS1: Preclinical evaluation of safety and efficacy
- RS2: Clinical trial design and analysis
- RS3: Postmarketing review of safety and optimal utilization
- RS4: Health policies, including social aspects of regulatory science

From this taxonomy, it is possible to develop a list of the multidisciplinary research expertise needed in regulatory science. (See Box 3-3

[1] This section is based on the presentations by Barry Coller, Vice President for Medical Affairs, Physician-in-Chief, and David Rockefeller Professor, The Rockefeller University, and Rob Califf, Professor of Medicine and Vice Chancellor for Clinical and Translational Research, Duke University Medical Center.

for a list of regulatory science competencies identified during the course of the workshop.)

Coller commented that the eight priority areas in FDA's 2011 strategic plan for regulatory science can be conceptualized within the regulatory science nomenclature of phases RS1 through RS4. For example, the FDA goals to modernize toxicology to enhance product safety, support new approaches to improve product manufacturing and quality, and ensure FDA readiness to evaluate innovative emerging technologies all fit within "RS1," the first phase of the regulatory science taxonomy. Others, such as implementation of a new prevention-focused food safety system to protect public health and facilitate development of MCMs to protect against threats to U.S. and global health and security, are crosscutting issues that integrate several phases of regulatory science.

Califf articulated FDA's definition of regulatory science ("regulatory science is the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products" [FDA, 2010]), which in his view is complementary to the definition offered by Coller but contemplates the conduct of activities that do not necessarily entail the application of the scientific method, such as policy development, and disciplines such as decision science, sociology, cognitive psychology, and behavioral economics. He also noted that regulatory science has multiple layers, and not every layer has the same goals.

Regulatory Science Training

It may be possible to create a training regimen for the regulatory sciences that builds on the existing translational science training programs, Coller said. Existing translational science meetings also may provide opportunities for disseminating new knowledge in regulatory science. Culturally, regulatory science could find an academic home within existing translational science centers and institutes. Similarly, existing journals focused on translational science may provide opportunities for publishing regulatory science scholarship. Building relationships between the regulatory and translational sciences may provide a path to creating a well-rounded discipline and earning the respect needed for any new field to succeed.

Califf applauded FDA for increasing the size of its workforce but added that the training systems for FDA scientists need to be improved. More thorough training should occur before FDA scientists start their duties at the agency so that they do not have to be trained so extensively on the job. FDA regulators need lifelong education, he added.

Many clinical researchers are ill at ease with regulatory science, said Califf. Much of this unease arises from the fact that regulations are not

well integrated with an understanding of what is needed to conduct first-rate clinical research. Researchers from the growing number of disciplines involved in clinical research, such as informatics specialists, data managers, psychologists, sociologists, economists, and even Institutional Review Board (IRB) members, must be given a better grounding in the relationship between regulation and clinical research, he said.

Even within the medical products industry, regulatory science training often occurs on the job. Califf suggested that organizations such as the Regulatory Affairs Professional Society (RAPS) become more involved in establishing a more formal mechanism for regulatory science training.

DEFINING REGULATORY SCIENCE AS SCIENCE OF EVALUATION OF REGULATIONS[2]

Several speakers called for a component of regulatory science to include the evaluation of regulations. The concept was discussed in depth by Clifford Lane, Deputy Director for Clinical Research and Special Projects, National Institute of Allergy and Infectious Diseases (NIAID), NIH. As defined by Lane, regulatory science is "the intellectual and practical activity encompassing the systematic study of the structure and behavior of the regulatory world through observation and experiment to determine the impact of the rules, principles, and laws governing FDA-regulated research." This definition gets to the notion that regulatory science should address the value that regulations provide. Regulatory science first would look at the purpose of the original regulation and then generate a testable hypothesis about the impact of the regulation. Research then would examine how successful the regulation has been at achieving its original purpose, determine if the regulation produced any unintended or unanticipated consequences, and quantify the broadly defined cost of implementing the regulation. The analysis of the data would in turn provoke a discussion on the overall value of the regulation and lead to a conclusion about whether the regulation should be modified, eliminated, or left unchanged.

Lane highlighted one law and one regulation that could be tested using this research strategy:

- The FDA Amendments Act of 2007, Title VII, called for the expansion of ClinicalTrials.gov with the aim of enhancing patient enrollment and providing a mechanism to track subsequent progress of clinical trials. A testable hypothesis could be that the expansion

[2] This section is based on the presentation by Clifford Lane, Deputy Director for Clinical Research and Special Projects, NIAID, NIH.

of ClinicalTrials.gov to include a results database has enhanced patient enrollment and provided a way to track progress of clinical trials without generating excessive costs. Studies could compare the rates of enrollment by several metrics, such as the total number of patients in clinical studies, the percentage of studies filled within a specified timeframe, the number of published papers using data from ClinicalTrials.gov, and website utilization statistics. The impact of additional regulation could be measured by looking at new informed-consent language and additional staff needed to comply with the regulation.

- Title 21, Chapter 2, Subchapter D, Part 314, Subpart I addresses the approval of new drugs when human efficacy studies are not ethical or feasible, also known as the Animal Rule. The purpose of this regulation was to enable the licensure of products that have been studied for their safety and efficacy in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances; for which definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers; and for which field trials have not been feasible. A testable hypothesis could be that products in this category that would not have been licensed have been licensed since the regulation was developed. Research could identify potential products that fall into this category and assess the impact of the regulation on the ability of those products to be licensed.

In the subsequent discussion session, Califf commented that regulators need a well-developed understanding of why the regulations exist and what they are supposed to accomplish, particularly emphasizing the application of regulations to real clinical trials.

Coller noted that the regulatory process is part of the political process and that regulatory science should include efforts to better understand the relationship between the two. This has direct bearing on the research scheme that Lane proposed because it has an impact on how the end effect of regulation can differ from the intended effect. Mary Dwight, Vice President for Government Affairs, Cystic Fibrosis Foundation, amplified this comment by noting that political drivers are overwhelming regulatory concerns today. Patient education must be part of the solution to this problem so that patients can speak out about their needs for more effective, efficient therapeutic development models based on good regulatory science. Lane noted that policy makers are largely driven by data; provide them with good data and they will make scientifically sound decisions, but in the absence of data, they will make decisions driven by politics and

opinion, he said. Regulatory science can tilt this process in favor of good decision making by generating good data.

CASE STUDIES: REGULATORY SCIENCE IN PRACTICE

Two speakers presented case studies that could serve as examples of the practice of regulatory science. Dwight presented a case study involving the development of a therapeutic agent (see Box 3-1). Munir Pirmohamed, Deputy Director, Medical Research Council Centre for Drug Safety Science (CDSS), University of Liverpool, discussed a case study involving an issue of drug safety (see Box 3-2).

CORE COMPETENCIES OF REGULATORY SCIENCE

As part of a panel discussion of the core competencies that a regulatory science workforce should have, Steven Galson, Vice President for Global Regulatory Affairs, Amgen Inc., listed certain core competencies that would be helpful in addressing the types of research questions relevant to the impact of regulation on clinical research. (See Box 3-3 for a list of regulatory science competencies identified during the course of the workshop.) He added that FDA has long taken advantage of training opportunities at NIH by sending staff to work in clinics and laboratories there, but if FDA does expand its regulatory research, there may be a need to create a specialized division at FDA that funds and conducts this research.

Several panelists from federal agencies provided comments on regulatory science workforce capacity needs to carry out their agency missions.

FDA Center for Biologics Evaluation and Research (CBER). Carolyn Wilson, Associate Director for Research, CBER, FDA, commented that CBER regulates a broad spectrum of therapeutic biologics, including complex entities such as gene therapies, cell therapies, and xenotransplants. Many of these therapeutics cannot be terminally sterilized and may not even be subjected to methods that might remove or inactivate infectious agents, raising issues such as how to ensure the safety of these entities, determine appropriate preclinical animal models, and ensure that there are not species-specific toxicities or therapeutic responses. To deal with these issues, CBER needs scientists who are trained in a variety of broad, scientific disciplines, including immunology, biochemistry, cell biology, developmental biology, microbiology, genetics, and the new "omics" sciences. According to Wilson, this workforce needs excellent analytical skills, the ability to adapt to new technologies and research paradigms, and the expertise to apply findings in a way that is not "checkbox regulation." Solid training in the scientific method is critical, along with experience doing team science.

BOX 3-1[a]
Collaboration in Cystic Fibrosis Research

Dwight described the Cystic Fibrosis Foundation's role in a successful collaborative effort to develop new therapeutics to treat cystic fibrosis (CF). The key to this effort was that the partners stayed focused on the desired goal but were flexible enough to adapt to changing circumstances experienced during the drug development process. She recounted how the mission of the foundation has changed since its founding in 1955, from caring for patients to finding treatments for the disease. This change reflects the tremendous advances in understanding the molecular basis of disease that have occurred since the discovery of the CF gene in 1989.

Collaboration has always been a core tenet of the CF community of patients and their parents; physicians, nurses, nutritionists, respiratory therapists, and social workers; and researchers. The tremendous advances in life expectancy that have occurred can be traced in part to a team approach to patient care.

Collaboration among three teams of researchers played a key role in the discovery of the CF gene. More recently, the development of promising therapeutics has been a result of collaboration among scientists in academia, industry, and FDA. Each of these collaborations required a cultural change. In the case of drug development, research teams needed to learn to share data among themselves and with pharmaceutical companies. At FDA, regulators needed to adapt their concepts of risk to recognize that risk has a different definition for patients suffering a certain early death from their disease without new treatments. The Cystic Fibrosis Foundation, Dwight explained, played the role of facilitator, coordinating and encouraging communications among all of the groups participating in this endeavor.

Dwight noted that FDA was very responsive to the particular needs of this work. In particular, large multicenter clinical trials would have been difficult to conduct given the patient population. FDA also strengthened its staff expertise and facilitated communications with trial sponsors.

However, the process is still too slow for patients living with chronic, life-threatening diseases, Dwight said. Direct communication between patient groups and regulators needs to be enhanced to inform how FDA balances risk and reward when it approves the design of even the earliest stages of the clinical trials processes.

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[a] Based on the presentation by Mary Dwight, Vice President for Government Affairs, Cystic Fibrosis Foundation.

FDA Center for Tobacco Products (CTP). Regulatory science sits at the core of what the CTP is now charged to do to protect the nation's health, but until now the country has never attempted to create science-based regulations for tobacco products. Doing so requires a pool of professionals in the biological and chemical sciences, toxicology, pharmacology, and product engineering, said Laurence Deyton, Director of CTP, FDA. It also

BOX 3-2[a]
Drug Safety

Adverse drug reactions impose a tremendous burden on human health. They account for some 2.5 percent of emergency room visits and 6.5 percent of hospital admissions in the United Kingdom and are a major problem for the pharmaceutical industry. Between 1990 and 2005, FDA and the European Medicines Agency (EMA) ordered 24 drugs to be withdrawn from the market because of adverse drug reactions. Most of these withdrawals occurred not long after the drugs reached the market, long before the costs of developing those drugs were recovered.

To better understand the fundamental biochemical mechanisms underlying adverse drug reactions, the Medical Research Council established the Centre for Drug Safety Science (CDSS). In addition to developing better methods for predicting adverse drug responses, CDSS aims to train researchers in the science of drug safety. Toward this end, the CDSS has established both research and clinical pharmacology training fellowships that focus on drug safety and personalized medicine. The center also offers master's and Ph.D. degrees in drug safety science.

An important piece of the center's training mission focuses on the collaborative relationships that CDSS has formed with regulators, academia, industry, and public advocacy groups. When CDSS identifies a research question, staff identify the appropriate clinical networks in the United Kingdom and develop collaborative hypothesis-testing research programs. The center then holds workshops involving academics, regulators, industry scientists, and health care officials to disseminate the results of those programs and develop recommendations to guide regulators.

As an illustration of CDSS's approach, Pirmohamed discussed the development of a new genetic biomarker for carbamazepine hypersensitivity in Caucasians. He described some of the research that identified this marker and then discussed the implications of these findings. Regulators, for example, need to consider that this biomarker was validated in at least three populations, but all from case-control analyses, not prospective clinical trials. Regulators can consider changing the prescribing label for this drug to require that all Caucasian patients be tested for the biomarker before the drug is prescribed, or they might simply provide this information to physicians. Only through the application of good science, said Pirmohamed, can regulators make good decisions about such issues.

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[a] Based on the presentation by Munir Pirmohammed, Deputy Director, Medical Research Council CDSS, University of Liverpool.

requires public health experts, medical professionals, lawyers, educators, communications specialists, and behavioral scientists, all of whom understand and appreciate the role of regulatory science as it applies to tobacco product regulation, said Deyton.

Centers for Disease Control and Prevention (CDC). Melinda Wharton, Deputy Director, National Center for Immunization and Respiratory

BOX 3-3[a]
Disciplinary Components of Regulatory Science

- Basic investigation
- Bioengineering
- Bioethics
- Bioinformatics
- Biology
- Bionutrition
- Biostatistics
- Chemistry
- Clinical investigation and clinical trial design
- Clinical pharmacology
- Clinical research operations
- Communication
- Decision theory
- Drug/device discovery and development
- Drug disposition and metabolism
- Economics
- Epidemiology
- Genetics
- Government/policy
- Information technology
- IRB experience
- Law
- Medical informatics
- Medicine
- Metrics
- Microbiology
- Monitoring and quality assurance
- Nutrition
- Pharmacology (whole animal)
- Pharmacy
- Protection of human subjects
- Public health
- Regulatory knowledge
- Research pharmacy
- Risk assessment and communication
- Surveying/methods
- Systems analysis
- Systems biology
- Technology transfer
- Toxicology
- Veterinary

[a] This box provides an integrated list of disciplinary components of regulatory science offered throughout the workshop by speakers and audience members.

Diseases, CDC, discussed the type of workforce CDC needs to conduct regulatory science, particularly in assessing risks and benefits. CDC's list of required disciplinary expertise encompasses epidemiologists, biostatisticians, and laboratory scientists such as microbiologists, chemists, and toxicologists who focus on the identification and quantification of disease burden. CDC also needs health economists who can study cost effectiveness, she said, along with risk communications experts. She emphasized the need for all staff to be comfortable working in a collaborative environment across disciplines and with external investigators.

Galson remarked that an understanding of how payers make reimbursement decisions is also a critical competency, given that many decisions about how new therapies will be used are being made not by regulators or physicians but by those who pay for these therapies. Increasing the pool of scientists trained in regulatory science who can conduct comparative effectiveness studies would benefit the entire field. A participant commented that FDA commissioned Duke University's business school to teach a course that included modules on funding drug development, pricing, and reimbursement.

A member of the audience with prior experience at FDA noted that a critical skill needed by FDA's workforce is an understanding of the difference between predictability and probability, noting that FDA makes probability-based decisions. He noted that ability to conduct quantitative analyses is a core competency, emphasizing bioinformatics, statistics, and other quantitative sciences.

DEFINING REGULATORY SCIENCE

A number of definitions of the term—and discipline—of regulatory science were submitted by various speakers throughout the course of the workshop. As described earlier, Coller conceptualized regulatory science as falling along a set of phases analogous to those recognized in translational science. A participant observed that Lane's definition to include the evaluation of regulations could be seen to fall within the "RS4" stage in Coller's taxonomy. Other definitions offered related, complementary perspectives on the definition and components of regulatory science.

Alastair Wood, Partner and Managing Director, Symphony Capital LLC, remarked that, although science includes them both, innovation and discovery are different things. Implementation, including adopting, understanding, using, and modifying knowledge that already exists, is also distinct from the process of discovery and from innovation. Wood suggested that defining the science—and developing and training the workforce to practice the science—should acknowledge and focus on the difference in the domains involved, which demand different styles,

and these skills, in turn, could be acquired in different settings (e.g., a focus on discovery in academics; a focus on innovation, implementation, and adoption in industry).

Carl Peck, Professor of Pharmacology and Medicine, University of California, San Francisco (UCSF), distinguished regulatory science from regulatory research. Regulatory science, he said, is the entire body of knowledge practiced by FDA and by those regulated by FDA, including law, economics, and an overriding ethic of protecting the public health. Regulatory research is the development of that body of knowledge as well as new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products.

Several participants noted that it may not be necessary or desirable to conceptualize regulatory science as a single, stand-alone discipline. It was suggested by a participant that all facets of therapeutics development are subject to science-based regulation. On this basis it was suggested that regulatory science could be viewed not as a freestanding discipline but rather as a subspecialty within every core discipline forming the basis of drug development science. Others conceptualized regulatory science as a multidisciplinary effort, and several workshop participants called for the establishment of academic "homes" that would centralize and support the workforce engaging in the practice of the regulatory sciences.

It was also noted that the fact that there is not a commonly agreed definition of regulatory science should not necessarily be seen as a barrier for advancing the field. Rather, it is an opportunity to create a multicomponent discipline that is adaptive and responsive to the needs of the field.

4

Education and Training of a Regulatory Science Workforce

Key Messages

- Some successful regulatory science education and training programs offer a menu of educational opportunities that build core competencies while allowing participants to focus on aspects of regulatory science relevant to their specific areas of interest.
- Multiple levels of recognized training could be employed, including professional certificates, master's degrees, doctoral degrees, and fellowships and rotations that blend work and training.
- A broad range of training and fellowship programs are available at FDA and within other agencies that create opportunities for scientists at all career stages to become more well versed in regulatory science and to have careers in regulatory science.

Defining a workforce that, taken as a whole, fosters the core competencies in regulatory science calls for a concerted effort to educate and train the existing and next generation workforce. The workshop discussions on education and training sought to identify current gaps and specific opportunities, including collaborative approaches, to strengthen the education and training of a regulatory science workforce. The workshop also examined barriers to implementing education and training strategies and potential ways to overcome these barriers.

Carl Peck, UCSF, presented an overview of certain existing training programs in regulatory science. Emma Meagher, Director of Translational Research Education, University of Pennsylvania Perelman School of Medicine, and Annette Mollet, Head of Training and Education, European Center of Pharmaceutical Medicine (ECPM), University of Basel, discussed the necessary components of an effective education and training strategy and how to develop those components. A panel discussion focused on fellowship and exchange programs.

AN OVERVIEW OF EXISTING TRAINING PROGRAMS[1]

Training Opportunities Within FDA

FDA is the major locus of regulatory research and training in the United States, Peck observed. Peck noted that the so-called "Subpart E Regulation," passed by Congress in 1989, included a provision that gave FDA authority to conduct regulatory research: "At the discretion of the agency, FDA may undertake focused regulatory research on critical rate-limiting aspects of the preclinical, chemical/manufacturing, and clinical phases of drug development and evaluation."[2]

Regulatory research is an inherent component of FDA's activities, and the agency has contributed to the advancement of the drug development field through its work with sponsors to advance development and evaluation of products more rapidly. FDA advancements span a wide range and include, for example, evaluation of diagnostic biomarkers for HIV/AIDS. FDA has innovated in clinical trial design and in modeling and simulation. FDA's Critical Path Initiative also has led to the establishment of numerous consortia for advancing the development of predictive safety biomarkers and advanced physiologically based modeling. Over the past 3 years, FDA scientists have published more than 1,000 papers.[3]

Peck commented that FDA has created a university-like environment that generates both debate and important science. And, as with any good university, FDA has developed strong training programs, according to

[1] This section is based on the presentation by Carl Peck, Professor of Pharmacology and Medicine, UCSF. The section is intended to offer a broad but brief look at certain regulatory research and training opportunities currently available. It is not necessarily complete or exhaustive.

[2] 21 CFR § 312.86, Focused Regulatory Research, available at http://www.gpo.gov/fdsys/pkg/CFR-2011-title21-vol5/pdf/CFR-2011-title21-vol5-sec312-86.pdf (accessed November 28, 2011).

[3] Vicki Seyfert-Margolis, Senior Advisor for Science Innovation and Policy, Office of the Commissioner, FDA, commented that, as of September 2011, there was a total FDA workforce of 13,800.

Peck. The Center for Drug Evaluation and Research (CDER) Staff College includes over 50 courses covering a wide range of graduate-level subjects. A committee on advanced scientific education certifies these courses and the faculty members who teach them. CDER also has a program that has defined the competencies necessary for regulatory scientists working at FDA who review drug applications and provide counsel to drug developers. In 2011, FDA expanded this latter effort and created the CDER Federated Training Model, which has published a public list of the competencies expected by discipline.[4] The agency has developed an outreach program to educate consumers, clinical investigators, and other key constituencies. In addition, FDA has established the Commissioner's Fellowship Program (CFP), a 2-year program for academics to come to FDA, learn the craft of regulation, and become engaged in a research project.

Additional information about FDA fellowships and training opportunities is provided below.

Training Opportunities Outside FDA

Peck described a number of courses offered outside of FDA, most of which fall within the category of regulatory affairs (rather than innovative regulatory science or regulatory research).[5] Specific training programs in regulatory research are rare, said Peck, though many universities have produced new methodologies and good scientists who have contributed to advances in regulatory science. These advances have come largely from pharmaceutical science departments at schools of pharmacy in the United States and Europe, clinical pharmacology research fellowships, clinical investigator fellowships, and some NIH programs (such as the year-long clinical pharmacology course that has a regulatory framework), as well as the University of Liverpool CDSS and the UCSF Center for Drug Development Science, he said.

ECPM has a two-decade history of developing and offering sophisticated courses in drug development science and regulatory science. An offshoot of this effort is the American Course on Drug Development and Regulatory Sciences offered by UCSF, which was launched in 2007 and modeled after the program developed by ECPM. It is offered by the UCSF Department of Bioengineering and Therapeutic Sciences and operates with substantial input from FDA, other universities, and industry. This

[4] See http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM263365.pdf (accessed November 28, 2011).

[5] Both the Regulatory Affairs Association and Drug Information Association have a large catalog of courses on specific issues pertaining to regulatory affairs.

intensive, 2-year course is given at the UCSF Mission Bay campus and in Washington, DC, with the participation of 120 faculty members drawn largely from industry and FDA. The course has been given three times in Washington and twice in San Francisco. The course consists of six "sessions" (each containing 4 days of lectures and case studies), and a 3-hour final exam.

Master's degree programs offering a research training component include the Regulatory Science Program at the University of Southern California (USC), as well as similar programs at Temple University, the University of Maryland, and the Liverpool CDSS. A participant added that USC School of Pharmacy has developed international M.S., Pharm.D./M.S., and D.R.Sc. (Doctorate in Regulatory Science) programs, with an initial three doctoral students graduating in 2011.

DEVELOPING EDUCATION AND TRAINING PROGRAMS IN REGULATORY SCIENCE[6]

Meagher described an approach to developing education programs in regulatory science that leverages what has been learned in the development of training programs for translational scientists, and this model for regulatory science program development is being refined and adopted by all of the institutions that are part of the CTSA network.

The target audience for such an education program is broad, and Meagher noted that it is necessary to break out of the mindset that regulatory science resides totally with FDA and that the field's obligation is to create a workforce that will function within the confines of FDA. Regulatory science is a collaborative effort that goes beyond FDA.

To better identify their audience, the Department of Translational Research Education at the University of Pennsylvania Perelman School of Medicine surveyed the many constituencies that have a stake in regulation and drug development. Meagher noted the following findings from the survey:

- Geographic location should not limit opportunities for educational encounters or for training programs.
- Attrition is a significant problem; the lack of a defined career path and professional recognition are the major reasons for the high rate of attrition the field is experiencing.
- Different groups have differing definitions of regulatory science; curricula need to be flexible and heterogeneous although still integrated.

[6] This section is based on the presentation by Emma Meagher, Director of Translational Research Education, University of Pennsylvania Perelman School of Medicine.

Critical needs for a regulatory science training program include understanding research and scientific methodology, pharmacology, toxicology, therapeutics, and the science that underpins the regulatory process. Competency areas include

- Biostatistics, decision theory, and information technology
- Fundamentals of pharmacology
- Scientific methodology
- Clinical trial design
- Drug and device discovery and development
- Clinical research
- Monitoring and quality assurance
- Food, drug, and device law and regulation

Effective training programs will incorporate rapidly changing science. As new technologies drive the development of many technological platforms capable of evaluating drugs efficiently, training programs could adapt and evolve to incorporate understanding of these new technologies and how they might be used in a regulatory setting.

Meagher suggested that programs include both professional certificate programs that would be suitable for such professionals as quality assurance specialists, regulatory coordinators, research nurses, project managers, research directors, and lawyers, as well as master's degree programs that would be suitable for FDA scientists, investigators, research directors, and lawyers. These types of tangible achievement-oriented programs help define a career path for professionals interested in regulatory science. The survey found, too, that most professionals prefer part-time programs that enable them to mix work responsibilities and interests with training opportunities; they prefer to be trained while remaining a part of the workforce.

Incorporation of opportunities to create and participate in internships outside of the university setting is a valuable component of a training program because it offers research training opportunities at FDA and within the pharmaceutical and biotechnology industries.

Evaluation will help determine if the programs are valuable and are meeting the needs of the stakeholders in regulatory science. Metrics would assess whether training increases the ability of the research workforce to meet the needs of the regulatory science initiative, whether the programs create a viable career structure, and whether the training improves the quality of research management. At the individual level, metrics can show if a program enables a student to demonstrate knowledge in core concepts and to apply that knowledge through completion of a mentored project designed to enhance the individual's professional abilities.

MODELS FOR EDUCATION AND TRAINING[7]

In 1999 Europe established the Bologna Process to harmonize higher education across the continent. Curricula for training developed within the Bologna system include programs for bachelor's and master's degrees as well as postgraduate training leading to a diploma of advanced studies, a master's of advanced studies, and a Ph.D. The Bologna system allows students mobility and flexibility to complete different training modules at different universities. The system includes common quality assurance standards for continuing professional education and training, which provides employers with the means to assess the quality of training prospective employees have received regardless of where they received their degree.

ECPM established a three-tier modular approach through its training curricula that were originally founded in 1991. Over the past 20 years, ECPM's program has trained more than 1,200 participants from 31 countries, with current enrollment standing at 147 participants. Like the UCSF program, there are multiple modules consisting of 4 days of training—3 days that cover state-of-the-art drug development science and 1 day that addresses current hot topics.

The Innovative Medicines Initiative (IMI) Training Excellence Programme is a large 5-year collaborative program run jointly by the European Union (EU) and the European Federation of Pharmaceutical Industries Association in partnership with academia and regulatory agencies. Funding for the IMI, which totals 2 billion euros (with 1 billion euro contribution from industry and 1 billion euro contribution from the EU), pays for training and collaborative research projects that cover safety, efficacy, education and training, and knowledge management. The following four education and training programs currently receive IMI funding: the European Medicines Research Training Network, the European Modular Education and Training Programme in Safety Sciences for Medicine, the European Programme of Pharmacovigilance and Pharmacoepidemiology, and the Pharmaceutical Medicine Training Programme (PharmaTrain).

PharmaTrain was started in May 2009 with a goal of harmonizing the syllabus for training, teaching, and examination across the European Union. Currently, 25 universities, 13 learned societies, and 15 companies participate in PharmaTrain. PharmaTrain has established a three-tier postgraduate track that builds core competencies through a set of base courses, creates expertise through a series of extension modules, and

[7] This section is based on the presentation by Annette Mollet, Head of Training and Education, ECPM, University of Basel.

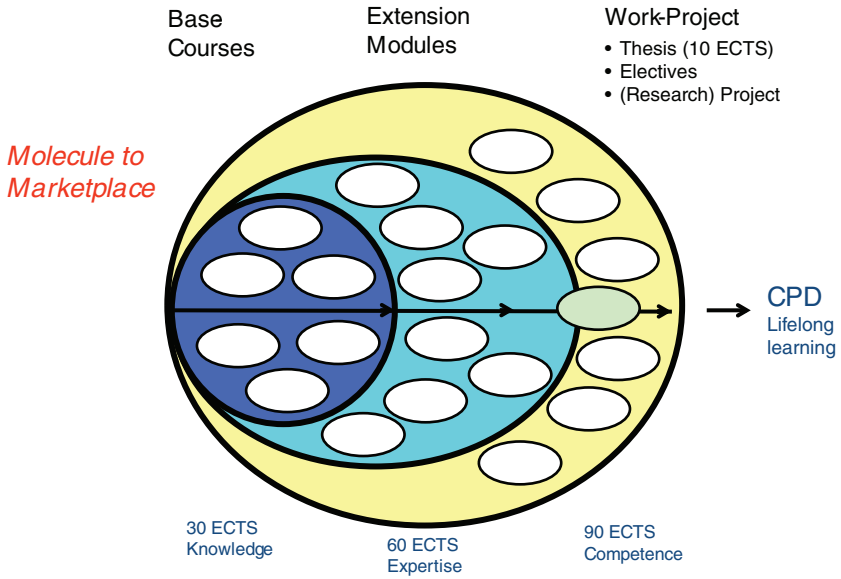

FIGURE 4-1 PharmaTrain has a three-tier program of postgraduate training with optional extension after completing each level.
NOTE: CPD, continued professional development; ECTS, European Credit Transfer and Accumulation System.
SOURCE: Mollet, 2011. Presentation at IOM workshop on Strengthening a Workforce for Innovative Regulatory Science in Therapeutics Development.

develops expertise through electives and research experience (Figure 4-1). Students can choose to stop upon completion of each level, and they can return for further modular education and training at a later date. A mechanism for lifelong learning or continued professional development also exists.

FELLOWSHIPS AND EXCHANGE PROGRAMS

Fellowships and Exchange at FDA

Leslie Wheelock, Director, Office of Scientific Professional Development, Office of the Chief Scientist, FDA, described FDA's CFP. This 2-year training fellowship program, which began in October 2008, has three primary goals: attracting scientists to FDA, training scientists in regulatory science, and retention of those scientists at FDA. FDA has recruited up to 50 fellows annually. The fellows are hired into the Office of the Chief

Scientist and then placed with preceptors across the agency. During the 2-year program, fellows complete about 210 hours of classroom training in four content areas, including content specific to the center and office in which they will carry out their research projects. Each project is identified by the centers as being of critical importance to address a scientific regulatory issue. Wheelock noted that FDA promotes this program widely to academic institutions and trade organizations in recognition that the agency presents a nontraditional career path for scientists calling for broad promotion and efforts to increase understanding and familiarity with science careers at FDA.

Among the first class of fellows, which graduated in fall 2010, all 48 fellows completed the program, and 38 accepted permanent positions at FDA (a retention rate of 79 percent), according to Wheelock. Five of the fellows took positions in industry, putting them in a position to serve as "ambassadors" between industry and FDA. The remaining fellows returned to academia.

Uros Djekic, Senior Regulatory Reviewer/Policy Analyst, CBER, FDA, provided the perspective of someone who participated in the CFP (as a member of the inaugural group of fellows from 2008 to 2010). He described the CFP as a collaborative paradigm for supporting regulatory science. Fellows apply their scientific expertise to a specific project directed by a "sponsor" at FDA. The fellow and sponsoring FDA staff member commit to finish the project during the 2 years in which the fellow continues to receive training. At the moment, he said, there are only about 30 fellows—a number limited by funding, not by opportunity. About half of the projects, he noted, are laboratory based, while the other half are examining issues of regulatory policy. A list of past, current, and proposed projects is available on FDA's website.[8] Example projects include

- Djekic's project, which looked at policy issues involving over-the-counter HIV tests, particularly concerning the clinical trials that would be necessary for such products to receive regulatory clearance.
- A project to develop the proposed International Consortium of Orthopedic Registries.

Carolyn Wilson, of FDA's CBER, added that FDA's staff fellowship program is an umbrella program that incorporates the CFP as well as two

[8] See http://www.fda.gov/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/CommissionersFellowshipProgram/default.htm (accessed November 28, 2011).

additional tracks: (1) a support-scientist fellowship that starts as a 4-year postdoctoral fellowship, with the possibility of extension of an additional 3 years and opportunity to be considered for conversion to a permanent support scientist; and (2) a senior staff fellowship track that recruits investigators to develop their own independent research, also with the opportunity after a 7-year period to be considered for permanent hiring as a senior investigator. These positions require that the fellows spend about half of their time engaged in regulatory review activities. In that regard, the fellows engage in all of the same activities that full-time reviewers do, including conducting inspections, reviewing submissions, participating in advisory committees, writing guidance documents, and developing policy. FDA also offers more traditional postdoctoral fellowships that can last up to 5 years, which do not include any regulatory duties.

CTP has created a Tobacco Regulatory Science Fellowship Program, which Laurence Deyton, FDA, described. The program, which is CTP's first initiative to help build its workforce, is designed to incorporate the best practices of the FDA's CFP, the NCI's Cancer Prevention Fellowship, and others. The fellowship will involve a core curriculum related to regulatory science and FDA operations. It also will include a research component that will require fellows to take charge of projects. CTP hopes to attract midcareer professionals for the first few of the program's cycles to develop a cadre of experienced professionals who then can advise CTP on how best to build and expand its efforts while also serving as mentors.

Kate Ahlport, Executive Director, Health Research Alliance (HRA), described two new collaborative models at FDA that grew out of the HRA. The HRA is a national consortium of 48 nonprofit, nongovernmental funders of biomedical research and training that are interested in maximizing the impact of the nation's investment in biomedical research. The HRA has decided to fund the two new initiatives at FDA to further its interest in and support for regulatory science:

- *New Frontiers in Science Distinguished Lectureship Program.* The purpose of this program is to bring scientific expertise to the agency in the priority areas identified in FDA's strategic plan for regulatory science in the form of quarterly guest lecturers. Lecturers will spend 1 to 3 days at FDA giving seminars, meeting with staff, and providing tutorials in their area of scientific expertise. Lecturers will receive an honorarium and reimbursement of travel expenses.
- *Distinguished Scholar's Pilot Program (proposed).* A distinguished scholar's pilot program is in the discussion and planning stage. This program would be similar to the FDA's CFP but focused on senior-level scholars who would be selected competitively to

spend up to a year at FDA and work on special regulatory science projects that cut across disease areas. It is expected that benefits will flow both directly to FDA (in the exchanges with scholars) and to the broader scientific community (as scholars bring back to their home institutions or companies a new level of knowledge and understanding of FDA).

Fellowships and Exchange Sponsored by NIH

Juan Lertora, Director, Clinical Pharmacology Program, NIH Clinical Center, described the NIH Clinical Center's Rotations for Clinical Research Fellows at FDA. This program identifies scientists from the NIH Clinical Center for placement in short-term rotations in FDA's Office of Clinical Pharmacology or the Office of New Drugs. The rotations last a minimum of 8 weeks and provide learning experiences focused on the issues that would enable fellows to file an IND application. Fellows are assigned to mentors at FDA in their areas of interest, and they participate in the review of preclinical and clinical data on investigational drugs. They also attend specialized therapeutic team meetings, participate in IND 30-day safety review approvals and in meetings with sponsors, and enroll in a curriculum of educational modules and courses at FDA. Since the program's inception in 2008, 10 fellows from a number of NIH institutes and the Clinical Center have completed rotations. Three of the initial 10 rotating fellows have since joined the Office of New Drugs as medical review officers, said Lertora.

Jonathan Wiest, Director for Training and Education, NCI, NIH, described a postdoctoral training program that emerged from work of the FDA-NCI Interagency Oncology Task Force (IOTF). The IOTF Joint Fellowship Program, which is a direct collaboration between the NCI Director's Office and the FDA Commissioner's Office, aims to increase the number of reviewers capable of handling the large number of cancer drugs that are moving through the development pipeline by recruiting individuals trained in cancer biology into the program. A second program goal is for some fellows to go to industry, where they can build awareness of regulatory requirements into the early stages of the product development process and improve planning throughout the research and regulatory review process.

Four types of fellowships are included in the program.[9] NCI funds the program and develops a training plan for each fellow. FDA provides the mentors and the regulatory training opportunities. Fellows are required to take courses in drug law, reviewer training, statistics, and clinical trial design. Depending on background and experience, fellows also take classes on risk assessment and risk management, good manufacturing practice and good laboratory practice, technical writing, presentation skills, IND regulations, and NDA regulations. Fellows also participate in the review process, with at least 50 percent of a fellow's time being spent on research under the supervision of a mentor. Mentors also must meet certain requirements, including having an active regulatory research program, evidence of productivity, and a record of outstanding mentoring.

Currently, there are 12 fellows, with 4 getting ready to transition out, said Wiest. Two of these fellows will be staying at FDA, and one will be joining a biotechnology company. Twelve past fellows work at FDA, four have joined pharmaceutical companies, one joined NCI, one went into consulting, and one works in the health care industry.

[9] The first two programs are targeted to cancer researchers with an M.D. or M.D./Ph.D.; one offers a medical oncology residency (for up to 3 years) and the other is for board-certified or board-eligible oncologists (for up to 1 year). The second two are targeted to M.D. scientists; one is for basic scientists and molecular biologists (for up to 2 years) and the other is a cancer prevention fellowship (for up to 3 years).

5

Career Paths Within Academia and Industry

Key Messages

- The lack of defined funding and other career support mechanisms for regulatory scientists presents challenges to attracting qualified candidates to the field.
- Though regulatory science is a multidisciplinary field with a broad set of core competencies, it may be a more effective career path for a scientist-investigator to associate with a particular established discipline, which can provide the means for obtaining funding, publication, and recognition needed for a successful academic career.
- Regulatory scientists can fill a gap in expertise at their home academic institution, offering the opportunity to demonstrate the importance of regulatory science and build institutional support for the field.

Attracting talent to the field of regulatory science requires that there be solid career paths for regulatory scientists. The workshop examined career paths and career development opportunities, both within and outside of academia, that are currently available—or that would need to be available—to strengthen and support regulatory science in therapeutics development. William Chin, Executive Dean for Research, Harvard Medical School; David DeMets, Professor, Department of Biostatistics and Medical Informatics, University of Wisconsin-Madison; and Kathy

Giacomini, Professor and Co-Chair, Department of Bioengineering and Therapeutic Sciences, UCSF, presented their ideas on academic career paths for regulatory scientists. Henrietta Ukwu, Senior Vice President for Global Regulatory Affairs, PPD, Inc., then offered comments on regulatory science career paths in industry.

CAREER PATHS IN ACADEMIA

Barriers and Opportunities in Academia[1]

Given the lack of established programs in regulatory science in academia, this gap could be addressed by increasing opportunities for exchanges among academia, industry, and government, as described in this chapter and in Chapter 7. Such collaborative approaches would support an ecosystem that will foster the development of career paths within all three sectors. Chin listed questions for consideration in defining a regulatory science career path:

- Is there a clear definition of the field?
- Are tools and technologies available to answer research questions?
- Are multiple training options available that involve innovative research?
- Who are the role models?
- Is the career track clear, and is there a clear path for professional development and promotion in an academic home?
- What is the availability and sustainability of research funding?
- Are academic societies and publications available that provide opportunities for impact and recognition?
- Are alternative career pathways available?

The biggest barrier to the development of an academic discipline is that the nature of academia does not lend itself to a regulatory mindset, said Chin. Furthermore, the unsupportive funding climate makes it unlikely that many universities would commit the resources needed to create the necessary educational and research programs that would cross disciplinary boundaries.

There are, however, opportunities to associate regulatory science with areas that are getting support, such as translational science and therapeutics, or with rapidly developing fields whose progress eventually will depend on good regulatory science, including personalized medi-

[1] This section is based on the presentation by William Chin, Executive Dean for Research, Harvard Medical School.

cine, regenerative medicine, and gene therapy. For example, biologically inspired engineering is an emerging discipline that applies biological principles to develop new engineering solutions that meet real-world needs, with potential to produce tissues-on-a-chip that accelerate drug development and replace animal tissues. Regulatory science advances are needed to advance development of such devices as drug development tools. Moreover, associating regulatory science with such scientific fields can help raise the visibility of the discipline and ultimately overcome the barriers, such as lack of acceptance and credibility, impeding the development of regulatory science as an academic discipline.

Issues Confronting Academic Regulatory Scientists[2]

DeMets offered remarks geared toward establishing credibility for expertise in regulatory science in academic institutions. Because regulatory science is inherently multidisciplinary, it is unreasonable for any one person to be well versed in all the involved fields of science. Given that the structure of academic institutions is still based overwhelmingly on single disciplines, investigators with an interest in regulatory science should structure their approach to research in such a way as to put an established discipline, such as biostatistics, at the center of their work. A key to this approach is to find problems in a given field that tie directly into regulatory science. As an example, DeMets discussed several important and interesting gaps in biostatistics, such as the need for tools for comparative effectiveness research or for assessing composite and surrogate outcomes.

DeMets also noted that most universities have a real need for expertise in regulatory science even if they do not acknowledge it. Few universities have faculty who are well versed in regulatory requirements and guidelines. Being the expert who joins research teams can be one way to build support for regulatory science in academic institutions. Demonstrating the value of such expertise can then open the door to creating training opportunities for other members of a multidisciplinary research team, which in turn can help start the process of institutionalizing regulatory science.

Building a Home for Regulatory Science in Academia[3]

Giacomini provided observations about the relationship between the disciplines of regulatory science and translational medicine and thera-

[2] This section is based on the presentation by David DeMets, Professor, Department of Biostatistics and Medical Informatics, University of Wisconsin-Madison.

[3] This section is based on the presentation by Kathy Giacomini, Professor and Co-Chair, Department of Bioengineering and Therapeutic Sciences, UCSF.

peutic sciences and, in that context, presented a case study from her own institution illustrating the challenges of recruiting and retaining regulatory scientists. She commented that the already-defined core competencies for translational medicine and therapeutic sciences can provide a framework in which would reside a subset of competencies needed for the regulatory sciences. As with any inherently broad-based field, such as systems pharmacology or pharmacogenomics, the field comprises multiple core competencies, but each regulatory scientist would acquire a deeper understanding in a defined, smaller area, and that discipline would serve as the base for developing an academic career.

Giacomini cited an example from her home department, the UCSF Department of Bioengineering and Therapeutic Sciences, a multidisciplinary department that came about through the merger of three departments spanning pharmacy, biopharmaceutical sciences, and bioengineering. The department confronted challenges recruiting and retaining a regulatory scientist for an identified position. In recruiting they found that the pipeline for training regulatory scientists for academic research careers is sparse. Moreover, concerns arose relating to academic sustainability, both in terms of grant support and opportunities for publication and recognition that are essential to building an academic career. UCSF at one time had a core group of pharmaceutical scientists doing research in physiologically based pharmacokinetics and drug delivery. Seven of these individuals left academia not because they were unsuccessful but because there was no NIH support for creative research in these fields, she said, adding that, to be successful, regulatory science as a discipline needs to encourage funding from NIH, FDA, and other parties to make this a sustainable academic career track. Giacomini also cited the lack of departmental homes for regulatory scientists as a key barrier to development of a workforce in the field.

Advancing Academic Regulatory Science

It was emphasized by several of the panelists that regulatory science workforce development is dependent on career advancement opportunities and visibility and credibility of the work. Otherwise, training programs are for naught. Moreover, to ensure that teaching and training is current, training opportunities and programs could have mechanisms to evolve in parallel with the anticipated growth in regulatory science and research. Workshop discussants noted that to seed the practice of regulatory science, support the advancement and credibility of the discipline, and provide clear, discernible career paths, it is important to identify, fund, and pursue the "big questions" in regulatory science. Chin characterized these as the problems or questions that are of ultimate impor-

BOX 5-1
A Nonexhaustive List of the "Big Questions" Identified by Participants

- Need for appropriate science experiments that will define risk and benefit in better ways.
- Evaluate and better understand the preclinical to clinical transition.
- Need for better predictions of human clinical outcomes. Need for better selection of animal models and improved correlation with whole animal studies to human disease outcomes.
- How to develop and regulate drug combinations.
- How to address drug-drug interactions. Developing *in vitro* methodologies for predicting drug-drug interactions is suited to academic research, for example.
- Need for a collaboratively developed national research agenda in regulatory science.
- Develop better understanding of methods to analyze huge volumes of data and use big databases to answer questions in regulatory science.
- Need for a science-based process to identify and qualify biomarkers.
- Develop and refine novel approaches to clinical trial design.

tance for the innovation ecosystem. Discussion at the workshop collected a nonexhaustive list of those potential big questions, which are compiled in Box 5-1 as an integrated summary of speakers' and participants' remarks and discussions, and which should not be construed as reflecting consensus or endorsement by the participants, planning committee, the Forum, or the National Academies. Several participants noted that further work could be done to compile and catalog these "big questions" to help advance the discipline.

CAREER PATHS IN INDUSTRY[4]

Ukwu identified the locus of the emergence of regulatory science in the "perfect storm" of 2006, in which industry saw a decline in productivity and rise in product failures, which highlighted that the current paradigm for drug development was unsustainable (Figure 5-1). She stated that the challenges plaguing industry forced introspection, leading to identification of a number of emerging regulatory trends, such as the use of adaptive trial designs and the ability to collaborate more closely with regulatory agencies during the development process.

[4] This section is based on the presentation by Henrietta Ukwu, Senior Vice President for Global Regulatory Affairs, PPD, Inc.

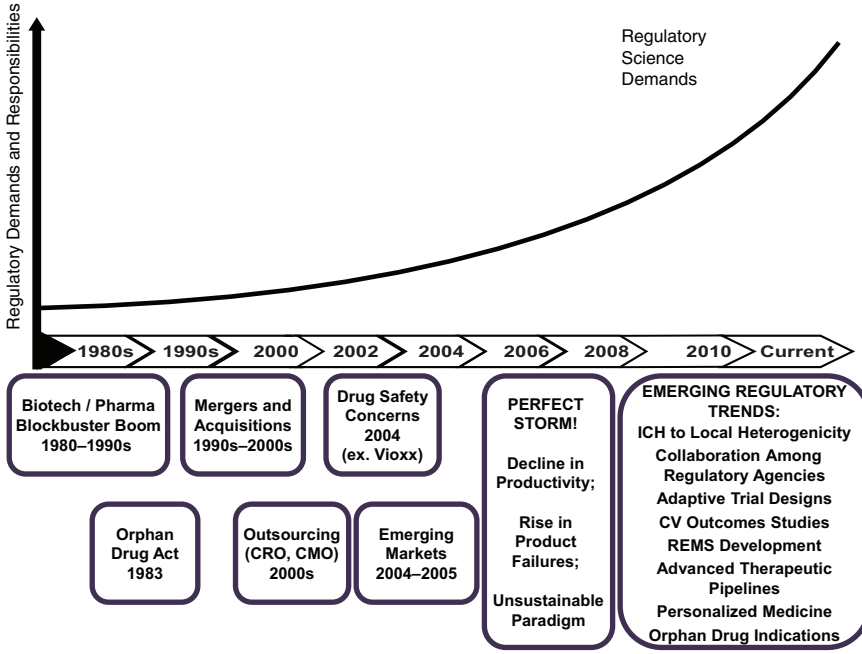

FIGURE 5-1 Trends in the pharmaceutical industry led to a "perfect storm" leading to increased regulatory science demands.
NOTE: CMO, Contract Manufacturing Organization; CRO, Contract Research Organization; CV, cardiovascular; ICH, The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; REMS, Risk Evaluation and Mitigation Strategies.
SOURCE: Ukwu, 2011. Presentation at IOM workshop on Strengthening a Workforce for Innovative Regulatory Science in Therapeutics Development.

Regulatory science could lead to better incorporation of scientific, translational, and clinical knowledge into regulatory development planning for industry. Regulatory scientists could liaise between multidisciplinary groups and could bring clinical reasoning and scientific methodology to a process-driven field. The need for precision, prediction, and intelligence in adapting the regulatory process to product development then could introduce proactive approaches to drug development and lead to the incorporation of better analytical processes. Regulatory scientists also could contribute to the business development process by providing input to licensing and outsourcing strategies and to partnerships in contract research organizations (CROs).

Regulatory scientists working in industry typically have a terminal

clinical or scientific degree, with a background in translational research or medicine and expertise in a therapeutic area. A regulatory scientist should also have experience in data review and actively participate in relevant professional organizations. A regulatory scientist's responsibilities would combine strategic and operational excellence in program development planning, strategic regulatory intelligence, regulatory meetings, clinical trial design using advanced methodologies, global regulatory issues, and supervising in a matrix-organization environment. In this regard, Ukwu observed, industry highly values regulatory agency fellowship programs because they turn out regulatory scientists who meet these needs.

Ukwu also described career development paths for regulatory scientists in a CRO. Because CROs provide advice and guidance to industry, there is a clear need for regulatory scientists who can help a client identify gaps in a development plan and strengthen the position of products early in the development process. These efforts increase the odds of the client's product succeeding both with regulators and in the marketplace.

6

International Applications of Regulatory Science

Key Messages

- Global regulatory harmonization would lower barriers for drug developers, but payers and, in many countries, health technology assessment bodies still determine if a drug that makes it to the market will succeed.
- Efforts to increase regulatory capacity in the developing world, combined with cooperation and assistance from regulatory agencies in the developed world, hold promise for increasing the number of drugs developed and approved to treat global diseases, including neglected diseases.
- An emphasis on training and education will help to overcome the challenges of developing therapeutics for global neglected diseases.

The development of therapeutics is a global endeavor, calling for a global workforce. In addition, regulatory science can enable the development of therapeutics for diseases that affect primarily the developing world.

Xavier Luria, Head, Safety and Efficacy of Medicines, EMA, described efforts to incorporate regulatory science into regulatory decision making from the perspective of a European regulator. Michael Brennan, Senior Advisor for Global Affairs, Aeras Global TB Vaccine Foundation, presented an update on regulatory science needs to develop drugs for neglected diseases that affect primarily developing countries.

MAINTAINING A ROBUST GLOBAL THERAPEUTICS PIPELINE[1]

Luria provided a worldwide forecast of drug sales in 2016. Oncology drugs are predicted to hold the biggest market share of any drug class, with anticoagulants undergoing explosive sales growth. Antirheumatics, antivirals, antidiabetics, vaccines, and dermatologicals also are expected to show robust growth in sales over the next 4 to 5 years. The number of drugs that will be seeking approval during that time will tax global regulatory mechanisms, he stated. To meet this projected need, the global drug development community will need both more regulators and enhanced regulatory science to improve the efficiency of the regulatory process.

The requirements to approve a drug for marketing can differ across countries. In the EU, pharmaceutical law says that drug approval rests on showing that the balance of benefits and risks is positive, with no mention made of effectiveness, relative effectiveness, or cost-effectiveness. EU law also states that regulators should refuse marketing authorization if quality, safety, or efficacy is not demonstrated sufficiently based on objective criteria, which is aimed at making decisions transparent. EU regulators can grant conditional approvals with a requirement for follow-up measurements, so long as there are adequate data to support such an approval. Luria noted, however, that he does not believe these efforts are succeeding at speeding up drug approvals.

The traditional approach to improving efficiency is through processes such as the EU's harmonization program, which is knitting together the regulatory systems of 27 member nations. This same type of approach could be tried in other regions, said Luria.

Progressive Approval

EMA has developed a 2015 roadmap (EMA, 2010). One of the items in this roadmap, which according to Luria is quite similar to efforts under way in the United States, Canada, and Singapore, is a staggered or progressive approval pathway that is based on sponsors showing a progressive reduction of uncertainty. The proposed new paradigm calls for progressively authorizing increased indications for a drug as knowledge and investment increase. Through iterative phases of information gathering followed by regulatory evaluation and action, progressive authorization seeks to align regulatory decision making with emerging information on benefits and risks. It seeks to maximize the positive impact of new drugs

[1] This section is based on the presentation by Xavier Luria, Head, Safety and Efficacy of Medicines, EMA.

on public health by balancing timely access for patients with the need to provide appropriate information on benefits and risks.

For this approach to work, good regulatory science must be done to answer questions about how to design clinical trials to broaden treatments in increasingly eligible populations, how best to use adaptive clinical trial design, and how to reduce uncertainty around given end points. Regulatory science will be needed to enable combination therapies in this model, to ensure effectiveness beyond simply balancing risks and benefits, and to address rare adverse events.

This approach faces several obstacles, said Luria. First, a progressive approval pathway may not be allowable under current statutes. Second, there is concern that the approach will result in inappropriately lowered approval standards. Issues of alignment among regulators, payers, and prescribers are a concern, as is the possibility that a different reward structure will be needed to incentivize drug development.

The Efficacy-Effectiveness Gap

While it is increasingly difficult to bring new drugs to market, it will be even harder to keep them on the market because of the "efficacy-effectiveness gap," according to Luria. Regulators evaluate each drug on its own merit based on benefits and risks. Payers and health technology assessment bodies make their decisions to maximize health within a finite budget, forcing them to make allocation decisions between two or more drugs. In a place like the EU, where there is one regulatory authority but 30 different health technology assessment methodologies, each making independent decisions, drug developers face a growing risk that they will receive an approval but not be able to keep a drug on the market.

Luria discussed possibilities for interactions between regulators and health technology assessment bodies. Ongoing efforts include one aimed at integrating more effectiveness data into the European Public Assessment Reports that EMA issues every time regulators take an action for a drug. Another pilot effort involves creating parallel scientific advisory committees in conjunction with health technology assessment bodies. Other opportunities lie in aligning postmarketing research activities with health technology assessment bodies across the member states and in developing scientific guidelines for judging relative efficacy and effectiveness. Such guidelines would require new methods based on scientific data, which points toward the increasing role for academia in the dialogue between regulators and industry.

THERAPEUTICS DEVELOPMENT FOR GLOBAL NEGLECTED DISEASES[2]

The development of drugs for global neglected diseases has entered a new paradigm over the past decade, with the emergence of product development partnerships (PDPs). PDPs are intended to lead development of vaccines, therapeutics, and diagnostics for infectious diseases such as AIDS, tuberculosis (TB), and malaria. PDPs must meet all the usual regulatory requirements and approvals for authorization and global distribution of a product. PDPs and other product development sponsors face a landscape of disparate regulation, and often frequent delays in the regulatory review process. Collaboration in the regulatory arena would be very beneficial to save time and to ensure timely regulatory consideration without compromising quality. Brennan also called for capacity building to strengthen local regulatory authorities, including the improvement of clinical trials and inspection processes, as well as to streamline and harmonize regulatory submissions.

FDA assistance can contribute significantly to improving the regulatory environment in these countries. Brennan noted that FDA could

- host exchange programs,
- offer training opportunities,
- increase its acceptance of non-U.S. clinical data,
- conduct joint reviews of clinical protocols, and
- sign memoranda of understanding that would enable data exchange between FDA and national review agencies.

FDA has also released guidance documents for sponsors who are developing drugs and vaccines for global illnesses:

- In September 2008, FDA issued a document entitled "General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases," which stated that FDA can license vaccines to protect against infectious diseases or conditions not endemic in the United States.[3]
- The agency has prepared a new document, "Guidance for Industry Neglected Tropical Diseases of the Developing World: Developing Drugs for Treatment and Prevention," that was released in draft

[2] This section is based on the presentation by Michael Brennan, Senior Advisor for Global Affairs, Aeras Global TB Vaccine Foundation.

[3] For more information, see http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074762.htm (accessed November 28, 2011).

form for comment in August 2011.[4] In the draft guidance, FDA reiterates the agency's commitment to facilitating access to therapies in the developing world. The document reflects the realities of conducting clinical trials for neglected tropical diseases where infrastructure is lacking, said Brennan, noting that for a neglected tropical disease 50 to 60 percent efficacy can save tens of thousands of lives, even though that level of efficacy is not what regulatory authorities in countries such as the United States are used to seeing. Reflecting this, the draft states that the agency would have "considerable latitude to exercise its scientific judgment to determine the kind and quality of data and information . . . required . . . to meet standards for approval." Because many countries base their approvals on actions taken by the United States or the European Union, actions such as these could have powerful effects in poorer countries, said Brennan.

Brennan offered four potential solutions to the problems that organizations face in developing products for global neglected diseases:

- Establish structures for information sharing among regulators within regional settings.
- Increase the involvement of regulators from endemic countries in assessment of new products.
- Expand internationally the model of regional centers of excellence in regulatory science.
- Build sustainable regulatory capacity in endemic countries by systematizing training programs and exchange programs.

[4] Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269221.pdf (accessed November 28, 2011).

7

Collaborative Models and New Paradigms for Supporting Regulatory Science Research and Practice

Key Messages

- Collaboration involving all stakeholders is a key element to creating a new ecosystem that is more efficient at turning discovery into therapeutics that benefit human health.
- Real-world pilot demonstration projects that apply regulatory science to the development of therapeutics can generate important insights while keeping collaborators engaged and committed to their partnerships.
- An initiative to create a self-sustaining Virtual Development Institute comprising a network of university-based organizations could be initiated using funds from existing translational research programs.
- A "champion" for regulatory science could help define and promote the discipline.

Given budgetary constraints that are unlikely to ease in the near future, efforts to develop the discipline of regulatory science and a regulatory science workforce may increasingly seek to rely on indirect support more than direct funding. To explore this issue, the workshop discussed funding opportunities and collaborative models that would need to be available to strengthen and support regulatory science research and practice in therapeutics development. Workshop presentations and discussions also examined whether there are institutions, public or private, that

could offer funding to create an infrastructure and ecosystem to support innovative regulatory science.

Gigi Hirsch, Executive Director, Center for Biomedical Innovation, Massachusetts Institute of Technology (MIT), described a new initiative designed to transform the drug development ecosystem. William Greenlee, President and Chief Executive Officer, the Hamner Institutes for Health Sciences at Research Triangle Park, summarized the Hamner Institutes' approach to collaborative efforts among government, industry, and academia. Theodore Reiss, Research Professor of Medicine, Vanderbilt University School of Medicine, proposed a new model for research and education that would reflect the needs of today's world. A discussion followed that explored the resources and stakeholder engagement needed to build the discipline of regulatory science and establish regulatory science career paths.

CREATING A COLLABORATIVE ENVIRONMENT IN AN ACADEMIC SETTING[1]

In an attempt to repair dysfunction in the drug development ecosystem, MIT created the New Drug Development Paradigms (NEWDIGS) initiative. NEWDIGS is a collaborative environment for innovation and learning that takes a systems approach to transforming processes, technologies, and policy elements of innovation. The stakeholder community, Hirsch said, includes major pharmaceutical companies, the global regulatory community, academia, payers, and patient advocacy groups. A group of MIT faculty serves as strategic advisors to the initiative. NEWDIGS emphasizes tight coordination between real-world pilot projects and academic research in engineering, science, management, and clinical medicine. Lessons learned by NEWDIGS might offer useful ideas and insights for approaches to strengthening a workforce for innovative regulatory science in drug development, said Hirsch.

After identifying a high-impact area of need or opportunity within the innovation space, NEWDIGS convenes a subteam that is interested in this topic and proceeds in a modular fashion (Figure 7-1). The first module takes a regulatory science approach to focus on "adaptive licensing" (including staggered approval, progressive licensing). The second module focuses on oncology, specifically codevelopment of two or more investigational compounds in combination therapies and helping FDA develop a guidance document on the subject. A proposed payer-centric third module would examine value-driven innovation. Within each mod-

[1] This section is based on the presentation by Gigi Hirsch, Executive Director, Center for Biomedical Innovation, MIT.

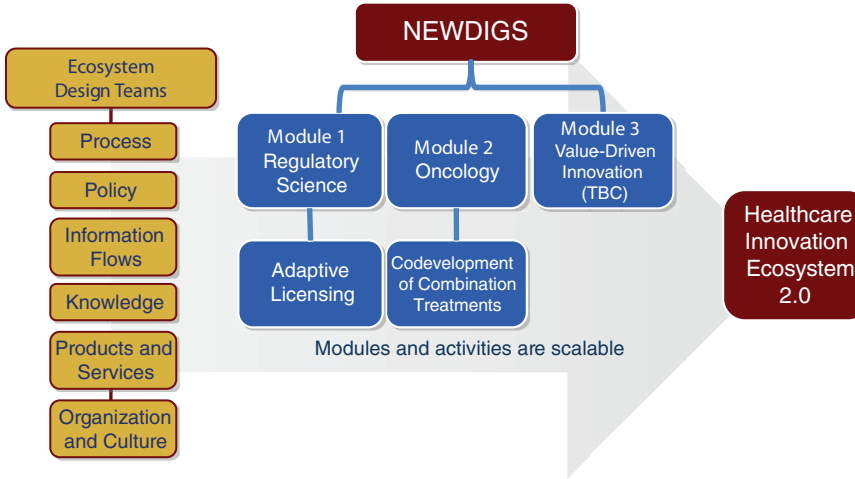

FIGURE 7-1 The New Drug Development Paradigms (NEWDIGS) initiative involves design teams that progress through established modules to engage in innovative regulatory science activities.
SOURCE: Hirsch, 2011. Presentation at IOM workshop on Strengthening a Workforce for Innovative Regulatory Science in Therapeutics Development.

ule, NEWDIGS researchers build test beds that are designed to combine stakeholders, real-world demonstration projects, and academic research in a way that enables rapid-cycle learning.

NEWDIGS also looks across the modules it has established to find improvements in the architecture of the overall innovation system. The cross-module approach relies on methodologies that focus on preserving value. In this way, everything in the drug development environment enables and contributes to innovation through understanding of how to improve processes, policies, and information flows.

Adaptive Licensing

NEWDIGS has adopted the approach of taking advantage of an opportunity for proactive, strategic design of policy with broad stakeholder input, followed by the empiric evaluation of these designs to inform discussions about change. Regulatory agencies, major pharmaceutical companies, two payers, and researchers from MIT and Harvard are participating in this effort and are designing initial demonstration projects involving compounds in development that will be implemented

in Singapore in collaboration with the Singapore Health Sciences Authority. The group has been using simulations to try to understand what adaptive licensing might look like across different drugs and different drug classes.

Collaboration among the participants is well integrated. Data sharing about drugs currently in the pipeline is undertaken pursuant to formal confidentiality agreements. The work includes an active academic and educational component, including monthly research seminars. Hirsch noted that some 30 students are participating and learning about regulatory science through the project.

Developing a Collaborative Workforce

Hirsch described a regulatory science workforce as a virtually collaborative workforce of individuals from different disciplines and market sectors. She offered the following observations for supporting such a workforce:

- Establish a "safe haven" environment through specific ground rules for workshops as a critical element for enabling learning and innovative thinking. These ground rules include items such as "no decisions are made in workshops" and "individuals do not speak on behalf of their organizations."
- Systems approaches to design and problem solving are critical but challenging given the enormously complex interdependencies across disciplines and the silos that inhibit communication and sharing. NEWDIGS has been experimenting with a variety of systems engineering methodologies, finding that they are falling somewhat short when they are applied across an entire industry. In addition, a diversity of expertise and perspectives is critical. Thus, it is particularly important to involve individuals from outside of the health care industry.
- Having a safe-haven "test bed" for ideas is important not only for making progress but to fight "consortium fatigue" and to keep participants involved in working on solutions to problems involving regulatory science. Ability to demonstrate that the learning and innovation activities that fuel continuous improvement in execution have been central to the sustainability of NEWDIGS.

A COLLABORATIVE MODEL FOR RESEARCH, TRAINING, AND BUSINESS DEVELOPMENT[2]

The fundamental philosophical paradigm of the Hamner Institutes is that publication of findings is not the end game of research. Rather, the goal is to capture research knowledge in a way that will improve global public health by driving the development of safer medicines, informing public health policy, and realizing economic development.

The Hamner Institutes' Institute for Drug Safety Sciences was launched 3 years ago in partnership with the University of North Carolina at Chapel Hill (UNC), and involving faculty from Duke University and North Carolina State University. This new entity operates on the principle that modernizing toxicology is not about hazard identification. Rather, it is about understanding environmental perturbation on biological systems and being able to understand the health outcomes of that perturbation. The institute is developing approaches that link postmarketing surveillance, clinical studies, and advanced animal model systems. The institute is also collaborating with investigators in China to develop virtual models of the Caucasian and Asian liver to understand subtle differences in drug response between these two populations.

The Hamner Institutes is now developing additional partnering relationships that aim to bring academia, industry, and government to the same table as a means of accelerating drug development. These new partnerships will also involve the Hamner Biosciences Accelerator, which has dedicated staff, education and training support through postdoctoral fellowships, and a business development mindset to move discoveries into technology development programs and out into the market. One partnership that has developed out of this effort involves an effort to accelerate drug development in China under U.S. regulatory standards with the goal of bringing products to market worldwide.

REGULATORY SCIENCE: SOLVING FOR A LARGER CONTEXT[3]

Regulatory science must be addressed within a broader context to address important public health needs and accelerate drug development. This broader context starts with the drug development environment; the pharmaceutical industry is experiencing transformational trends, including very difficult scientific challenges and rapidly increasing expenses and price pressures, while the public sector and academia are developing new skills

[2] This section is based on the presentation by William Greenlee, President and Chief Executive Officer, the Hamner Institutes for Health Sciences at Research Triangle Park.

[3] This section is based on the presentation by Theodore Reiss, Research Professor of Medicine, Vanderbilt University School of Medicine.

and capabilities for drug discovery and development. Taken together, these trends suggest collaborative solutions for a new and broader educational, scientific, and funding environment. Reiss laid out a set of foundational principles for collaboration around development and regulatory science:

- Addressing issues piecemeal will have limited impact.
- Industry, government, and academia must collaborate to create a vision for a more integrated biomedical science environment.
- Academia must value and promote translational, development, and regulatory thinking, and it must bring industry scientists to the table to help with this transformation.
- The new environment must be efficient and robust and leverage structures already in place, such as the CTSA institutions.

A model organization would be university centered, according to Reiss, and would involve NIH, with a department of "bench-to-bedside science." The faculty would have expertise in development, regulatory issues, and translation and would serve as a center for collaborative translational projects. These projects would include scientists from other academic departments as well as from industry, regulatory agencies, and foundations. The department would serve as a center to teach translational, development, and regulatory science, instilling a team-oriented, collaborative mindset in students and postdoctoral fellows. It also would be linked across institutions through the CTSAs into what Reiss termed a "Virtual Institute of Drug Development."

Reiss acknowledged that there are real barriers to creating such an organization. Universities lack exposure to and comfort with this type of broad versus deep thinking. The cognitive framework of academia will need to change from one focused on absolute knowledge to one that considers confidence in benefits and risks based on significant, consistent evidence. The polarization among academia, industry, and the regulatory sector will need to be reduced. The lack of reward structure for translational, development, and regulatory projects is a significant barrier, as is the lack of coordinated teaching, training, and research programs within today's academic structure.

Funding such an initiative will require a concerted effort from all stakeholders. Reiss suggested that initial funding should come from the proposed NCATS, with universities following by providing matching infrastructure funds, adding that NIH should ensure that there is a balanced portfolio of funding initiatives between discovery and development projects.

Reiss noted that such an initiative would provide a critical signal to investigators regarding potential careers in development, translational, or regulatory science.

Other sources of funds also need to be available, said Reiss. The pharmaceutical industry—both large and small companies—and foundations should contribute through collaborative projects and by participating operationally in the Virtual Development Institute. Though a tax may currently have trouble finding support, Reiss argued that an "approval tax" on drugs, or a revenue tax on sales exceeding $1 billion, should be considered at some point to provide a self-sustaining source of funding.

CLOSING PANEL[4]

In a closing panel session, several workshop speakers engaged in a panel discussion with the workshop co-chairs and the workshop participants to discuss resources, stakeholder engagement, and next steps needed to build a discipline of regulatory science and establish career paths in innovative regulatory science. This section lists ideas presented by the panelists and workshop participants. Statements, recommendations, and opinions expressed are those of individual presenters and participants and are not necessarily endorsed or verified by the Forum or the National Academies, and they should not be construed as reflecting any group consensus.

The following are observations by the panelists:

- There is increasing participation by the nonprofit sector to advance the discipline of regulatory science.
- There continues to be a lack of respect within academia for the field of regulatory science.
- There are roles for every sector in the drug discovery ecosystem to participate in the development of a regulatory science workforce.
- Existing programs in regulatory science do not include or emphasize the social sciences.
- Without a separate discipline of regulatory science, it will be difficult to train a workforce with the necessary mindset to understand the needs of regulatory versus discovery science.

[4] Participants in the summary panel were Barry Coller, Vice President for Medical Affairs, Physician-in-Chief, and David Rockefeller Professor, The Rockefeller University; Elaine Gallin, Principal, QE Philanthropic Advisors; Steven Galson, Vice President for Global Regulatory Affairs, Amgen Inc.; William Greenlee, President and Chief Executive Officer, the Hamner Institutes for Health Sciences at Research Triangle Park; Gigi Hirsch, Executive Director, Center for Biomedical Innovation, MIT; Carl Peck, Professor of Pharmacology and Medicine, UCSF; Theodore Reiss, Research Professor of Medicine, Vanderbilt University School of Medicine; and Alastair Wood, Partner and Managing Director, Symphony Capital LLC.

- There are more career opportunities and paths for regulatory scientists than might be commonly understood, including international, national, and state regulatory agencies, the Federal Trade Commission, Congress, payers, investors, and journals.
- The collaborative, multidisciplinary nature of innovative regulatory science may undermine the ability to identify a champion or lead stakeholder charged with advancing the science.
- Considering that one goal of the investment in basic health sciences research is to improve health outcomes, investing in regulatory science could support the case for such investment.

The following are suggestions for a way forward from the panelists:

- Create a standing panel sponsored by FDA and/or NIH that would focus on ways to strengthen the regulatory science workforce.
- Ensure that social science research and evidence is built into regulatory science research and practice.
- Identify a champion that can take responsibility for advocacy for support of regulatory science and the workforce to support regulatory science. It was suggested that proposed NCATS could serve as a key champion for the discipline.
- Design regulatory science training programs to reflect the different training backgrounds of the individuals who come to regulatory science. The "menu" approach applied in the European PharmaTrain program could be a good model.
- Convene a series of conferences that would be charged with defining the big needs or "big questions" in regulatory science. Link this effort to RFAs that would support pursuit of these big questions.
- Opportunities to increase interest in the discipline among students and investigators include reinvigorating and expanding research fellowships in clinical pharmacology and embedding regulatory science research fellowships in translational medicine and therapeutics through such programs as the CTSA institutions and the proposed NCATS.
- Researchers who have lost jobs as the pharmaceutical industry has downsized could offer a pool of scientists that could be recruited to do regulatory science in the federal agencies and in academia through innovative and creative pilot projects.
- Make it clear that "if innovation is the goal, regulatory science is essential."

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Appendix A

Workshop Agenda

Strengthening a Workforce for Innovative Regulatory Science in Therapeutics Development: An Institute of Medicine Workshop

September 20-21, 2011

National Academy of Sciences
Keck Building, Room 100
500 Fifth Street, N.W.
Washington, DC 20001

Background:

The Food and Drug Administration (FDA) has defined *regulatory science* as the ***science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products*** (FDA, 2010). The FDA Science Board, in Science and Mission at Risk (FDA Science Board, 2007), described 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." A number of gaps in the regulatory science discipline and infrastructure have been identified. They include workforce and resource constraints; cultural differences and systemic barriers to collaboration and exchange among the agency, academia, and industry; and deficiencies in the network and infrastructure necessary to forge the collaboration and communication needed to advance regulatory science. There has been recognition that collaborative approaches are necessary to advance regulatory science. In early 2010, FDA and NIH announced a unique collaboration, with establishment of a joint FDA-NIH leadership council to enable cross-agency efforts to improve regulatory science.

This workshop will explore issues related to strengthening a workforce for innovative regulatory science in therapeutics development. The workshop will (1) consider opportunities and needs for advancing innovation in the discipline of regulatory science for therapeutics development through an interdisciplinary regulatory science workforce and (2) examine specific strategies for developing a discipline of innovative regulatory science through development of a robust workforce within academia and industry and at FDA.

Meeting Objectives:

- Define and discuss the current regulatory science workforce, with particular attention to discussion of the disciplines involved and professional training opportunities.
  - — Identify gaps between the essential components of a workforce that will produce innovation in regulatory science and the current reality.
- Consider workforce development needs in areas identified as key components of a robust discipline of innovative regulatory science in therapeutics development.
- Examine application and advantages of collaborative (multisector and multidisciplinary) approaches for strengthening of a robust national regulatory science workforce.
  - — Identify and discuss specific opportunities for enhancing collaboration and coordination—among relevant federal programs and between FDA and the extramural community—to strengthen a regulatory science workforce supporting innovation in therapeutics development.
  - — Identify barriers to implementation of collaborative models, and discuss potential solutions to address those identified barriers.
- Explore the resources and stakeholder engagement needed, not only within FDA and other federal agencies, but also throughout

the extramural sector, to build the discipline and establish career paths in the area of regulatory science innovation for therapeutics development.

SEPTEMBER 20, 2011

8:30 a.m. Welcome and Introductions

BARRY COLLER, *Workshop Co-Chair*
Vice President for Medical Affairs and Physician-in-Chief
David Rockefeller Professor
The Rockefeller University

ELAINE GALLIN, *Workshop Co-Chair*
Principal
QE Philanthropic Advisors

Session I: Defining a Discipline of Regulatory Science

Session Objectives:

- Discuss the promise of and role for innovative regulatory science in therapeutics development.
- Define the discipline of regulatory science in therapeutics development.

8:40 a.m. Keynote Address, Food and Drug Administration

VICKI SEYFERT-MARGOLIS
Senior Advisor for Science Innovation and Policy
Office of the Commissioner
Food and Drug Administration

9:00 a.m. Keynote Address, National Institutes of Health

STORY LANDIS
Director
National Institute of Neurological Disorders and Stroke
National Institutes of Health

9:20 a.m. Keynote Address, Industry

ANDREW DAHLEM
Vice President & Chief Operating Officer, Lilly Research Laboratories
Eli Lilly & Co.

9:40 a.m. Keynote Address, Academia

RALPH SNYDERMAN
Chancellor Emeritus
Duke University

10:00 a.m. Panel Discussion with Keynote Speakers: ***Components of a Robust Academic Discipline of Regulatory Science***

Objectives:

- Define "innovation" in regulatory science. What are the benchmarks and metrics of success in a discipline of regulatory science?
- Propose and discuss the essential, core components of a robust discipline of innovative regulatory science in therapeutics development.
- List key skills, techniques, and areas of expertise needed by a regulatory science workforce.

ELLEN SIGAL, *Panel Moderator*
Chair and Founder
Friends of Cancer Research

Panelists:

- Keynote speakers (FDA, NIH, Industry, and Academia represented above)

Session II: Core Competencies of an Innovative Regulatory Science Workforce

Session Objectives:

- Consider the core components of an innovative regulatory science discipline and essential competencies of a regulatory science workforce.
- Through case studies, provide examples of the practice of regulatory science and the needed skill set of the workforce involved.

STEVEN GALSON, *Session Chair*
Vice President for Global Regulatory Affairs
Amgen Inc.

Case Studies: ***Components and Application of Innovative Regulatory Science***

10:30 a.m. Therapeutics Development

MARY DWIGHT
Vice President for Government Affairs
Cystic Fibrosis Foundation

10:50 a.m. Drug Safety

MUNIR PIRMOHAMED
Deputy Director
MRC Centre for Drug Safety Science, University of Liverpool

11:10 a.m. Components of Regulatory Science Through the Lens of Translational Science

BARRY COLLER
Vice President for Medical Affairs and Physician-in-Chief
David Rockefeller Professor
The Rockefeller University

ROB CALIFF
Director, Duke Translational Medicine Institute
Professor of Medicine
Vice Chancellor for Clinical and Translational Research
Duke University Medical Center

11:45 a.m. Panel Discussion: Perspectives on Core Competencies for a Regulatory Science Workforce

Session Speakers and Additional Discussants:

STEVEN GALSON, *Panel Moderator*
Vice President for Global Regulatory Affairs
Amgen Inc.

MARY DWIGHT
Vice President for Government Affairs
Cystic Fibrosis Foundation

CLIFFORD LANE
Deputy Director for Clinical Research and Special Projects
National Institute of Allergy and Infectious Diseases
National Institutes of Health

MUNIR PIRMOHAMED
Deputy Director
MRC Centre for Drug Safety Science, University of Liverpool

MELINDA WHARTON
Deputy Director, National Center for Immunization and Respiratory Diseases
Centers for Disease Control

12:40 p.m. LUNCH

Session III: Education and Training of a Regulatory Science Workforce

Session Objectives:

- Discuss education and training opportunities needed to develop a robust workforce in regulatory science in therapeutics development. Identify gaps between those needed components and the current reality.
- Identify and discuss specific opportunities, including collaborative approaches, to strengthen education and training opportunities for a regulatory science workforce.
- Examine barriers to implementation of those strategies and discuss potential solutions to those identified barriers.

ALASTAIR WOOD, *Session Chair*
Partner & Managing Director
Symphony Capital LLC

1:40 p.m. Overview of Existing Training Programs in Regulatory Science

CARL PECK
Professor, Pharmacology and Medicine
University of California, San Francisco

2:00 p.m. Education and Training: What Is Needed and How Do We Get There?

2:00 p.m. EMMA MEAGHER
Director, Translational Research Education
Institute of Translational Medicine and Therapeutics
University of Pennsylvania Perelman School of Medicine

2:15 p.m. ANNETTE MOLLET
European Center of Pharmaceutical Medicine
University of Basel, Switzerland

2:30 p.m. Panel Discussion with Speakers

ALASTAIR WOOD, *Panel Moderator*
Partner & Managing Director
Symphony Capital LLC

3:00 p.m. BREAK

Session IV: Regulatory Science Career Development and Advancement: Career Paths Within and Outside Academia

Session Objectives:

- Discuss career and career development opportunities that currently are available, or that would need to be available, to strengthen and support research and practice of regulatory science in therapeutics development.
- Discuss regulatory science careers outside academia, including industry, FDA, and other federal agencies. Focus on career tracks in innovative regulatory science (as distinguished from regulatory affairs and compliance).

- Identify and discuss specific opportunities, including collaborative approaches, to encourage the career development for a workforce in regulatory science in therapeutics development. Examine barriers to implementation of those strategies and discuss potential solutions to those identified barriers.

3:20 p.m. Session Overview and Introductory Remarks

CARL PECK, *Session Chair*
Professor, Pharmacology and Medicine
University of California, San Francisco

Panel 1: ***Regulatory Science Career Paths in Academia***

3:25 p.m. WILLIAM CHIN
Executive Dean for Research
Harvard Medical School

3:35 p.m. DAVID DEMETS
Professor, Department of Biostatistics & Medical Informatics
University of Wisconsin-Madison

3:45 p.m. KATHY GIACOMINI
Professor and Co-Chair, Department of Bioengineering and Therapeutic Sciences
University of California, San Francisco

Panel 2: ***Regulatory Science Career Paths Outside Academia***

4:00 p.m. LESLIE WHEELOCK
Office of the Chief Scientist
Food and Drug Administration

4:10 p.m. JONATHAN WIEST
Director for Training and Education, Center for Cancer Research
Office of Training and Education, National Cancer Institute
National Institutes of Health

4:20 p.m. HENRIETTA UKWU
Senior Vice President for Global Regulatory Affairs
PPD, Inc.

4:30 p.m. Panel Discussion with Speakers: Career Development Pathways: What Is Needed and How Do We Get There?

CARL PECK, *Panel Moderator*
Professor, Pharmacology and Medicine
University of California, San Francisco

5:30 p.m. ADJOURN

SEPTEMBER 21, 2011

8:30 a.m. Welcome and Introductions

Workshop Co-Chairs

BARRY COLLER
Vice President for Medical Affairs and Physician-in-Chief
David Rockefeller Professor
The Rockefeller University

ELAINE GALLIN
Principal
QE Philanthropic Advisors

Session V: International Applications

ELAINE GALLIN, *Session Chair*
Principal
QE Philanthropic Advisors

8:35 a.m. Regulatory Science Workforce Needs to Maintain a Robust Global Therapeutics Pipeline

XAVIER LURIA
Head, Safety and Efficacy of Medicines
Human Medicines & Evaluation
European Medicines Authority

8:55 a.m. Regulatory Science Workforce Needs to Support Therapeutics Development for Global Neglected Diseases

MICHAEL BRENNAN
Senior Advisor for Global Affairs
Aeras Global TB Vaccine Foundation

Session VI: Collaborative Models and New Paradigms for Supporting Regulatory Science Research and Practice

Session Objectives:

- Discuss funding opportunities that would need to be available to strengthen and support research and practice of regulatory science in therapeutics development. What institutions, public or private, could offer research funding and other support to create an infrastructure and habitat for innovative regulatory science? Outline a sustainable funding model.
- Identify and discuss specific opportunities for enhancing collaboration and coordination to strengthen a regulatory science workforce supporting innovation in therapeutics development.
- Identify barriers to implementation of funding strategies and collaborative models, and discuss potential solutions to address those identified barriers.

BARRY COLLER, *Session Chair*
Vice President for Medical Affairs and Physician-in-Chief
David Rockefeller Professor
The Rockefeller University

9:15 a.m. GIGI HIRSCH
Program Director, NEWDIGS
Executive Director, Center for Biomedical Innovation
Massachusetts Institute of Technology

9:30 a.m. WILLIAM GREENLEE
President & CEO
The Hamner Institutes

9:45 a.m. THEODORE REISS
Research Professor of Medicine
Vanderbilt University School of Medicine

10:00 a.m. Panel Discussion Led by Workshop Co-Chairs: Fellowship/Exchange Programs

FDA CTP Regulatory Science Fellowship (pilot)

LAWRENCE DEYTON
Director
Center for Tobacco Products
Food and Drug Administration

FDA Commissioner's Fellows Program

UROS DJEKIC
Commissioner's Fellow (2008-2010)
Senior Regulatory Reviewer/Policy Analyst
Center for Biologics Evaluation and Research
Food and Drug Administration

CBER Regulatory Science Activities

CAROLYN WILSON
Associate Director for Research
Center for Biologics Evaluation and Research
Food and Drug Administration

Visiting Lecturer/Expert Programs at FDA

KATE AHLPORT
Executive Director
Health Research Alliance

FDA Rotation for Clinical Research Fellows at the NIH Clinical Center

JUAN LERTORA
Director
Clinical Pharmacology Program
NIH Clinical Center

10:45 a.m. Q&A with Panelists

Session VII: Setting the Agenda

Session Objectives:

- Explore resources and stakeholder engagement needed to build the discipline and establish career paths in the area of regulatory science innovation for therapeutics development.
- Discuss specific next steps for stakeholders to strengthen a workforce for innovative regulatory science in therapeutics development.

11:00 a.m. Discussion with Panelists and Workshop Attendees Led by Workshop Co-Chairs

BARRY COLLER, *Workshop Co-Chair*
Vice President for Medical Affairs and Physician-in-Chief
David Rockefeller Professor
The Rockefeller University

ELAINE GALLIN, *Workshop Co-Chair*
Principal
QE Philanthropic Advisors

STEVEN GALSON
Vice President for Global Regulatory Affairs
Amgen Inc.

ALASTAIR WOOD
Partner & Managing Director
Symphony Capital LLC

CARL PECK
Professor, Pharmacology and Medicine
University of California, San Francisco

GIGI HIRSCH
Program Director, NEWDIGS
Executive Director, Center for Biomedical Innovation
Massachusetts Institute of Technology

WILLIAM GREENLEE
President & CEO
The Hamner Institutes

THEODORE REISS
Research Professor of Medicine
Vanderbilt University School of Medicine

12:00 p.m. ADJOURN

Appendix B

Participant Biographies

Barry S. Coller, M.D. (*Workshop Co-Chair*), is the David Rockefeller Professor of Medicine; Head, Laboratory of Blood and Vascular Biology; Physician-in-Chief of The Rockefeller University Hospital; and Vice President for Medical Affairs at The Rockefeller University. He also serves as the founding Director of the Rockefeller University Center for Clinical and Translational Science and the Principal Investigator of the University's CTSA from the National Center for Research Resources of NIH. From 1993 to 2001, Dr. Coller was the Murray M. Rosenberg Professor of Medicine and Chairman of the Samuel Bronfman Department of Medicine at Mount Sinai School of Medicine in New York City. Dr. Coller received his B.A. degree, magna cum laude, from Columbia College in 1966, and his M.D. from New York University School of Medicine in 1970. He completed his residency in internal medicine at Bellevue Hospital in New York City and advanced training in hematology and clinical pathology at NIH. He joined the faculty at Stony Brook in 1976 as an Assistant Professor of Medicine in the Division of Hematology. During his years at Stony Brook he was the Clinical Director and Head of the Hematology Division, and Associate Director for Biomedical Research of the Biotechnology Center for Advanced Technology. He was awarded the title of Distinguished Service Professor of Medicine and Pathology at Stony Brook in 1993. Dr. Coller is a member of Phi Beta Kappa, Alpha Omega Alpha, the American Society for Clinical Investigation, the Association of American Physicians, the IOM of the National Academies, and the National Academy of Sciences. He is a Fellow of the New York Academy of Medicine,

the American Association for the Advancement of Science, and the American Academy of Arts and Sciences, and a Master of the American College of Physicians. Dr. Coller served as President of the American Society of Hematology in 1997-1998 and as the founding President of the Society for Clinical and Translational Science from 2008 to 2010. He is a member of the Advisory Council of the National Heart, Lung, and Blood Institute and the national Principal Investigators' CTSA Consortium Steering Committee. Dr. Coller's research interests have focused on hemostasis and thrombosis, in particular platelet physiology. He developed a monoclonal antibody that inhibits platelet function and a derivative of that antibody (abciximab; ReoPro; Centocor/Eli Lilly) was approved for human use by FDA in 1994. It is now in clinical use throughout the United States, Europe, Scandinavia, Australia, and portions of Asia to prevent ischemic complications of percutaneous coronary interventions such as angioplasty and stent insertion. More than 4 million patients have been treated with abciximab. He also developed an assay to assess platelet function, and automated derivatives of that assay to monitor therapy with abciximab, aspirin, and clopidogrel (Plavix™) have been approved for human use by FDA (VerifyNow; Accumetrics). Dr. Coller is the recipient or a co-recipient of 14 U.S. patents.

Elaine K. Gallin, Ph.D. (*Workshop Co-Chair*), is currently a partner at QE Philanthropic Advisors, a consulting firm established in 2010 that serves nonprofits specializing in biomedical research, science and math education, and international health. From 1999 through February 2010, Dr. Gallin served as the Doris Duke Charitable Foundation's (DDCF's) first Program Director for Medical Research. In that capacity, she led the creation and management of a portfolio of grant programs that committed more than $185 million to supporting clinical research. Dr. Gallin also designed and led DDCF's $65 million African Health Initiative. Launched in September 2007, this initiative supports large-scale health services delivery projects designed to provide integrated primary health care linked to rigorous operations and implementation research in several sub-Saharan African communities. Before joining DDCF, Dr. Gallin spent two decades working for the U.S. government, first as a research physiologist and then as research administrator where she last served as the Deputy Director of the Office of International Health Programs in the U.S. Department of Energy overseeing health research programs in countries of the former Soviet Union. During this period, she also spent a sabbatical year working in the Science Committee of the U.S. House of Representatives as a Congressional Science Fellow. Dr. Gallin has participated in numerous professional committees and review panels including several for the IOM and NIH. She was a founding member and the first Vice Chair of HRA (an

alliance of not-for-profit, nongovernment research funders). Dr. Gallin is currently a member of the Sickle Cell Disease Advisory Committee at the National Heart, Lung, and Blood Institute, the Forum on Drug Discovery, Development, and Translation at the IOM, the Scientific Advisory Board for the Avon Foundation, and the President's Council of Cornell Women. Dr. Gallin received her B.S. from Cornell University and her Ph.D. from the City University of New York and completed postdoctoral fellowships in Physiology at Johns Hopkins University Medical School and Columbia University Medical School.

Kathryn (Kate) N. Ahlport, M.S.P.H., is the Executive Director, HRA. In the 6 years since she joined the Alliance, Kate Ahlport has overseen the transformation of an informal network of 15 funders into an independent, 501(c)(3) national consortium of 49 not-for-profit, nongovernmental funders of health research and training, the HRA. HRA member organizations work together to maximize the impact of investment in biomedical research and training to improve human health by fostering open communication and collaboration among members, by providing comprehensive data and analysis about the funding of biomedical research and training by member organizations, by identifying gaps in funding and facilitating innovative grantmaking, and by addressing issues key to accelerating research discovery and its translation. As the chief executive officer, Kate is responsible for administration, programs, and all other functions and activities of the Alliance, serving also as a member of the HRA Board of Directors. Prior to joining the Alliance, Kate served as Vice President of the Moses Cone-Wesley Long Community Health Foundation in Greensboro, North Carolina, formed as part of the merger of two community hospitals. Ms. Ahlport's career has also included the management of acute health care facilities, jointly and wholly owned outpatient health care services, and a managed care plan. Ms. Ahlport received her M.S.P.H. degree in health care administration from UNC School of Public Health and is ABD in the doctoral program in health behavior at UNC. She is a Diplomate of the American College of Healthcare Executives and has served as an adjunct lecturer in the Department of Health Policy and Administration at the UNC School of Public Health. Ms. Ahlport has been involved in numerous statewide and community health and civic initiatives throughout her career.

Michael Brennan, Ph.D., is the Senior Advisor for Global Affairs at the AERAS Global TB Vaccine Foundation. He develops strategies for the timely introduction of new TB vaccines into low-income countries, and he works closely with national regulatory authorities that are responsible for clinical trial approval and new product licensure. Brennan also

heads projects on the development of correlates and biomarkers for TB vaccines. Prior to joining AERAS, he spent more than 20 years at FDA, where he was an associate director at the Office of Vaccines Research and Review and was also head of the TB vaccine program. In 2001, he worked in Geneva assisting the World Health Organization (WHO) in its development of a new Tuberculosis Vaccine Initiative. Brennan has published more than 90 scientific articles on vaccines and infectious diseases, and his early research paved the way for widespread whooping cough immunizations. An authority on vaccine development and regulatory review, he sits on several international advisory committees, including the Stop TB Partnership, WHO, and NIH. He received a Ph.D. from Albany Medical College.

Robert Califf, M.D., graduated from Duke University, summa cum laude and Phi Beta Kappa, in 1973 and from Duke University Medical School in 1978, where he was selected for Alpha Omega Alpha. He performed his internship and residency at the University of California, San Francisco and his fellowship in cardiology at Duke University. He is board certified in internal medicine (1984) and cardiology (1986) and is a Master of the American College of Cardiology (2006). He is currently Vice Chancellor for Clinical Research, Director of the Duke Translational Medicine Institute (DTMI), and Professor of Medicine in the Division of Cardiology at the Duke University Medical Center in Durham, North Carolina. For 10 years he was the founding Director of the Duke Clinical Research Institute (DCRI), the premier academic research organization in the world. He is the editor-in-chief of Elsevier's *American Heart Journal*, the oldest cardiovascular specialty journal. He has been author or co-author of more than 800 peer-reviewed journal articles and a contributing editor for www.theheart.org, an online information resource for academic and practicing cardiologists. He was recently acknowledged as one of the 10 most cited authors in the field of medicine by the Institute for Scientific Information (ISI). Dr. Califf led the DCRI for many of the best-known clinical trials in cardiovascular disease. With an annual budget of over $100 million, the DCRI has more than 1,000 employees and collaborates extensively with government agencies, the medical products industry, and academic partners around the globe in all therapeutic areas. In cooperation with his colleagues from the Duke Databank for Cardiovascular Disease, Dr. Califf has written extensively about the clinical and economic outcomes of chronic heart disease. He is considered an international leader in the fields of health outcomes, quality of care, and medical economics. Dr. Califf's role as Director of the Duke Translational Medicine Institute, which is funded in part by an NIH CTSA, includes service as co-chairman of the Principal Investigators Steering Committee of the CTSA. Dr. Califf has

served on the Cardiorenal Advisory Panel of the FDA and the Pharmaceutical Roundtable of the IOM. He served on the IOM committees that recommended Medicare coverage of clinical trials as well as the removal of ephedra from the market and on the IOM's Committee on Identifying and Preventing Medication Errors. He is currently a member of the IOM Forum on Drug Discovery, Development, and Translation and a subcommittee of the Science Board of FDA. He was the founding director of the coordinating center for the Centers for Education and Research on Therapeutics (CERTs), a public-private partnership among the Agency for Healthcare Research and Quality, FDA, academia, the medical products industry, and consumer groups. This partnership focuses on research and education that will advance the best use of medical products. He is now the co-chairman of the Clinical Trials Transformation Initiative (CTTI), a public-private partnership focused on improving the clinical trials system.

William W. Chin, M.D., is the Executive Dean for Research at Harvard Medical School (HMS). In this role, Dr. Chin spearheads efforts to design and implement the vision for research at HMS, with special emphasis on interdisciplinary and translational research that crosses departmental and institutional boundaries. Chin is a Harvard-trained endocrinologist and longstanding faculty member. He was Professor of Medicine, HMS; Chief, Division of Genetics and Senior Physician, Brigham and Women's Hospital; and Investigator, Howard Hughes Medical Institute. His impressive career is exemplified in part by his extensive bibliography of nearly 300 papers, chapters, and books, most of which were generated during his 25 years at HMS. As a pioneering molecular endocrinologist at HMS, Dr. Chin embraced the early use of emerging DNA technology to make important discoveries regarding the structure, function, and regulation of hormone genes. His investigations often demonstrated a translational research theme, connecting basic laboratory discoveries to their physiologic relevance in animal models and humans. He has been honored with numerous awards for research, mentorship, and leadership. Prior to HMS, Dr. Chin was at Eli Lilly & Co., where he had worked for the last decade, most recently as Senior Vice President for Discovery Research and Clinical Investigation.

Andrew M. Dahlem, Ph.D., was named Vice President and Chief Operating Officer for Lilly Research Laboratories (LRL) and LRL Europe in February 2007. He has previously served as Vice President of Toxicology, Drug Disposition, Pharmacokinetics, and Lilly Research Laboratories in Europe since January 2003 and a member of Lilly senior management. Dr. Dahlem received a bachelor of science degree in wildlife biology from The Ohio State University in 1982 and a doctor of philosophy degree

in toxicology from the University of Illinois at Urbana-Champaign in 1989. Dahlem joined Lilly in 1990 as a senior pharmacologist. He became head of biochemical toxicology in 1992. He was named Director of Drug Disposition and Biochemical (investigative) Toxicology in 1993. He was promoted to Executive Director for Toxicology and Drug Disposition in 1998, and he assumed responsibility for LRL in Europe in 1999 and for discovery operations in 2000. In December 2001 he was promoted to Vice President. Dr. Dahlem serves as adjunct professor of toxicology in the College of Veterinary Medicine at Purdue University, the University of Illinois at Urbana-Champaign, and at The Ohio State University. He is also a member of the Ohio State University College of Pharmacy Corporate Council and the Illinois Professional Science Master's Board. Dr. Dahlem currently serves on the board of directors for Indigo Biosystems, the YourEncore board of advisors, and is a member of the Indiana State Museum Foundation Board. He is a member of the IOM Forum on Drug Discovery, Development, and Translation and the Translational Research and the Critical Path for Tuberculosis Drug Regimens for the Gates Foundation. He is a member and past president of Indianapolis/Cincinnati Discussion Group of the American Association of Pharmaceutical Scientists. He is also a member of the International Society for the Study of Xenobiotics, the Society of Toxicology, and the American Association for the Advancement of Science.

David L. DeMets, Ph.D., is currently professor and former Chair of the Department of Biostatistics and Medical Informatics at the University of Wisconsin-Madison. Since receiving his Ph.D. in 1970 from the University of Minnesota, he has been active in the design, conduct, and analysis of clinical trials in several disease areas. He spent 10 years (1972-1982) at the National Heart, Lung, and Blood Institute at NIH. In 1982, he joined the University of Wisconsin-Madison and developed the Department of Biostatistics and Medical Informatics. He has co-authored or edited four texts, *Fundamentals of Clinical Trials*, *Data Monitoring in Clinical Trials: A Case Studies Approach*, *Data Monitoring Committees in Clinical Trials: A Practical Perspective*, and *Statistical Methods for Clinical Trials*. He has served on numerous NIH and industry-sponsored Data Safety and Monitoring Committees for clinical trials in diverse disciplines. He served on the board of directors of the American Statistical Association, as well as having been President of the Society for Clinical Trials and President of the Eastern North American Region (ENAR) of the Biometric Society. In addition he was Elected Fellow of the International Statistics Institute in 1984, the American Statistical Association in 1986, the Association for the Advancement of Science in 1998, the Society for Clinical Trials in 2006, and the American Medical Informatics Association in 2008.

Lawrence Deyton, M.D., M.S.P.H., described by FDA Commissioner Margaret Hamburg as "the rare combination of public health expert, administrative leader, scientist, and clinician," became the Center for Tobacco Product's first director on August 19, 2009. Prior to joining FDA, Dr. Deyton was Chief Public Health and Environmental Hazards Officer for the U.S. Department of Veterans Affairs. Previously, Dr. Deyton served for 11 years in leadership positions in the NIAID at NIH, 6 years in the Office of the Assistant Secretary for Health at HHS, and as a legislative aide with the House of Representatives Subcommittee on Health and the Environment in the 1970s. He was a founder in 1978 of the Whitman Walker Clinic, a community-based AIDS service organization in Washington, DC. He is a graduate of the University of Kansas, the Harvard School of Public Health, and the George Washington University School of Medicine. Dr. Deyton's postdoctorate medical training was at USC/Los Angeles County Medical Center. He is board certified in internal medicine and continues to care for patients on a regular basis.

Uros V. Djekic, Ph.D., is a Senior Regulatory Scientist and Policy Analyst at CBER's Office of Blood Research and Review. Dr. Djekic focuses on regulatory review of blood donor screening assays and HIV diagnostics while simultaneously developing policy at the center and agency levels. He is a member of FDA's Transparency Task Force which evaluates current agency practices, regulations, and policies in order to facilitate transparency and improve public health. In 2008, he matriculated to the FDA CFP during which he developed and implemented a variety of policies related to approval and use of CBER-regulated *in vitro* diagnostics as well as initiated and drafted guidance documents. Dr. Djekic was instrumental in contributing to the Blood Products Advisory Committee discussion on home-use HIV test kits. During his tenure at the Pharmaceutical Research and Manufacturers of America (PhRMA) Division of Scientific and Regulatory Affairs, Dr. Djekic drafted a variety of pamphlets on potential bioterrorist agents, provided analyses of bioequivalence of generic drugs, and contributed to discussions relating to preparedness response to emerging and reemerging infections. Dr. Djekic completed his Ph.D. and postdoc at the University of Alabama at Birmingham. The former focused on HIV replication and primer selection, while the latter investigated the underlying principles of inflammation in the lung with a neutrophilic component.

Mary Dwight, M.D., is Vice President of Government Affairs for the Cystic Fibrosis Foundation. Dr. Dwight directs the Foundation's public policy agenda and grassroots activities. She has been a catalyst for accelerating efforts to remove barriers to clinical drug development. Dwight

also leads the strategic development of the Foundation's efforts to enable and expand access to CF care, integrating the organization's public policy, advocacy, strategic communications, and medical research and care delivery programs. Prior to coming to the Foundation, Dwight was a Vice President at Spitfire Strategies where she crafted successful policy strategy for clients such as the David and Lucile Packard Foundation, the Robert Wood Johnson Foundation, First Focus, and the Juvenile Diabetes Research Foundation. Dwight began her career with Representative Diana DeGette (D-CO), a member of the House Energy and Commerce Committee. Dwight graduated cum laude from Williams College.

Steven K. Galson, M.D., M.P.H., is Vice President of Global Regulatory Affairs at Amgen as of October 2010. He was the Senior Vice President for Civilian Health Operations and Chief Health Scientist at Science Applications International Corporation. In October 2009, he completed 23 years of government service, most recently—for 2 years—as Acting Surgeon General of the United States. Previously, he served as Director of FDA's CDER from July 2005, where he provided leadership for the center's broad national and international programs in pharmaceutical regulation. Dr. Galson began his Public Health Service (PHS) career as an epidemiological investigator at CDC after completing a residency in internal medicine at the Hospitals of the Medical College of Pennsylvania. He has held senior-level positions at the Environmental Protection Agency (EPA); the Department of Energy, where he was Chief Medical Officer; and the Department of Health and Human Services. Prior to his arrival at FDA, he was Director of EPA's Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances. Dr. Galson joined FDA in April 2001 as CDER Deputy Director. He is the recipient of numerous awards, including the Surgeon General's Medallion and three Secretary of Energy Gold Awards. Dr. Galson has been a board member of the National Board of Medical Examiners and a peer reviewer for medical journals. He holds a B.S. from Stony Brook University, an M.D. from Mt. Sinai School of Medicine, and an M.P.H. from the Harvard School of Public Health. He is board certified in preventive medicine and public health and occupational medicine.

Kathy Giacomini, Ph.D., is Professor and Co-Chair of the Department of Bioengineering and Therapeutic Sciences at UCSF. Dr. Giacomini received her Ph.D. in pharmaceutical science from the State University of New York at Buffalo and completed a postdoctoral fellowship at Stanford University. She is considered a leader in the field of pharmacogenomics of membrane transporters, having led the discovery and functional characterization of genetic variants in over 100 membrane transporters that

play a role in drug response in ethnically diverse populations. Her studies link genetic variants to clinical drug response. Dr. Giacomini has co-authored over 150 manuscripts, mentored over 20 Ph.D. students and several junior faculty, and has received many awards for her research including the Dawson Award of the American Association of Colleges of Pharmacy, and, most recently, the Scheele Award of the Swedish Academy of Pharmaceutical Scientists. In 2007, she was inducted into the IOM of the National Academies.

William Greenlee, Ph.D., is President and Chief Executive Officer of The Hamner Institutes for Health Research (formerly CIIT Centers for Health Research) and Chief Executive Officer of the Health Research and Education Foundation in Research Triangle Park, NC. He received his B.S. and M.S. degrees in chemistry from San Jose State University and a Ph.D. degree in pharmacology from the University of Rochester. After completing a postdoctoral fellowship at CIIT in 1980, Dr. Greenlee was appointed Assistant Professor of Toxicology at the Harvard School of Public Health and held a joint appointment in the Program in Cellular and Developmental Biology at the Harvard Medical School. He later returned to CIIT as a member of the senior scientific staff and in 1988 was appointed Head of the Department of Cellular and Molecular Toxicology. He was recruited to Purdue University in 1991 as Professor and Head of the Department of Pharmacology and Toxicology. From 1995 to 1999, Dr. Greenlee was Professor and Chair of the Department of Pharmacology and Molecular Toxicology at the University of Massachusetts Medical School in Worcester, Massachusetts. Dr. Greenlee is widely recognized for his research and education contributions in molecular toxicology and has published benchmark studies on the molecular basis of dioxin actions in humans. He has served on editorial boards of several journals and government advisory panels. In 2009, Dr. Greenlee was recognized as one of the 50 most powerful NC Business Leaders by *Business Leader* magazine and received the Benjamin Rush Award from Dickinson College for exceptional leaders in business or government who uphold humanistic values and whose accomplishments exemplify the value of a liberal arts education.

Gigi Hirsch, M.D., brings nearly 30 years of clinical and business experience in the health care industry to MIT's Center for Biomedical Innovation (CBI). She joined CBI in March 2006 as Senior Advisor, and became Executive Director in 2007. Her current efforts at CBI are focused largely on leading NEWDIGS, a unique collaboration focused on transforming the global health care innovation system to deliver greater value to all stakeholders and to ensure its sustainability. Dr. Hirsch has held a number of leadership roles that leverage her broad clinical background (internal

medicine, emergency medicine, and psychiatry) along with her passion for innovation, entrepreneurship, and improving patient care. Prior to joining CBI, she served as Director of Academic and Professional Relations in a biopharmaceutical company (Millennium Pharmaceuticals) and was founder and CEO of a boutique entrepreneurial venture (MD IntelliNet) that spun out of an academic research and consulting firm that she founded in partnership with Boston's Beth Israel Hospital. Dr. Hirsch completed her residency training in internal medicine and psychiatry, and practiced full-time emergency medicine for nearly 5 years at Brigham and Women's Hospital in Boston. She was an instructor in psychiatry at Harvard Medical School from 1992 to 1997. She previously held appointments in internal medicine at Harvard Medical School and Brown University after receiving her medical degree at the University of Cincinnati in 1981.

Story C. Landis, Ph.D., has been Director of NINDS since September 1, 2003. As the Director of NINDS, Dr. Landis oversees an annual budget of $1.5 billion and a staff of more than 900 scientists, physician-scientists, and administrators. The Institute supports research by investigators in public and private institutions across the country, as well as by scientists working in its intramural laboratories and branches in Bethesda, Maryland. Since 1950, the Institute has been at the forefront of U.S. efforts in brain research. Dr. Landis joined NINDS in 1995 as Scientific Director and worked with then-institute director Zach W. Hall, Ph.D., to coordinate and reengineer the Institute's intramural research programs. Between 1999 and 2000, under the leadership of NINDS Director Gerald D. Fischbach, M.D., she led the movement, together with NIMH Scientific Director Robert Desimone, Ph.D., to bring some sense of unity and common purpose to 200 laboratories from 11 different NIH Institutes, all of which conduct leading-edge clinical and basic neuroscience research. A native of New England, Dr. Landis received her undergraduate degree in biology from Wellesley College in 1967 and her master's degree (1970) and Ph.D. (1973) from Harvard University, where she conducted research on cerebellar development in mice. After postdoctoral work at Harvard University studying transmitter plasticity in sympathetic neurons, she served on the faculty of the Harvard Medical School Department of Neurobiology. In 1985 she joined the faculty of Case Western Reserve University School of Medicine in Cleveland, Ohio, where she held many academic positions including Associate Professor of Pharmacology; Professor and Director of the Center on Neurosciences; and Chairman of the Department of Neurosciences, a department she was instrumental in establishing. Under her leadership, Case Western's Neuroscience Department achieved worldwide acclaim and a reputation for excellence. Throughout

her research career, Dr. Landis has made many fundamental contributions to the understanding of developmental interactions required for synapse formation. She has garnered many honors and awards and is an elected fellow of the Academy of Arts and Sciences, the American Association for the Advancement of Science, and the American Neurological Association. In 2002, she was named the President-Elect of the Society for Neuroscience. In October of 2009, she was elected to the membership of the IOM.

H. Clifford Lane, M.D., is Deputy Director, Clinical Research and Special Projects, NIAID, NIH. Dr. Lane, a native of Detroit, Michigan, received his M.D. degree from the University of Michigan in 1976. He then completed an internship and residency at the University of Michigan Hospital, Ann Arbor, Michigan. In 1979, Dr. Lane came to NIH as a clinical associate in the Laboratory of Immunoregulation (LIR) at NIAID. In 1985, he was appointed Deputy Clinical Director, NIAID, and in 1989 he became the Chief of the Clinical and Molecular Retrovirology Section (CMRS) of the LIR, a position he still holds. In 1991, Dr. Lane became Clinical Director of NIAID and, in 2006, Director of the Division of Clinical Research and Deputy Director for Clinical Research and Special Projects. In the laboratory, Dr. Lane's early work involved studies aimed at dissecting the normal immunoregulatory mechanisms controlling the human immune response to specific antigen challenge. Within a brief time, the AIDS epidemic emerged and Dr. Lane became one of the first investigators to study immunopathogenic mechanisms of HIV disease, ultimately making seminal observations that helped establish the field of HIV immunopathogenesis. In the clinical arena, Dr. Lane has studied innovative approaches to therapy and has used experimental therapeutic interventions as a means of furthering our understanding of HIV pathogenesis. As Clinical Director of NIAID he has led efforts to identify and reduce barriers to clinical research. Dr. Lane is a member of the IOM, the American Federation for Clinical Research, the American Society for Clinical Investigation, the Association of American Physicians, the American Association of Immunologists, the American College of Physicians, the Infectious Diseases Society of America, and the Clinical Immunology Society. He has served on the editorial boards of *The Journal of Clinical Immunology* and *AIDS Research and Human Retroviruses*. He is currently on the editorial boards of *PLoS Medicine*, the *Journal of Acquired Immune Deficiency Syndromes*, *Clinical Immunology and Immunopathology*, and *AIDS Patient Care and STDs*.

Juan J. L. Lertora, M.D., Ph.D., has been Director, Clinical Pharmacology Program, Office of Clinical Research Training and Medical Education, NIH Clinical Center since July 2006. Previously, he was Professor of Medicine

and Pharmacology and Section Head of Clinical Pharmacology at Tulane University School of Medicine in New Orleans, Louisiana (1981-2006). He was Program Director, Tulane-Louisiana State University-Charity Hospital General Clinical Research Center (1998-2005) and Principal Investigator, Tulane-LSU Adult AIDS Clinical Trials Unit (1996-2005), both funded by NIH. Dr. Lertora is a graduate of the Faculty of Medicine, National University of the Northeast, Corrientes, Argentina, and the Graduate School, Department of Pharmacology, Tulane University. He received a Merck Sharp and Dohme International Fellowship in Clinical Pharmacology at Tulane, completed training in internal medicine at the University of Connecticut, and a clinical pharmacology fellowship at the University of Iowa. He was Assistant Professor of Medicine and Pharmacology, Clinical Pharmacology Center, Northwestern University in Chicago (1977-1981) and received a Faculty Development Award from the Pharmaceutical Manufacturers Association Foundation (now the PhRMA Foundation). Dr. Lertora serves on the editorial board of *Clinical Pharmacology and Therapeutics*, the FDA Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology, and the Board of Directors of the American Society for Clinical Pharmacology and Therapeutics (2007-2011). He is Adjunct Professor of Medicine at Duke University. Dr. Lertora conducted phase I-II safety and efficacy clinical trials and studied pharmacokinetics-pharmacodynamics, drug metabolism, pharmacogenetics, and drug interactions of antiretroviral drugs. Previous research included erythropoietin's role in the anemia of chronic renal disease, the dose-related cardioselectivity of practolol, the antiarrhythmic-inotropic actions of NAPA (N-acetylprocainamide), the cardiovascular actions of NAPADE (desethyl-N-acetylprocainamide), CYP2E1, and chlorzoxazone metabolism, and pharmacokinetics of ribavirin and peg-interferon alfa-2a in HIV-infected patients.

Xavier Luria, M.D., is a qualified medical doctor, postgraduate fellow in internal medicine, and postgraduate qualifications in pharmaceutical medicine, in biostatistics, and in clinical pharmacology, drug development, and regulation. Dr. Luria worked in Barcelona (Spain) as an internal medicine physician, as assistant of physiology, and assistant in gastrointestinal and psychosomatic disorders. In 1987, he joined a pharmaceutical company as a medical doctor in clinical research and in 1990 became Head of Clinical Research. In 1995 he was nominated Medical Director with responsibility for international clinical development, biometry, pharmacovigilance, and global medical affairs. He has been a member of working groups in the Spanish (Farmaindustria) and European pharmaceutical industry associations (EFPIA). He participated in a number of ICH initiatives and was also a member of the DIA Steering Committee Europe until 2004. He has been involved in a number of activities with

FDA, Japanese health authorities, and European national regulatory bodies. He has contributed as a speaker in several training courses and conferences and as a lecturer in some university master's degree programs. He joined the EMA, London, in December 2005 as Head of Safety and Efficacy of Medicines.

Emma Meagher, M.D., was born in Dublin, Ireland. She graduated with her medical doctorate degree from the Royal College of Surgeons in Ireland and following completion of a residency in internal medicine she was appointed as Senior Registrar/Lecturer of Cardiovascular Medicine at Mater Hospital, University College Dublin, Ireland. She joined the faculty at the University of Pennsylvania in 1995 and is currently Associate Professor of Medicine and Pharmacology and Director of the Translational Research Training Programs at the University of Pennsylvania School of Medicine. In addition she serves as a Co-PI on the Penn CTSA and is the Executive Chair of the University of Pennsylvania IRB.

Annette Mollet, Ph.D., received her M.Sc. in pharmacy in 1989 from the University of Basel. She worked on her thesis in developmental neurobiology at the Swiss Federal Institute of Technology (ETH) in Zurich, where she received her Ph.D. in 1994. During that time she taught pharmacology and toxicology at the School of Oral Hygiene in Zurich. Dr. Mollet worked at F. Hoffmann-La Roche in the Clinical R&D department until 1996. Subsequently she conducted clinical trials in the field of AIDS and anticoagulation therapeutics and worked as a medical and product manager responsible for oncology at Roche Pharma (Schweiz). Dr. Mollet's present position is Head of Education and Training at the ECPM at the University of Basel. She became a member of the Expert Committee for the Evaluation and Registration of Radioactive Drugs at the Swissmedic (Swiss Agency for Therapeutic Products) and the BAG (Swiss Federal Office of Public Health) in 1993 and was elected president in 2008. Since 1999, Dr. Mollet has been a member of the board of the Swiss Association of Pharmaceutical Professionals (SwAPP) and specialized in pharmaceutical medicine in 2000. She chaired the commission for specialty training and continuous education (CPD) of SwAPP until 2009. Dr. Mollet is also involved in the creation of a European Specialist title in Pharmaceutical Medicine and a Master title in Drug Development Sciences within the IMI joint undertaking, PharmaTrain.

Carl Peck, M.D., obtained a B.A. in mathematics and chemistry from the University of Kansas in 1963 and an M.D. in 1968. Following training in internal medicine, he undertook a research fellowship in clinical pharmacology at the University of California, San Francisco (1972-1974). From

1974 to 1980, Dr. Peck was employed at the Letterman Army Institute of Research, San Francisco, California, as Chief of the Army Blood Preservation Research Program. In 1980, Dr. Peck became Director of the Division of Clinical Pharmacology and Professor, Departments of Medicine and Pharmacology, Uniformed Services University, Bethesda, Maryland. Dr. Peck joined FDA as Director, CDER, in October 1987. He was promoted to Assistant Surgeon General in the Public Health Service in October 1990. Retiring from FDA in late 1993, Dr. Peck was appointed "Boerhaave" Professor of Clinical Drug Research at Leiden University in The Netherlands. In 1994 Professor Peck joined the faculty of the Georgetown University Medical Center as the founding Director of the Center for Drug Development Science. In 1999, Dr. Peck received the FDA Distinguished Alumnus Award. Sweden's University of Uppsala conferred an honorary doctorate degree (Doctor Honoris Causa) to Dr. Peck in January 2002 in recognition of "outstanding contributions to the science of drug development." Dr. Peck founded NDA Partners LLC in 2003 and, in 2004, CDDS moved to UCSF, located in the UC-Washington Center. Throughout his career, he has mentored more than 40 postdoctoral fellows and graduate students and co-founded the American (2007) and Chinese (2009) Courses in Drug Development and Regulatory Science (ACDRS, CCDRS). Dr. Peck's research interests center on optimizing informativeness, efficiency, speed, and economy of drug development and regulation using advanced concepts and techniques of clinical pharmacology, trial designs, and pharmacostatistical modeling and simulation to generate causal evidence of effectiveness and safety. He is an author of more than 150 original research papers, chapters, and books.

Munir Pirmohamed, Ph.D., qualified in medicine in 1985, undertook a Ph.D. in pharmacology in 1993 and was appointed consultant physician at the Royal Liverpool University Hospital in 1996. He was awarded a Personal Chair in Clinical Pharmacology at the University of Liverpool in 2001, and in 2007, was appointed to the NHS Chair of Pharmacogenetics. He is Director of the Wolfson Centre for Personalised Medicine, Deputy Director of the Medical Research Council CDSS in Liverpool, and Head of the Department of Molecular and Clinical Pharmacology at the University of Liverpool. Professor Pirmohamed is a Member of the Commission on Human Medicines and Chair of its Pharmacovigilance Expert Advisory Group. His main area of research is in pharmacogenetics and drug safety. Adverse reactions to drugs are a major cause of illness in the population. The research aims to maximize the benefits of drugs and minimize their harms. This is being achieved through the use of different strategies ranging from improvements in prescribing to the development of genetic

and other tests for predicting and monitoring individual susceptibility to toxicity.

Theodore F. Reiss, M.D., was born in New Jersey. He attended the University of Pennsylvania, with majors in history and biology, and Vanderbilt Medical School, where he served his medical internship. His medical residency was performed at Columbia University and he performed his clinical training in pulmonary and critical care and his research training in airway pharmacology at UCSF. Thereafter, he joined Merck Research Laboratories, where he worked for 18 years, ultimately serving as Vice President, Clinical Research. He was responsible for development across a number of therapeutic areas including bone/muscle, gastroenterology, urology, and most importantly respiratory and allergy, where he led the team responsible for the development of the leukotriene antagonist montelukast. He also made significant scientific contributions to other therapies, notably alendronate and aprepitant. In 1998 he received the Merck Directors' award, the company's highest award for scientific achievement, for his work on montelukast. Following his time at Merck, he served as Corporate Vice President, Global Integrated Drug Development, at Covance and has taught translational science and drug development at the University of Pennsylvania School of Medicine. He currently serves as Research Professor of Medicine at Vanderbilt University School of Medicine and is a candidate for a master of bioethics at the University of Pennsylvania.

Vicki L. Seyfert-Margolis, Ph.D., is Senior Advisor within Science Innovation and Policy for the FDA Commissioner's Office. Dr. Seyfert-Margolis focuses on initiatives in regulatory science, personalized medicine, and scientific computing and informatics. Previously, she served as Chief Scientific Officer at Immune Tolerance Network (ITN), a nonprofit consortium of researchers seeking new treatments for diseases of the immune system. At ITN, she oversaw the development of more than 20 centralized laboratory facilities and the design and execution of biomarker discovery studies for over 25 Phase II clinical trials. As part of the biomarker efforts, she established construction of a primer library of 1,000 genes that may be involved in establishing and maintaining immunologic tolerance and co-discovered genes that may mark kidney transplant tolerance. Dr. Seyfert-Margolis was also an adjunct associate professor with the Department of Medicine at UCSF. Prior to academia, she served as Director of the Office of Innovative Scientific Research Technologies at NIAID, NIH, where she worked to integrate emerging technologies into existing immunology and infectious disease programs. Dr. Seyfert-Margolis completed her Ph.D. in immunology at the University of Pennsylvania's School of Medicine.

Dr. Seyfert-Margolis co-authored an article in the *New England Journal of Medicine* July 15, 2010, issue titled "Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis."

Ellen V. Sigal, Ph.D., is Chairperson and Founder of Friends of Cancer Research ("Friends"), a cancer research thinktank and advocacy organization based in the Washington, DC, metropolitan area. Friends is dedicated to accelerating the nation's progress toward prevention and treatment of cancer by mobilizing public support for cancer research funding and providing education on key public policy issues. For more than 14 years, Friends has pioneered innovative public-private partnerships, organized critical policy forums, educated the public, and brought together key communities to develop collaborative strategies in the field of cancer research. 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 FDA. She serves on the NIH Foundation Board chairing its Public-Private Partnerships Committee, the American Association for Cancer Research Foundation Board, and the Research!America Board. Dr. Sigal is a member of 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 holds leadership positions with a broad range of cancer advocacy and public policy organizations, and leadership positions with academic health centers including the M.D. Anderson Cancer Center External Advisory Board, the Duke University Cancer Center Board of Overseers, and the Sidney Kimmel Comprehensive Cancer Center Advisory Council. She serves on the C-Change Research Committee and the Entertainment Industry Foundation Oversight Committee for the Biomarker Discovery Project. Dr. Sigal was recently named to the Patient-Centered Outcomes Research Institute (PCORI) Board of Governors as a representative of patients and health consumers. During her more than 20-year commitment to cancer research, Dr. Sigal has served in a number of critical public positions. She served on the NCI Board of Scientific Advisors from 2003 to 2009, and the NIH Director's Council of Public Representatives from 2003 to 2006. She was a Presidential Appointee to the National Cancer Advisory Board from 1992 to 1998, where she chaired the Budget and Planning Committee that oversees the federal cancer budget. In 1998, Dr. Sigal was named Vice Chairman of the Board of The March, a national grassroots advocacy group that brought thousands of volunteers to Washington to liaise with Congress and to set a new advocacy agenda for cancer research and treatment. She is a past member of the American Society of Clinical Oncology Foundation Board. Dr. Sigal has also been instrumental in harnessing the

energies of Hollywood on behalf of cancer research, serving as President of the Creative Community Task Force for Cancer Research.

Ralph Snyderman, M.D., served as Chancellor for Health Affairs and Dean of the School of Medicine at Duke University from 1989 to July 2004 and led the transition of this excellent medical center into an internationally recognized leader of academic medicine. During his tenure, the medical school and hospital achieved ranking among the nation's best. He oversaw the development of the Duke University Health System, one of the most successful integrated academic health systems in the country, and served as its first President and Chief Executive Officer. Dr. Snyderman has played a leading role in the conception and development of Prospective Care, a novel approach to personalized health and an evolving model of national health care delivery. He was among the first to envision and articulate the need to move the current focus of health care from treatment of disease events to personalized, predictive, preventative, and participatory care. His approach, termed Prospective Care, embraces strategic health planning rather than reactive responses to late-stage chronic disease. Dr. Snyderman has been widely recognized for his contributions to the development of more rational, effective, and compassionate models of health care. He was awarded the first Bravewell Leadership Award for outstanding achievements in the field of integrative medicine in 2003. Dr. Snyderman received the 2007 Leadership in Personalized Medicine Award in November 2007 from the Personalized Medicine Coalition for his efforts in advancing predictive and targeted therapies on a national scale. In May 2008, he received the prestigious Industrial Research Institute's Medal for his outstanding accomplishments in technological innovations that contribute to the development of industry and to the benefit of society. In November 2008, Dr. Snyderman received Frost & Sullivan's North American HealthCare Lifetime Achievement Award for his pioneering spirit and contributions to medicine. In March 2009, he received the Triangle Business Journal's Healthcare Lifetime Achievement Award. In February 2010, Procter & Gamble named Dr. Snyderman an honorary member of the Victor Mills Society for his leadership and impact on innovation. In April, he was awarded the Clinical Research Forum's 2010 Leadership in Academic Health Centers award. Dr. Snyderman was recognized as a Bioscience Leader Emeriti by the North Carolina Association for Biomedical Research in 2010, honoring North Carolina research leaders for their outstanding leadership in research and development and in the transformation of the state through scientific discovery and innovation. Dr. Snyderman has played a prominent role in the leadership of such important national organizations as the Association of American Physicians, the IOM, and the Association of American Medical Colleges. He is

a member of the IOM and the American Academy of Arts and Sciences. He served as Chair of the AAMC in 2001-2002 and President of AAP in 2003-2004. He chaired the IOM's National Summit on Integrative Medicine and the Health of the Public held in February 2009. Dr. Snyderman accepted his first faculty appointment at Duke in 1972 and, by 1984, he was the Frederic M. Hanes Professor of Medicine and Immunology. His research contributed to the understanding of how white blood cells respond to chemical signals to mediate host defense or tissue damage and he is internationally recognized for his contributions in inflammation research. In 1987, Snyderman left Duke to join Genentech, Inc., the pioneering biomedical technology firm, as Senior Vice President for Medical Research and Development. While at Genentech, he led the development and licensing of several major biotechnology therapeutics. He is the recipient of numerous other honors, including the CIBA GEIGY Award in 1992, the highest prize in inflammation research; the 1993 Bonazinga Award for Excellence in Leukocyte Biology Research; and the award of designation as the American College of Rheumatology Master in 2005. Snyderman was honored with the Lifetime Achievement Award from the Arthritis Foundation in 1997. In 1995, Downstate Medical Center of the State University of New York awarded him with their Distinguished Alumni Achievement Award and, in 1996, an honorary doctor of science degree. In 2003, he received the Ellis Island Medal of Honor presented to outstanding Americans who have distinguished themselves among their specific ethnic groups and have made significant contributions to our country. Snyderman received the George Eastman Medal from the University of Rochester School of Medicine in May 2003 and, in 2004, received an honorary doctor of science degree from Washington College. A graduate of Washington College in Chestertown, Maryland (1961), Snyderman received his M.D., magna cum laude, in 1965 from the Downstate Medical Center of the State University of New York. He served his internship and residency in medicine at Duke and later worked as a Public Health Officer doing research in immunology at the NIH (1967-1972). His bibliography exceeds 375 manuscripts as well as numerous books.

Henrietta N. Ukwu, M.D., FACP, FRAPS, is Senior Vice President, Global Regulatory Affairs, PPD Inc. Dr. Ukwu is a physician-internist and infectious disease specialist. She completed her fellowship in infectious diseases at Vanderbilt University, Nashville, Tennessee; her residency in internal medicine at Baptist Hospital, Nashville, Tennessee; and her internship in internal medicine at Meharry–Hubbard Hospital, Nashville, Tennessee. Dr. Ukwu holds medical and surgical degrees from the University of Jos, Nigeria. Dr. Ukwu, an internist and infectious disease physician, is a biopharmaceutical industry executive and industry

thought leader with extensive global regulatory experience across many biopharmaceutical therapeutic platforms and all regions. Currently, she is Senior Vice President and Head of Global Regulatory Affairs for PPD Inc. Dr. Ukwu recently authored *Global Regulatory Systems: A Strategic Primer for Biopharmaceutical Products Development and Registration*—a landmark first-of-its-kind textbook for regulatory and biopharmaceutical industry professionals. Beginning her pharmaceutical industry career at Merck & Co. in 1992, Dr. Ukwu became Vice President and Head of Vaccine Worldwide Regulatory Affairs in 1998, and Vice President of Global Regulatory Policy in 2002. She joined Wyeth Pharmaceuticals in 2004 as Vice President of Global Regulatory Affairs, with responsibility for all therapeutic areas across all platforms—vaccines, biologics, and pharmatherapeutics. In 2009, she became Vice President of Worldwide Regulatory Affairs for Pfizer Inc. Dr. Ukwu has led regulatory efforts for vaccines, biologics, and pharmatherapeutics platforms in the United States, Canada, Europe, Asia Pacific, Latin America, Middle East, Africa, and the WHO. She has been responsible for overseeing strategic product development and registration plans, regulatory interactions with boards of health, human subject protection for clinical/preclinical development, rigorous regulatory standards, and successful registration of new drugs/biologics. She has been involved in many product development activities and has directly led the successful original regulatory development, filings, and approvals of 14 new products. Dr. Ukwu has built strategic regulatory teams, led major initiatives to drive regulatory excellence, and made significant contributions to developing and enriching the regulatory profession. Under Dr. Ukwu's leadership, PPD's global regulatory affairs organization, which encompasses global regulatory development, global regulatory consulting, and strategic intelligence, global chemistry, manufacturing and controls, global medical writing, global devices/diagnostics, and global regulatory operations is strengthening its focus on the provision of strategic regulatory intelligence and expertise to enable Bio-Pharma to successfully navigate today's dynamic and complex global regulatory landscape. A fellow of both the American College of Physicians (ACP) and RAPS, Dr. Ukwu is an adjunct professor at the Graduate School of Pharmacy, Division of Quality Assurance and Regulatory Affairs, at Temple University in Pennsylvania. She has received numerous awards for her outstanding contributions to medicine, science, and industry, including recent recognition as one of 100 most inspiring leaders by PharmaVoice, July 2011. She has authored professional and scientific publications and has given many lectures, keynote speeches, and presentations.

Melinda Wharton, M.D., M.P.H., was appointed Deputy Director of the National Center for Immunization and Respiratory Diseases at CDC in

August 2006. Dr. Wharton is a Captain in the U.S. Public Health Service (USPHS). She holds an M.D. from Harvard Medical School and an M.P.H. from the Johns Hopkins School of Hygiene and Public Health. She completed internship and residency in internal medicine at the University of Michigan Medical Center and her infectious diseases fellowship at the Duke University Medical Center. Dr. Wharton was commissioned as a CDC epidemic intelligence service officer in 1986 and was assigned to the Tennessee Department of Health and Environment in Nashville. In 1989, she joined CDC as a Medical Epidemiologist in the Epidemiology Program Office. She joined the National Immunization Program (NIP) in 1992, holding chief positions in the Infant Immunization Section, the Surveillance, Investigations, and Research Branch, and the Child Vaccine Preventable Diseases Branch, Epidemiology and Surveillance Division. She also served as Director of the Epidemiology and Surveillance Division. In January 2004, she became Acting Deputy Director of NIP. Dr. Wharton has authored or co-authored more than 80 scientific journal articles, book chapters, and CDC publications, including *Morbidity and Mortality Weekly Report* articles.

Leslie D. Wheelock, M.S., R.N., is the Director of the Office of Scientific Professional Development (OSPD) in the Office of the Chief Scientist at FDA. The OSPD manages FDA-wide scientific training and professional development programs to include the CFP, professional development activities, scientific exchanges, and scientific achievement award. Prior to her position as OSPD Director, she was the Director of the Division of Manufacturers Assistance and Training at the CBER, FDA, for 6 years. Previously, Leslie worked for the FDA's CDER, where she was as an Associate Director for Safety Outreach and Communication co-leading FDA's Mid-Progress Review for Healthy People 2010 Focus Area Chapter 17, Medical Product Safety. At CDER, she also worked as a Regulatory Health Education Specialist Team Leader serving as the Program Manager for CDER's Competency Based Training Program, which received the federal government's 2000 W. Edward Deming Outstanding Training Award. Before joining FDA in 1997, Leslie was Nurse Director of the Clinical Research Department at the Washington Cancer Institute, Washington Hospital Center, and she also worked as a Clinical Nurse Specialist and Clinical Nurse Educator at the NIH Clinical Center supporting the NCI's Intramural Research Program. As an oncology nurse, she held certifications from the Oncology Nursing Society as an Oncology Certified Nurse (OCN) and Advanced Oncology Certified Nurse (AOCN). Leslie earned a B.A. in biology from Hood College and M.S. in nursing from the University of Maryland. She additionally has graduate education in adult

learning and human resource development from Virginia Polytechnic Institute and State University.

Jonathan S. Wiest, Ph.D., obtained a bachelor's degree in analytical chemistry from the University of Wisconsin-Milwaukee in 1980. He worked as a production chemist synthesizing oligonucleotides for P-L Biochemicals until he began graduate school in 1982 at the Medical College of Ohio in Toledo. Dr. Wiest received a Ph.D. in biochemistry in 1988 and then did a postdoctoral fellowship at the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina. He rose to the rank of Senior Staff Fellow and then assisted in establishing a Cancer Research Institute in western Colorado. In 1996 he became an assistant professor at the University of Cincinnati, Department of Environmental Health, School of Medicine. Dr. Wiest joined the Center for Cancer Research at the NCI as the Associate Director for Training and Education in November 2001. In 2007 Dr. Wiest was appointed by the NCI Director to serve as the Acting Director for the Cancer Prevention Fellowship Program and in early 2008 the NCI Director also appointed Dr. Wiest to lead the formation of the Center for Cancer Training (CCT) as the director. The CCT is charged with coordinating the major training activities in the NCI in both the intramural and extramural communities. In 2003, Dr. Wiest received the NIH Director's Award for Mentoring as well as the NCI Outstanding Mentor award. In November 2007 he received an NIH Award of Merit for mentoring. The major focus of his research involves genetic alterations in lung tumorigenesis. He is involved in studies to identify tumor suppressor genes and altered signaling pathways in lung cancer.

Carolyn Wilson, Ph.D., received her Ph.D. in genetics from George Washington University while working in the laboratory of Dr. Robert Gallo for her dissertation research. For her postdoctoral fellowship, she worked in the laboratory of Dr. Maribeth Eiden identifying viral and cellular factors influencing viral entry. She joined the Division of Cellular and Gene Therapies (DCGT) at CBER, FDA, in 1993. As a researcher-reviewer in DCGT, she reviewed INDs and developed policy and guidance documents in two novel product areas: gene therapy and xenotransplantation. More recently, Dr. Wilson has served as the Associate Director for Research (ADR) at CBER. As ADR, Dr. Wilson ensures that CBER's research is relevant, high quality, and provides CBER with the appropriate scientific expertise, tools, and data to support regulatory decision making and policy development. Dr. Wilson still maintains her own laboratory program studying retroviruses which are either used as vectors for gene therapy clinical trials or are of concern in the xenotransplantation setting.

Alastair J. J. Wood, M.D., was Professor of both Medicine and Pharmacology, Assistant Vice Chancellor, and Associate Dean at Vanderbilt Medical School before being appointed Emeritus Professor of Medicine and Emeritus Professor of Pharmacology in 2006. His current academic appointments are Professor of Medicine and Professor of Pharmacology at Weill Cornell Medical College, New York. He is a Partner at Symphony Capital LLC, a New York–based Private Equity Company. Dr. Wood is a member of the IOM, the American Association of Physicians (AAP), the American Society for Clinical Investigation (ASCI); Honorary Fellow, American Gynecological and Obstetrical Society (AGOS); and Fellow of the American College of Physicians. Dr. Wood served on the *New England Journal of Medicine* (*NEJM*) Editorial Board and was the *NEJM* Drug Therapy Editor for many years. He authored the chapter in Harrison's *Principles of Internal Medicine* on adverse drug reactions from the 9th through the 15th editions. He was the chairman of the FDA's Nonprescription Drugs Advisory Committee until 2006 and chaired the 2005 FDA Advisory Committee on Cox-2 inhibitors. He previously served as a member of the Cardiovascular and Renal Advisory Committee of the Food and Drug Administration, and the FDA's Nonprescription Drugs Advisory Committee. His research interests have been focused on understanding the mechanisms for interindividual variability in drug response and toxicity. His research has resulted in over 300 articles, reviews, and editorials.