Advancing the Discipline of Regulatory Science for Medical Product Development: An Update on Progress and a Forward-Looking Agenda: Workshop Summary

DETAILS

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ADVANCING THE DISCIPLINE OF REGULATORY SCIENCE FOR MEDICAL PRODUCT DEVELOPMENT

An Update on Progress and a Forward-Looking Agenda

Workshop Summary

Morgan L. Boname, Amanda Wagner Gee, and Anne B. Claiborne,
Rapporteurs

Forum on Drug Discovery, Development, and Translation

Board on Health Sciences Policy

Health and Medicine Division

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This workshop summary has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published workshop summary as sound as possible and to ensure that the workshop summary 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 workshop summary:

Brian Alexander, Harvard Medical School
Jesse Goodman, Georgetown University
Peter Honig, Pfizer Inc.

Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the workshop summary before its release. The review of this workshop summary was overseen by **Barry S. Coller,** The Rockefeller University. He was responsible for making certain that an independent examination of this workshop summary was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this workshop summary rests entirely with the rapporteurs and the institution.

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Acronyms and Abbreviations

AD	Alzheimer's disease
ADPKD	autosomal dominant polycystic kidney disease
API	application program interface
BLAERS	Behavioral Log-Based Adverse Event Reporting System
BQRT	Biomarker Qualification Review Team
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CDRH	Center for Devices and Radiological Health
CERSI	Center of Excellence in Regulatory Science and Innovation
COU	context of use
C-Path	Critical Path Institute
CPIM	Critical Path Innovation Meeting
cTAP	collaborative Trajectory Analysis Program
CTSA	Clinical and Translational Science Award
DMD	Duchenne muscular dystrophy
EHR	electronic health record
EMA	European Medicines Agency
FAERS	FDA Adverse Event Reporting System
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act of 2007

FHIR	Fast Healthcare Interoperability Resources
fMRI	functional magnetic resonance imaging
FNIH	Foundation for the National Institutes of Health
HL7	Health Level Seven International
IND	Investigational New Drug
IOM	Institute of Medicine
IRSA	Innovations in Regulatory Science Awards
MDEpiNet	Medical Device Epidemiology Network
NDA	New Drug Application
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
P*h*RMA	Pharmaceutical Research and Manufacturers of America
PK/PD	pharmacokinetic/pharmacodynamic
PMDA	Pharmaceuticals and Medical Devices Agency
PSTC	Predictive Safety Testing Consortium
RCT	randomized controlled trial
UCSF	University of California, San Francisco

1

Introduction[1]

The field of endeavors known as "regulatory science" has grown out of the need to link and integrate knowledge within and among basic science research, clinical research, clinical medicine, and other specific scientific disciplines whose focus, aggregation, and ultimate implementation could inform biomedical product development and regulatory decision making. The U.S. Food and Drug Administration (FDA) defines regulatory science as "the science of developing new tools, standards, and approaches to assess the safety, effectiveness, quality, toxicity, public health impact, or performance of FDA-regulated products."[2] Substantial efforts have been devoted to defining regulatory science and communicating its value and role across the scientific and regulatory ecosystems. Investments are also being made in technology infrastructure, regulatory systems, and workforce development to support and advance this burgeoning discipline.

Since its inception, the Forum on Drug Discovery, Development, and Translation (the Forum) of the National Academies of Sciences, Engineering, and Medicine (the Academies) has focused on the need for strengthening the scientific basis of drug regulation. In February 2010, the Forum

[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. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the Forum or the Academies, and they should not be construed as reflecting any group consensus.

[2] See http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm268095.htm (accessed April 11, 2016).

held a workshop that was summarized in the Institute of Medicine (IOM) report *Building a National Framework for the Establishment of Regulatory Science for Drug Development: Workshop Summary* (IOM, 2011), which examined the state of the science of drug regulation and considered approaches for enhancing regulatory science. In September 2011, the Forum convened another workshop that was summarized in the report *Strengthening a Workforce for Innovative Regulatory Science in Therapeutics Development: Workshop Summary* (IOM, 2012), which considered opportunities and needs for advancing innovative regulatory science through workforce and career development.

Over the past several years, models to support the discipline of regulatory science have advanced. FDA's Centers of Excellence in Regulatory Science and Innovation (CERSIs) enhance training and educational opportunities for regulatory scientists. Private funders have also established programs; for example, in 2011, the Burroughs Wellcome Fund launched its Innovations in Regulatory Science Awards (IRSA) initiative, which aims to strengthen regulatory systems capacity by funding regulatory science–based research and collaborations.

On October 20–21, 2015, the Forum held a public workshop to facilitate dialogue among stakeholders about the current state and scope of regulatory science, opportunities to address barriers to the discipline's success, and avenues for fostering collaboration across sectors. The workshop, co-sponsored by the Burroughs Wellcome Fund, held discussion panels that explored key needs for strengthening the discipline of regulatory science, including considering what are the core components of regulatory science infrastructure to foster innovation in medical product development.

The field of regulatory science is broad and touches many aspects of research. This workshop did not attempt to comprehensively discuss all the challenges and opportunities facing the field. To focus the discussions, the planning committee adopted the theme of *innovation in regulatory science through integration of information*. Presenters and participants were invited to examine and discuss how large-scale generation of information, particularly in light of the recent advent of "big data," presents new opportunities to strengthen the connections among the regulatory science disciplinary components and advance the field (see Box 1-1 for the full Statement of Task).

ORGANIZATION OF THIS REPORT

This report is a summary of the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants and are not necessarily endorsed or verified by the Forum or the Academies, and they should not be construed as reflecting any group con-

BOX 1-1
Statement of Task

An ad hoc planning committee will plan a 1-day workshop, to be convened as a collaboration between the National Academies of Sciences, Engineering, and Medicine and the Burroughs Wellcome Fund, that will discuss issues related to the development of the discipline of innovative regulatory science for medical product development, focusing on infrastructure, systems, and workforce. Specifically, the workshop will explore (1) the current scope and status of federal, academic, and private regulatory science strategic priorities; and (2) progress made in establishing workforce training and other infrastructure to advance the discipline of innovative regulatory science.

Subject-matter experts will be invited to discuss key needs for further establishing and strengthening the discipline, and to explore priorities and potential opportunities for collaboration to address those needs. The workshop will include consideration of the core components of the regulatory science infrastructure that include the workforce, process, and systems in the public and private sectors needed to foster innovation in medical product development and evaluation methodologies, with attention to the entire product development life cycle.

The workshop will feature invited presentations and discussions that will:

- Explore current regulatory science priorities and strategies in federal, academic, and private-sector settings.
- Consider the current state of regulatory science as a discipline.
  - Discuss professional training successes.
  - Highlight opportunities to further support training, workforce, and career development.
- Explore the core components of a robust discipline of innovative regulatory science.
  - Consider gaps and key opportunities to address needs to support the discipline of innovative regulatory science.
- Examine needs and barriers to collaboration among, across, and within the public and private sectors.

sensus. The workshop was webcast live, and online participants were able to contribute to the discussions through the hashtag #RegulatoryScience. The presentations, videos, and tweets are archived on the Forum website.[3]

[3] For more information, see http://nationalacademies.org/hmd/Activities/Research/DrugForum/2015-OCT-20.aspx (accessed April 5, 2016).

The summary is organized as follows:

- Chapter 2 characterizes the current landscape of information integration in regulatory science presented at the meeting.
- Chapter 3 summarizes discussion of four case studies of regulatory science applications that served as focal lenses to illuminate how enhanced approaches to obtaining, accessing, and integrating information could advance the science throughout and across medical product development. The four case studies were as follows:
  - Identification and Development of Meaningful Biomarkers
  - Integrating Clinical Trial Data
  - Next-Generation Surveillance
  - Innovative Modeling for Integrating Data
- Chapter 4 describes needs for regulatory science infrastructure and workforce.
- Chapter 5 summarizes challenges, opportunities, and key focus areas for advancing regulatory science offered by individual workshop participants.

2

Characterizing the Regulatory Science Landscape

Key Messages Identified by Individual Speakers

- Regulatory science is a broad discipline, calling for integration of a large variety of subject areas and an ability to synthesize information from many sources. (Altman, Rogers, Stevens)
- Information available for regulators is growing exponentially, and this influences decisions about where the field is going. (Ostroff, Wood)
- The FDA has a critical need to develop and smoothly adopt innovative decision-making methods without compromising safety and efficacy standards; constant training of regulatory scientists and evaluation of the regulatory science field will help to improve the discipline over time and to attract new talent. (Fields, Meyer, Ostroff, Stevens, Weichold)

In considering ways to further advance the discipline of regulatory science, the workshop focused on ways in which information can be best generated, analyzed, integrated, and shared across regulatory science applications. In the opening session, workshop co-chair Alastair Wood, partner, Symphony Capital, and Professor of Medicine and Pharmacology, Weill Cornell School of Medicine, observed that there has been an explosion in the information available to the regulator that did not exist even 2 or 3 years ago. "We used to live in a data-poor, opinion-rich environment—now,

we live in a *data-rich*, opinion-rich environment," he said. Wood asked the workshop participants to consider how the field can progress toward achievable endpoints and to accomplish real, implementable change.

The discipline of regulatory science is grounded in a fundamental knowledge of basic and clinical science and medicine. Those involved in the regulatory science discipline could integrate an array of complex issues: in addition to having command over the science, they could have a working knowledge of governmental legislation and regulations, as well as of industry and academic standards and policies. In addition, they must be able to effectively communicate such complexities across diverse segments of society, said Mark C. Rogers, board chairman, Reagan-Udall Foundation. Jim Stevens, Distinguished Research Fellow, Eli Lilly, also emphasized the importance of the regulatory scientist's ability to integrate information longitudinally across dimensions. "We need to interpret data in a context of prior and future experience," he said, and "we need to be able to link known and unknown biology with safety outcomes." Stephen Ostroff, acting commissioner, FDA (at the time of the workshop), and workshop keynote speaker, noted that to accomplish these challenges, it would prove valuable for the greater scientific and clinical ecosystem to think broadly about the definition of the regulatory science endeavor, beyond FDA functions.

INNOVATIVE SCIENCE AT FDA

As the nation's principal consumer product protection agency and promoter of the nation's public health and health care systems, FDA serves as the linchpin of regulatory science. In its 2007 report *FDA Science and Mission at Risk* (FDA, 2007), the FDA Science Board concluded that FDA was suffering from scientific deficiencies and an inability to meet current and emerging responsibilities. Ostroff noted that since the report was issued in 2007 FDA has been the subject of increased regulatory responsibilities aimed at bolstering science at the agency.[1] Ostroff observed that a follow-up 2015 FDA Science Board report *Mission Possible: How FDA Can Move at the Speed of Science* took note of progress at the agency. "The responsiveness of FDA to the *Mission at Risk* report and those responsible for overseeing its work has been extensive, transformative, and laudable. Many substantive changes have been made in FDA's organization, authorities,

[1] Ostroff cited a number of initiatives as new or potential legislative mandates, including the FDA Amendments Act of 2007 (2007); the Tobacco Control Act (2009); the Food Safety Modernization Act (2011); the FDA Safety and Innovation Act (2012); the Drug Quality and Security Act (2013); and the U.S. House of Representatives' 21st Century Cures Act and the U.S. Senate's Medical Innovation Act (2015).

and programs that significantly address issues identified in 2007" (FDA, 2015, p. 4).

In addition to its accolades, the 2015 *Mission Possible* report included several recommendations for the agency. The recommendations addressed opportunities for improvement in the following areas:

- Medical product innovation
- Food safety and applied nutrition
- Product manufacturing and quality
- Modernizing toxicology
- Leadership and coordination

Ostroff summarized the report's recommendations with the following perspective, "We [at FDA] need to study and support development of innovative ways to streamline, supplement, and speed medical product availability without having any negative impact on what we consider to be the FDA gold standard of being able to evaluate product efficacy and safety."

Numerous workshop participants stressed that rigorous evaluation of the contemporary state of regulatory science will be instrumental in dynamically regulating the scientific and medical enterprises of the future. Many participants noted the difficulty in objectively evaluating regulatory science because it is not assessed by traditional scientific measures such as statistical analyses or peer-reviewed literature. Therefore, they suggested that the public health impact of regulatory decisions could serve as a benchmark for evaluating the effectiveness of certain regulatory science initiatives. In turn, there was support for the concept of integrating a process that allows regulatory science to respond in real time and learn from past or ongoing experiences within FDA's data and evaluation systems. Frank Weichold, director, Science and Innovation, Office of the Chief Scientist/Office of the Commissioner, FDA, commented that FDA has started to implement such a learning system of regulatory science with its inclusion of adaptive regulation, such as the use of accelerated pathways. Ostroff noted that the agency needs to continue to incorporate innovative decision-making methods to both supplement and support more traditional methodologies.

Workshop participants discussed specific areas of regulatory science on which to focus development and how to best adopt any changes. Ostroff noted that in *Mission Possible* the FDA Science Board offered recommendations related to the continued development of tools and methodologies that could be of applied value in regulatory decision making, such as advancing biomarkers, enhancing data mining and analytical tools, developing *in silico* modeling, and facilitating extramural collaborations. Stevens emphasized, however, that simply developing these tools is not sufficient to ensure their adoption. He reminded the audience that incentives must be in

place for organizations to adopt new technologies or share data, and that organizational management is essential to achieve transformation. Stevens cited Leavitt's Diamond—a model for organizational change management that states that technology, tasks, and the organization are all interdependent and should be managed together—to caution that if implementation of such tools is handled poorly and the dynamic tensions created by these interdependencies are not taken into account, negative tension may be created within an organization.

THE ROLE OF DATA SCIENCE IN REGULATORY SCIENCE: A CASE STUDY IN COLLABORATION

The University of California, San Francisco (UCSF)–Stanford CERSI, explained Russ Altman, the Kenneth Fong Professor of Bioengineering, Genetics, Medicine & (by courtesy) Computer Science, is FDA mission driven, not curiosity driven like traditional scientific pursuits. To realize this

BOX 2-1
Key Examples of the Role of Data Science in Regulatory Science as Identified by the UCSF–Stanford CERSI Leadership

1. Bringing structure to unstructured (textual) data for computational analysis of the enterprise-wide effort (knowledge management)
2. Integrating information across Phases I, II, III, and IV to detect efficacy and safety signals
3. Facilitating automated triage and prioritization of postmarket adverse event reports
4. Integrating spontaneous report data with electronic medical record infrastructure (for hypothesis testing and/or validation)
5. Building computational infrastructure and statistical models for "next-generation" biomarkers
6. Establishing standards for mobile health software quality control
7. Implementing validated electronic infrastructure for clinical trials and postmarketing data collection
8. Using social media to assess population trends in product use
9. Advancing systems pharmacology and modeling for deep understanding of mechanism and efficacy/toxicity
10. Creating electronic infrastructure for patient-recorded outcomes and elicitation of patient preferences

SOURCE: Altman presentation, October 20, 2015.

mission-driven focus, Altman and his CERSI colleagues reached out to FDA to explore potential collaborative projects that FDA would find meritorious and that would allow for the application of skills and resources available at Stanford and UCSF. Altman observed that the proposals received from FDA revealed that FDA recognizes that informatics and data science can create an important, immediate, and positive impact on regulatory science. Based on those proposals and additional conversations with European and U.S. regulatory agencies, the CERSI leadership identified 10 key examples of data science themes in regulatory science (see Box 2-1).

3

Regulatory Science Applications: Using Case Studies to Focus on Approaches to Advance the Discipline

Key Messages Identified by Individual Speakers

- Biomarker development could help to modernize product regulation and clinical practice. Establishing a common framework for development, standardizing evidentiary standards, defining clearly the precompetitive space, and using a consortium model could help facilitate biomarker development. (Amur, Lavezzari, Philbert, Sauer, Wagner)
- Postmarket safety evaluations offer many opportunities for innovative usage of big data, especially when clinical trial cohorts are not representative of the general population. (Angus)
- Specialized statistical techniques can be used to model relationships between endpoints in an ongoing trial and to integrate data longitudinally over time. (Alexander)
- It is possible to apply social science and health care economics techniques to get reliable analyses of smaller trials, as for rare diseases. (Ward)
- Considerations for driving good analyses and true conclusions are good data curation; clear terminology and data standards; and good characterization of data quality and limitations. (Corrigan, Jaffe, Landray, Platt, Salit)

- Web-based search logs, community discussion forums, and social media platforms can be used to gather population-level health data and track adverse events or public health impacts in unprecedented ways. (Brownstein, Holmes, Horvitz)
- Challenges associated with these Web-based tools include inconsistent syntax and vocabulary, anonymization of data, the effect of news media on public awareness, and influence on opinions by the broader community. (Brownstein, Holmes, Horvitz)
- Decisions about whether a product has enough associated data to bring it to market could be made using specialized statistical techniques. (von Stackelberg)

Workshop discussions during Session III were organized around four case study regulatory science applications that served as focal lenses to discuss how enhanced approaches to obtaining, accessing, and integrating information could advance regulatory science.

IDENTIFICATION AND DEVELOPMENT OF MEANINGFUL BIOMARKERS

John Wagner, senior vice president, head of clinical and translational sciences, Takeda Pharmaceuticals, observed that although biomarkers have been a subject of regulatory interest since 1999, progress in their development, standardization, and regulation has not met expectations. Indeed, biomarkers remain a priority, and improvements are being offered through a number of policy initiatives and programs, such as the U.S. House of Representatives' "21st Century Cures" bill, the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium, and the FDA Biomarker Qualification Program. With this confluence of activities, it will be important to harmonize ongoing efforts in biomarker development to avoid duplication and ensure the endeavors are separately and collectively worthwhile, Wagner said.

FDA Biomarker Qualification Pathways

Shashi Amur, scientific lead, FDA Center for Drug Evaluation and Research's (CDER's) Biomarker Qualification Program, discussed FDA's objective-dependent biomarker qualification pathways (see Figure 3-1). If the intent is to only use the biomarker for a single drug development application, the sponsor would combine biomarker qualification with a regulatory submission, such as an Investigational New Drug (IND) or New

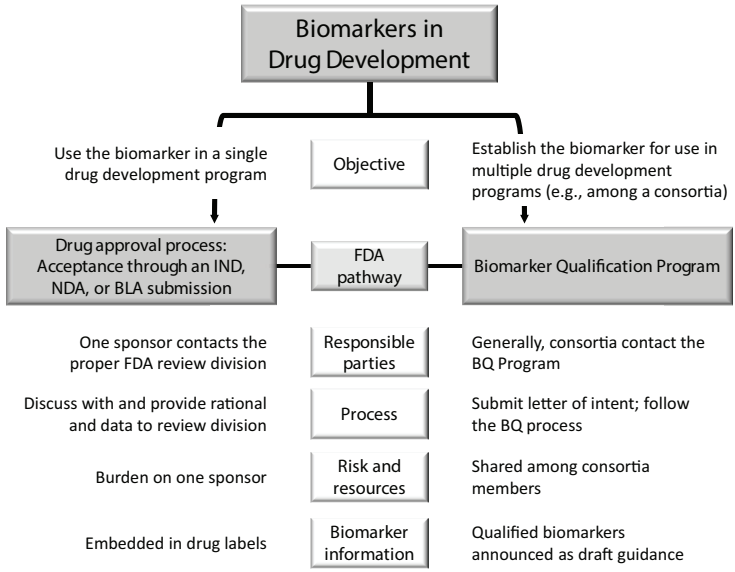

FIGURE 3-1 Pathways to integrate biomarkers in drug development at U.S. FDA.
NOTES: BLA = Biological License Application; BQ = Biomarker Qualification; IND = Investigational New Drug Application; NDA = New Drug Application.
SOURCE: Amur et al., *Clinical Pharmacology & Therapeutics* 98 (1):34–46, 2015 (presented by Amur on October 20, 2015).

Drug Application (NDA). The biomarker can therefore only be used by that sponsor, and the information is often included in the drug label after approval.

However, Amur said, if the biomarker is intended to be used for development of multiple drugs, it goes through a separate biomarker qualification process. Often, this approach is used when consortia identify a biomarker that each member later intends to use in a separate drug development application. After approval, the biomarker is publicized on FDA's website as draft guidance and it becomes public information.

When a biomarker is qualified, it is qualified for a specific context of use (COU), Amur said. The COU determines what level of evidence is needed, and that level of evidence then drives the qualification process. Each type of biomarker can have multiple COUs. FDA is currently involved in many ongoing biomarker projects, including efforts to establish a common taxonomy for types of biomarkers.

Amur used the example of a recently qualified biomarker, total kidney volume in autosomal dominant polycystic kidney disease (ADPKD), to illustrate several principles and best practices relating to biomarker qualification:

- Collaborative meetings (including cross-agency) facilitate scientific exchange.
- Early consultation with FDA Biomarker Qualification Review Teams (BQRTs) is critical.
- Data standardization including harmonized terminology, facilitates data aggregation and ensures that data are usable.
- The biomarker qualification process requires significant reviewer effort, including, for example, conducting additional analyses or developing an external cross-validation model.

Amur also cited initiatives to streamline biomarker qualification, including the Critical Path Innovation Meeting (CPIM) and FDA's Limited COU Qualification. CPIM was developed by CDER to address issues in drug development identified in the 2004 FDA publication *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*. CPIMs provide a means for CDER and investigators across industry, academia, patient advocacy groups, and government to communicate to improve efficiency and success in drug development.[1] FDA's CDER provides an avenue to qualify a biomarker for a "limited" COU in order to expedite the integration of the biomarker in drug development and to possibly generate additional data that can help in qualifying the biomarker for an "expanded" context of use.

Advancing Science and Infrastructure for Biomarker Development

Gabriela Lavezzari, assistant vice president, science and regulatory advocacy, Pharmaceutical Research and Manufacturers of America (P*h*RMA), characterized FDA's biomarker qualification process as having a lack of predictability, suggesting that FDA further outline what a qualification package should look like (i.e., what evidence, data standards, and assay validations are needed). By providing additional clarity on these parameters, Lavezzari said, the amount of time spent on the biomarker development process could decrease and the return on investment of researchers or consortia members could be maximized. She also encouraged conversations among stakeholders, including academia, industry, and consortia, around the development of a defined set of required evidence for qualification, commonly called "evidentiary standards," that could aid in streamlining and providing more predictability in the qualification process.

John Michael Sauer, executive director, Predictive Safety Testing Consortium (PSTC), C-Path, highlighted C-Path's consortium model for bio-

[1] For more information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm (accessed December 23, 2015).

marker qualification. C-Path's consortia create partnerships that function as neutral, precompetitive spaces for pharmaceutical companies, academics, and regulatory bodies (e.g., FDA, European Medicines Agency [EMA]) to have discussions to move qualification forward. Sauer noted two areas that could use further attention to aid consortia through the biomarker qualification process: (1) better define the qualification process, specifically evidentiary standards; and (2) identify ways to better collect and share data, possibly in a repository, to use with prospective analyses.

Sauer noted that one potential way to foster a collaborative environment that encourages data sharing could be to establish a means for masking shared data so that it cannot be traced back to the originating organization and impart undesired risk. Several workshop participants also noted a need for the establishment of a common definition of "precompetitive space" to foster more collaboration in the development of biomarkers.

INTEGRATING CLINICAL TRIAL DATA

The advent of technological advances such as electronic health records (EHRs), patient registries, and social media has ushered in an era of "big data" that holds promise for driving innovation in clinical research and application. "Big data" could take on different meanings depending on the user or situation—and, as noted by several workshop participants, use of the terminology is in and of itself divisive—but can be generally characterized by the "five Vs": volume, velocity, variety, veracity, and value, said Sam Shekar, chief medical officer, Northrup Grumman.

Developing Capabilities to Integrate and Use Big Data in Clinical Research

Martin Landray, professor of medicine and epidemiology and deputy director, Big Data Institute, University of Oxford, noted that big data can permit researchers to more effectively collect information on traditional clinical outcomes and provide greater insight into patients' symptoms and quality of life. Big data can also allow for novel assessment of both traditional disease features, such as exercise capacity or cognitive function, and of new disease features, such as keystroke speed, that are not currently incorporated into regulatory decision making because the symptom cannot be quantified. Finally, big data can promote thinking about the economic and social consequences of disease and treatment.

Despite the current hype surrounding big data and their potential positive impact on clinical medicine, "the fundamental principles of large-scale randomized trials remain unaltered," said Landray. When applying big data to the design of clinical trials, he noted, it is critical to focus on three areas:

the hypothesis being assessed, the intended interpretation, and the errors that could develop as a result of the analysis.

Landray outlined his key considerations in achieving reliable assessments of treatment effects in aggregated clinical trials:

- Scale—the number of participants and the number of outcomes; allows for good statistical power in the face of moderate treatment effects
- Breadth—the diversity of the populations under observation (e.g., co-morbidities, concomitant treatments), and assessments of safety and efficacy
- Length—the frequency and duration of the clinical trial or assessment
- Depth—the careful and detailed characterization of trial participants' outcomes

In light of these principles, Landray also cautioned that accurate data do not necessarily imply that results are reliable; they must be analyzed for errors. Results generated from large enough datasets are remarkably resilient to changes in outcome due to *random* errors, which do not add bias and can be overcome by adhering to the principles described above, he noted. He gave the example of a large randomized dataset, in which introducing 10 percent more false-positive events does not alter the conclusions or the statistical significance of the results. Introducing even 20 percent more false events will not alter the conclusions enough to change any regulatory or clinical decisions made from the data, he said. The same pattern holds true if the calculations are performed instead for similar rates of missing events. He added:

> You don't have to (have) perfect (data) to get reliable conclusions. You do have to understand in what way you are imperfect and to what extent that is going to matter to the type of conclusion you are trying to draw. It is the avoidance of (some) errors that matter to the decision making, not the avoidance of all errors.

The data must also be analyzed for *systematic* errors, Landray said, which cannot be corrected after the trial has been completed; if those exist, the trial will not generate reliable results in any analyses.

Postapproval Applications for Big Data

In addition to priorities in the preclinical and early clinical stages, participants discussed needs in the postapproval space. Derek Angus, Distinguished Professor and Mitchell P. Fink Endowed Chair, Department of Critical Care Medicine, University of Pittsburgh, discussed the need for a more defined structure in postapproval safety evaluations. He explained,

> The postapproval world can be characterized as a data-poor, opinion-rich environment. At the time a therapy arrives with approval, the randomized controlled trials (RCTs) evidence that led to that approval is both too broad—in that the overall treatment effect is considered average, not personalized—and too narrow, as the trial population is not considered representative of the general population.

To address these potential concerns, Angus noted, it could prove valuable to consider innovative ways in which appropriate information can be generated during the postapproval phase. He cited an example that blended a point-of-care trial, where randomized observational studies are conducted directly in a clinical setting, with a large platform trial, which uses broad inclusion criteria for admittance to the trial and relatively simple protocol design. As patients with severe pneumonia were admitted to hospitals in Europe, they were randomly assigned to 1 of 48 possible treatment regimens. Enrollment was triggered by entering admitting data into a patient's EHR. The trial took into account both causal inference and real-world effectiveness. It considered multiple therapies and generated treatment options in real time as more data were added to the algorithms.

Angus remarked that this model is not without problems, including concerns about how to report and disseminate results from an ongoing trial. Most importantly, Angus cautioned, having complex data for a large group such as this one does not obviate the need for randomization.

Adaptive Clinical Trials

Adaptive trials allow a researcher, in a prespecified manner, to harness accumulating data to decide when and how to modify a clinical trial. This modification could encompass, for example, moving patients to the most effective treatment arm or dropping less effective arms of the study as data accumulate. Brian Alexander, assistant professor of radiation oncology, Harvard Medical School, highlighted the use of Bayesian trial design to conduct randomized adaptive clinical trials. Importantly, the statistical method employed in Bayesian trial design automatically reflects uncertainty because it is a measure of probabilities that is continuously updated by new information.

Alexander and colleagues used Bayesian trial design to model how relationships between various endpoints could be evaluated during an ongoing trial. This method allows both for incorporation of immediately useful information in randomized assignments to designated treatment arms and for evaluation of how auxiliary endpoints are associated with survival. In addition, he described how incorporating data generated outside of the clinical trial itself, such as overall health, disease progression, or imaging

results, could be used to generate a "longitudinal model" that adds "shades of gray" to an otherwise binary survival endpoint. "Death is binary, but the probability of dying is not," he said.

Bayesian techniques also offer the potential to more formally include information generated prior to a particular clinical trial, and to apply trial results to making future decisions and evaluations. In this manner, barriers between preclinical, early phase, and late phase clinical trials can be traversed or broken down, potentially addressing some of the concerns previously described by Russ Altman and FDA, Alexander stated.

Although developing software and conducting simulations for models such as this are time-intensive, their implementation may be a worthwhile investment and enable better preparation of an overall plan for evidentiary development. More flexible clinical trial designs such as adaptive trial design could provide efficiencies by capturing data that are potentially lost during the extended process of a trial and allow clinical trial researchers to enroll new patients without the time constraints from predetermined clinical trial phase timeframes. These steps could potentially result in a better outcome from the trial and a more successful trial enterprise overall, said Alexander.

Nontraditional Approaches to Big Data Analyses: A Case Study in Rare Disease

Random errors could have a disproportionate effect on smaller clinical trials. This is because as the sample size becomes larger in any trial, outliers and missed events will have less of an effect and the model will still be accurate, as illustrated by Landray. Susan Ward, founder and executive director, the Collaborative Trajectory Analysis Program (cTAP), pointed out that in smaller trials, however, small variations in data can have an enormous impact on the model. This effect is particularly seen in trials involving rare diseases like Duchenne muscular dystrophy (DMD). In a DMD trial, Ward and colleagues noted large variations in the trial's primary endpoint (6-minute walk distance). To address the variance, Ward and her collaborators at cTAP applied latent class trajectory analysis. This methodology was developed in social sciences and health care economics to handle variance due to heterogeneity. The method assumes that a single mean exists for a "class," finds the optimal number of classes by minimizing variance, and allows visualization of multiple clusters of data.[2] Ward pointed out that this technique used for rare disease could also be applied to more common diseases. Common diseases are increasingly recognized as groupings of heterogeneous diseases with a set of common symptoms.

[2] Ward provided additional resources for the workshop participants: Leoutsakos et al., 2012; Muthen and Asparouhov, 2014; Muthen and Brown, 2009.

Techniques such as the one used by cTAP could help to tailor treatment to a particular subset of patients based on covariance or other factors, or to clarify a more significant effect for a treatment under evaluation.

Considerations for Use of Big Data

Big data can confer many benefits in such endeavors as measurement of novel outcomes, postapproval safety monitoring, and adaptive trial design. To realize these benefits, however, data need to be accessible and of sufficient format and quality for the researchers who wish to use them. Several workshop participants noted that the value of data depends on having a clear understanding of which ways the data may be of poor quality—that is, what errors, random or systematic, may have been introduced during their collection. Additionally, discussants noted the importance of understanding, when curating and analyzing data, the assays—i.e., the technologies and methodologies—that were applied in collecting the original data. Without proper understanding of the original purpose and collection methods, incorporating the data into trial design may prove challenging, if not impossible. For example, confounding factors in assays might not be obvious when looking at a database alone, but upon further review such factors could be revealed, precluding aggregation of the results.

Understanding data quality and variability also influences how confident the scientist can be in any conclusions drawn, whether those conclusions are used to interpret disease features, the social impact of treatment, or identification of new biomarkers. In any of those cases or many other applications of aggregated data, it would be detrimental and costly to focus on a perceived signal that is actually an artifact caused by failure to understand fully the variability inherent in the data and their subsequent aggregation, making high confidence in conclusions a key component of any application for big data. Marc Salit, leader, Genome-Scale Measurements, National Institute of Standards and Technology (NIST), shared his framework for understanding data, their sources of variability, and how to identify an artifact (see Box 3-1). He termed this framework a "three-legged stool." Confidence in a measurement can only be achieved when the units of measurement are understood (metrological traceability), the likely dispersion around the result is known (measurement uncertainty), and evidence establishes that the methodology used to obtain a result has been rigorously considered (method validation[3]; e.g., existing benchmark data and reproducible results from previous studies).

[3] With respect to method validation, Salit noted that analytic validation—the accuracy, precision, and reproducibility of a test—is distinct from clinical validation—the relevance of the test in an actual clinical condition—and is a key factor in moving forward with biomarker qualification.

BOX 3-1
Basic Science of Measurement:
Metrology for Principles of Biomarkers

To be confident that measurement results are not artifacts, are comparable to other results, and will take on a range of values with a known likelihood, consider the principles below to have confidence in your results, said Salit.

1. **Metrological Traceability:**
   a. Tying results to a common reference; usually realized with calibration
   b. Enables comparison of results among those using the common reference across space and time (e.g., meter, kilogram, second)
   c. Biomarkers are often traceable to a *control group*; enrichment of a molecular signal
2. **Measurement Uncertainty:**
   a. Estimated value that gives a reasonable expectation of dispersion around the result given the measurement system
   b. Combination of all sources of variability or limitations in knowledge through the process
3. **Method Validation:**
   a. Demonstration by provision of objective evidence that what is being measured is what was intended to be measured; proves results are more than artifacts
   b. Analytical validation is distinct from clinical validation

SOURCE: Salit presentation, October 20, 2015.

Data Collection, Curation, and Harmonization

Throughout the workshop, many participants emphasized the importance of key principles in data collection, curation, and harmonization. Original data are typically usable only for the purpose for which they were originally collected; repurposing data for other analyses, observed Richard Platt, professor and chair, Harvard Medical School Department of Population Medicine, Harvard Pilgrim Health Care Institute, usually necessitates a great deal of curation. Data curation, "the active and ongoing management of data through [their] life cycle of interest and usefulness to scholarship, science, and education," includes activities that enable "data discovery and retrieval, maintain quality, add value, and provide for re-use over time" (Cragin et al., 2007).

When data are ready to be repurposed, millions of dollars are spent on data curation and countless hours of work are dedicated to make the data fit for novel purposes, said Brian Corrigan, senior director, Pfizer Inc. He

stressed the importance of having trained professionals collect and curate the data acquired during the course of a study so that those data conform to established, acceptable data standards.

Another obstacle that can arise during the process of aggregating and repurposing previously collected data is incongruous terminology and units of measurement. Landray provided an example encountered during aggregation of intergenerational data from trials on thrombolytic therapy for treating myocardial infarction: "myocardial infarction" is now on its third universal definition. In describing his work with FDA Sentinel (see section in this chapter on Next-Generation Surveillance), Platt noted that there are 67 different units of measure for recording blood platelet counts alone in laboratory results from Sentinel data partners. To perform analytical work of value from such data, it is necessary to harmonize the data through careful curation, Platt said.

Sharing Clinical Trial Data

Aggregating data from clinical trials to create bigger datasets is of increasing interest. Kyle Myers, Center for Devices and Radiological Health (CDRH), FDA, pointed out that funders of research are more commonly requiring data sharing as a condition for receiving support. Robert Califf, deputy commissioner for medical products and tobacco, FDA (at the time of the workshop), mentioned legislative initiatives intended to incentivize broad consent from patient volunteers so that data could be more easily shared and used by multiple researchers. However, making data available for such purposes raises a number of concerns, from the need to protect patient privacy and safeguard intellectual property, to the costs of sharing and curating data (see Box 3-2).

Although numerous concerns are associated with making data available and fit for use by a wider audience, several participants offered potential solutions. Charles Jaffe, chief executive officer, Health Level Seven International (HL7), noting that data quality depends on the accuracy of data collection and storage, stressed the importance of interoperability[4] in harmonizing data and making exchange more seamless. "It is becoming increasingly clear," he said, "that we cannot continue to silo the data (in separate databases). . . . [I]t is expensive, error prone, and hard to manage." Jaffe argued that the future of health care interoperability will be

[4] Interoperability is "the ability of different information technology systems and software applications to communicate, exchange data, and use the information that has been exchanged. Data exchange schema and standards should permit data to be shared across clinicians, labs, hospitals, pharmacies, and patients regardless of the application or application vendor." Source: http://www.himss.org/library/interoperability-standards/what-is-interoperability (accessed February 19, 2016).

BOX 3-2
Potential Concerns for Data Sharing

1. Clinical trial participant views of and support for data sharing are not universal, and there may be a generational gap. (Wood)
2. Interpretation and legal application of informed consent forms can be variable, with many researchers and institutions determining that they must not share or disclose patient data in ways that are not explicitly covered during the informed consent process. (Ward)
3. The costs of anonymizing data are high, and risks cannot be entirely eliminated that the data could be unmasked or reidentified. (Nisen)
4. Other legal considerations and associated risks, such as concerns about protecting intellectual property or commercially confidential information. (Sauer)

SOURCE: Speaker presentations, October 20, 2015.

in application program interfaces (APIs) such as HL7's Fast Healthcare Interoperability Resources (FHIR) specification.

In the environment of a consortium, Enrique Avilés, chief technology officer, C-Path, found in his experience at C-Path that consortium members are willing to share data if each understands the rights of each member, the agreement, and the final use and dissemination of the end product. To accomplish this, Avilés recommended structuring collaboration around specific goals and governance criteria. Every data contribution received is handled based on predetermined agreements for the data: what can be done, how it can be shared, how to ensure appropriate anonymization and privacy, and how to integrate various data sources. All the data integrated are evaluated according to C-Path's key objectives and formatted to the Clinical Data Interchange Standards Consortium (CDISC) standards, already accepted by FDA, EMA, and the Pharmaceuticals and Medical Devices Agency (PMDA), for continuity and consistency. Sauer suggested that data sharing could be important to develop treatments for complex diseases. Participating in an organized consortium may be the most successful way of accessing data from multiple sources, Sauer said. Successful data sharing in the future will depend on common privacy standards, common data standards, and incentives to share data.

NEXT-GENERATION SURVEILLANCE

Several workshop presentations and discussions explored new tools, methodologies, and paradigms for collection, aggregation, and analysis of surveillance data. In the session Next-Generation Surveillance, panelists discussed new systems for data aggregation and efforts to leverage community search logs, discussion forums, and other Web-based platforms such as Twitter or Facebook. Panelists also examined how data analysis methodologies could be brought to bear to apply these Web-based data toward epidemiological studies, diagnosing and tracking illness over time, tracking adverse drug events, and even for gauging the black market for pharmaceuticals.

Although some workshop participants expressed enthusiasm for the possibilities of these types of developing tools, it was noted that all of them face further refinement before they would be suitable for use by FDA to identify risks. Brian Strom, chancellor of Biomedical and Health Sciences, Rutgers, the State University of New Jersey, and Platt observed that Sentinel is currently designed to strengthen existing hypotheses rather than generate new ones, as these other tools presented do, because of the difficulty in determining how much importance to assign to unanticipated effects. It would be a burden on FDA to follow up on a potentially vast number of false-positive events, they said.

Systematic Methods for Medical Product Reporting

Patients and clinicians do not always know that current adverse event reporting tools exist or how to use them, noted John Brownstein, associate professor, Harvard Medical School. MedWatcher[5] is one FDA-sponsored tool designed to allow patients to provide more detailed information about adverse events. Brownstein highlighted the power of these reporting platforms not only to inform adverse drug events, but also to illuminate the illegal use of drugs on the black market and to track the street value of medical products. These black market data, he said, could help inform a greater understanding of the public health impact of certain medical products. FDA has launched an ongoing informatics initiative, FDA Sentinel, which will incorporate electronic health data from at least 100 million people to assess the safety of marketed medical products. A description and update of FDA Sentinel given by Platt is summarized in Box 3-3.

[5] MedWatcher is a mobile application (app) that allows individuals to submit voluntary reports of serious medical device problems to FDA using a smart phone or tablet. For more information, see http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/ucm385880.htm (accessed December 23, 2015).

BOX 3-3
Update: FDA Sentinel

Platt presented one of FDA's ongoing informatics initiatives, FDA Sentinel. The impetus for the Sentinel system was the FDA Amendments Act of 2007 (FDAAA), which required FDA to develop a validated system for linking and analyzing safety data for marketed medical products, with the goal of including at least 100 million patients by 2012. Sentinel accesses many diverse sources of data for use in surveillance, including laboratory tests, public health registries, and electronic health records. Consequently, one of the issues that has frequently arisen is the lack of common data standards and the subsequent need for data curation.

Platt cited a favorable independent assessment of Sentinel, which stated that Mini-Sentinel (which was "a pilot program designed to test the feasibility of the core Sentinel precept: to access and analyze healthcare information from a variety of data sources, and to use that data to improve FDA decision making") met or exceeded the requirements of FDAAA and has successfully partnered with 19 data partners, providing source data for 178 million people (Sentinel Program Interim Assessment [FY15], 2015). While transitioning to a fully matured platform will require additional effort, FDA Sentinel's surveillance capabilities are currently more advanced than alternative surveillance platforms. Platt noted that efforts to integrate Sentinel into the regulatory decision-making process are ongoing and not without their challenges.

SOURCE: Platt presentation, October 20, 2015.

Because some medical devices may not undergo classical clinical trials, they are typically continuously assessed after they reach the market, said Danica Marinac-Dabic, director of epidemiology, CDRH, FDA. Registries linked to EHRs and unique device identifications will be valuable for continuous surveillance of medical devices. MDEpiNet[6] (the Medical Device Epidemiology Network Initiative) is a public–private partnership whose mission is "to bridge evidentiary gaps, to develop datasets and innovative methodological approaches for conducting robust analytic studies, and to improve medical device safety and effectiveness understanding throughout the device life cycle."

[6] MDEpiNet is part of the Epidemiology Research Program at FDA's CDRH. The initiative is a collaborative program through which CDRH and external partners share information and resources to enhance our understanding of the safety and effectiveness of medical devices after they are marketed. For more information see http://www.fda.gov/MedicalDevices/ScienceandResearch/EpidemiologyMedicalDevices/MedicalDeviceEpidemiologyNetworkMDEpiNet/default.htm (accessed December 23, 2015).

Web-Based Surveillance Data

Individuals are creating a new and continuous stream of data today via search engines, social media, and wearable fitness trackers, which offer unique vantage points for acquiring and aggregating health data compared to traditional clinical data sources. These new tools could be used on a global scale for tracking everything from emerging infectious disease to adverse drug events.

Search Engines and Web-Search Logs

Eric Horvitz, distinguished scientist and managing director, Microsoft Research, noted that approximately 72 percent of adult Internet users reported performing health-related inquiries online (Pew Center for Research, 2015). Bing and Google reported that about 10 percent of Web inquiries were health related. These search logs could serve as an immense source of health data, such as for surveillance of adverse reactions, he said. Horvitz highlighted that as a result of prolific use of cell phones and personal computers, individuals continuously self-report health data via Web searches. He observed that Web-based search, unlike more communicative forms of social media, may be less influenced by broader societal or communal attitudes and opinions. Combining these new techniques with traditional health care and claims data could prove informative on how to better harness the Internet for pharmaceutical surveillance and integrate nontraditional sources of information, he said.

Building off work from Altman and colleagues, who found through analysis of the FDA Adverse Event Reporting System (FAERS) that patient-reported hyperglycemia was higher when patients were taking two medications in combination, Paxil and Pravachol, than either drug alone, Horvitz and colleagues sought to confirm the real-world presence of this effect through analysis of Web-search logs. Using a generated set of terms obtained from BioPortal[7] and consumer-oriented search terms in Microsoft Bing, they analyzed 1 year of Web-search logs, which revealed that this drug interaction can be accurately identified in Web searches.

Microsoft Research has harnessed this concept by establishing a tool termed BLAERS (Behavioral Log-Based Adverse Event Reporting System). BLAERS provides ongoing monitoring of Web-search logs for adverse drug events. This and similar Web search–based tools provide an opportunity to complement traditional sources of adverse drug event reporting.

[7] BioPortal is a repository of biomedical ontologies developed by The National Center for Biomedical Ontology; see http://bioportal.bioontology.org (accessed December 23, 2015).

Online Discussion Forums

Online discussion forums could also serve as a profound source of non-traditional data to capture adverse drug events. John Holmes, professor of medical informatics, University of Pennsylvania, defined a discussion forum as "an online resource and a social media resource where people participate in actual conversations." People generally participate in a chat room to talk about a particular topic, meaning the population automatically tends to segregate; for example, forums on breast cancer might typically consist of women between the ages of 40 to 70. Holmes and colleagues analyzed discussion forums using a Web crawler and a set of controlled vocabulary to extract information and develop findings. In one study, Holmes and colleagues investigated the side effects of an aromatase inhibitor (used to treat some estrogen receptor–positive breast cancers) by looking at 1,000 randomly selected messages in the discussion threads for identified side effects. In reviewing the messages, they found that 18 percent of participants mentioned at least one side effect, with some individuals reporting side effects more frequently than stated on drug warning labels. Holmes cautioned that these data would only be valuable for hypothesis generation, however, as the data are limited by the fact that there is no denominator to the analysis and thus cannot be viewed as rates or proportions.

Challenges and Limitations to Web-Based Surveillance

Several participants discussed the challenges and limitations inherent in analyzing discussion forum chats, social media, and Web search (see Box 3-4). Many speakers emphasized the importance of having a standardized vocabulary to avoid complications in data analysis related to variations in syntax. On the other hand, it was noted that certain syntactical elements could help to personalize surveillance data by elucidating the sentiments and attitudes of the individual that are not currently captured in traditional methods, and thus could be of subjective value. It was also noted that researchers will need to develop and adhere to anonymization mechanisms when publishing and presenting data to address the lack of consent inherent in Web-based surveillance mechanisms. Holmes stated that the influence of current events on user searches and comments could have a profound influence on reporting patterns. For example, news reports on H1N1 resulted in over-reporting on Web-search logs by Google Flu Trends. Where these alterations in Internet searches and postings arise, conclusions will need to be adjusted to account for this, he said.

BOX 3-4
Selected Examples of Challenges and Limitations of Web-Based Surveillance

1. CAUSALITY—Patients may not correctly assess causality. *Define methods to measure probability of real world significance.*
2. VOLUME—Volume of reports likely to be large. *Reduce false positives and create automated tools to triage information.*
3. SIGNAL DETECTION—Very limited statistical methods to detect problems. *Collaborate with academia, industry, and regulators to refine methods.*
4. SYNTAX—Use of synonymy, abbreviations, hashtags, misspellings, emoticons and graphic interchange format (gifs). *Create a harmonized, common taxonomy.*
5. PRIVACY—Patient privacy expectations and fear of government oversight. *Use publicly available data only.*
6. REGULATION UNCLEAR—When is there an obligation to monitor or report? *Work with regulators and industry to clarify guidance.*

SOURCES: Presentations by Brownstein and Holmes, October 20, 2015.

INNOVATIVE MODELING FOR INTEGRATING DATA

Modeling can reveal effects and patterns in the data that are not apparent when only examining the raw results. Strategies and techniques for accurately modeling how a treatment is performing in either a clinical trial or a clinical application are rapidly evolving. Speakers discussed how incorporation of data collected outside of a clinical trial setting, such as medical record data, and better qualification and understanding of variability and its sources could lead to development of models that might be more effective at answering questions that arise in the postapproval space.

Quantifying and Addressing Uncertainty

Assumptions and uncertainties each increase variability in datasets, and variability affects the overall predictive power of a model. To accurately predict and build models of treatment response for clinical trials, both uncertainties and underlying assumptions should be taken into account, said Sandy Allerheiligen, vice president, Modeling and Simulation, Merck. Uncertainties in data can result from limited dataset size, bias in the sample population, heterogeneous response to treatment, or any number of effects that cannot be predicted or measured.

Statistical approaches known as value of information techniques could aid in quantifying uncertainty, said Katherine von Stackelberg, research scientist, Harvard Center for Risk Analysis. These techniques use Bayesian statistics to quantify the "opportunity loss from a decision made under uncertainty," determining whether more data should be collected in clinical trials before bringing a product to market and helping to calculate the expected benefit of further data collection. The techniques can also serve to estimate the number of patients needed in a clinical trial to observe a treatment effect or approximate the cost of bringing more patients into a trial. Therefore, these techniques could be powerful tools for evaluating and directing research priorities. "[Value of information techniques] quantify the value of the information and allow the regulator to prioritize where additional investment is really going to lead to maximal benefit and identify those areas that have the greatest likelihood of influencing clinical practice," said von Stackelberg.

Modeling the Placebo Effect

The placebo effect, or the measurable change in a patient's health status that cannot be attributed to the treatment being tested, is another source of variability.[8] Ariana Anderson, assistant research statistician, University of California, Los Angeles, noted the importance of modeling the placebo response in clinical trials. Modeling holds particular value in the case of rare diseases, where patient numbers are small and statistical power is low, and it may be unethical to assign patients to the placebo group, she said. If the placebo response could be predicted, it could help the clinical trial researcher to determine the magnitude of its effect in future trials. One such method for predicting and mapping the placebo response is through functional magnetic resonance imaging (fMRI) techniques. After a baseline fMRI is established in patients, this model can be used to predict treatment response over placebo for an individual patient, or potentially predict patients who would not respond to treatment because of increased susceptibility to placebo effect.

Modeling Within a Consortium Setting

One way to address variability is to approach clinical trial design and implementation via consortia. By having multiple organizations participate in a consortium, each organization can benefit from the expertise of the others and in turn can better address biases and heuristics inherent in data collection, said Corrigan. Consortia can expand the depth of data inputs and

[8] For further information on this technique, see Anderson and Cohen (2013).

aid in creating model constructs that are potentially more reliable, which can, in turn, promote better understanding of disease natural histories and therapeutics. However, the actual amount of data available, data standards, data-sharing policies, and clinical trial or modeling approaches can vary among the data-collecting organizations. For a consortium to be successful, these discrepancies should be proactively addressed, Corrigan said.

As an example of a successful consortium effort, the Coalition Against Major Diseases, a public–private partnership formed by C-Path, created a disease progression model of Alzheimer's disease (AD) that addresses critical concerns surrounding AD and the performance of treatments in clinical trials for AD, including dropout rates, placebo effect, covariants with the disease, and variability both in patient response and in the methodology used by different data collectors within the consortium. The model allows for users to quantitatively design clinical trials before they begin.

Corrigan outlined key components that lead to the successful generation of the AD model. He noted that, most importantly, success is a function of time, and consortia members should be prepared for potentially lengthy investment in constructing an effective model. Technical support, including enhancements and updates to the model, and infrastructure must be planned for in advance. Finally, establishment of data standards is critical, as is partnering with regulators early to qualify the tool and establish a context of use.

4

Regulatory Science Infrastructure and Workforce

Key Messages Identified by Individual Speakers

- Regulatory scientists influence both science and the general public, so multidisciplinary training and ability to integrate information from many sources could be advantageous. (FitzGerald, Honig, Ostroff, Philbert, Rogers)
- Fellowships and other collaborative training programs, particularly for recent graduates, can help break down the "silos" between academia, industry, and government. (Allerheiligen, Fields, Shekar, Steele)
- To attract new scientists, the regulatory science career path could be made more intentional through dedicated, specific training programs. (Cannon, Fields, Steele)
- The Clinical and Translational Science Award consortia and Center of Excellence in Regulatory Science and Innovation programs could be used to address immediate training needs. (Altman, Steele)
- A streamlined FDA hiring process, funding for regulatory science efforts, incentivizing and rewarding regulatory scientific accomplishments on their own terms rather than through traditional academic rewards, and generally making regulatory science more respectable will help attract scientific leaders to the field. (Abernethy, Honig, Landray, Ostroff, Philbert, Potter, Weichold, Wood)

Many workshop participants outlined a vision of a complex and diverse field of regulatory science that includes knowledge of and expertise in basic science, regulatory pathways, and the social sciences, among others. A robust regulatory science infrastructure could, for example, include and foster adequate funding, cross-sector collaboration and information sharing, and innovation in the face of rapidly advancing science and technologies. Perhaps most importantly, expressed Owen Fields, vice president, Regulatory Strategy, Pfizer Inc., is that a robust regulatory science infrastructure includes trained and expert scientists. Yet, regulatory science is often considered only as an alternative career path for basic science and clinical researchers. This chapter summarizes discussions held at the workshop to characterize the components of a well-working and robust regulatory science infrastructure, with an emphasis on training of regulatory scientists.

CHARACTERIZING THE DISCIPLINE OF REGULATORY SCIENCE

Regulatory Science as an "Enlightened Discipline"

Garret FitzGerald, professor of medicine and pharmacology, University of Pennsylvania, noted that the environment in which regulatory science is situated is undergoing a multidimensional shift influenced by many outside factors, including technology, trade, politics, intellectual property, global influence, a desire for transparency, and patient empowerment.

Those who engage in the discipline of regulatory science, whether in industry, government, or academia, often contend with the traditional segregation of seemingly disparate but often intertwined disciplines. One of the major challenges for the conduct of regulatory science is integrating information and expertise across these sectors, noted FitzGerald (see Box 4-1). Regulatory scientists use knowledge derived not only from their own background and expertise, but also from other disciplines that bear weight in the decision-making process, including statistics, informatics, or communication.

Peter Honig, senior vice president and head of worldwide safety and regulatory, Pfizer Inc., distinguished "collective competency" from "collective experts." The process of regulation relies on a wide collection of disciplinary expertise (collective experts), he noted, but "enlightened" regulatory science also relies on the *integrated confluence* of these disciplines (collective competency). The most successful regulatory scientists at FDA are those who can leverage and integrate effectively the diverse expertise available at FDA to make informed, enlightened regulatory decisions, he emphasized.

BOX 4-1
Examples of Regulatory Scientists as Multidisciplinary Communicators

FitzGerald and Honig emphasized that the true value of modern and future regulatory scientists will be in their ability to integrate knowledge across many different disciplines. They gave examples of a few of the areas of expertise necessary, and discussed the increasing importance of working with teams of "collective experts" for successful regulatory scientists to understand the true meaning of data.

- Medical Product Regulation and Pharmacology
- Clinical Pharmacology
- Toxicology
- Epidemiology
- Clinical Trial Design
- Combination Therapies
- Influence of Diet
- Intellectual Property
- Communications
- Data Science and Informatics
- Clinical Validity of Biomarkers

SOURCES: FitzGerald and Honig presentations, October 21, 2015.

Navigating the Interface Between Science and Society

Regulatory scientists participate in a social discourse that extends far outside of the laboratory and clinic, and correspondingly, regulatory decisions do not influence just the scientific community, but also the public at large, noted Martin Philbert, professor and dean, University of Michigan School of Public Health. Frank Weichold highlighted the importance of communicating priorities and dialogue with external stakeholders, such as policy makers, patient groups, and academia. Mark C. Rogers suggested that a liberal arts background or communications training could aid the regulatory scientist in better communicating to such a broad audience.

Proficiency in the behavioral sciences also underlies success in regulatory science. For example, patient adherence to a prescribed medication regime can have an enormous impact on perceived efficacy and thus can be just as important as other clinical endpoints, observed Stephen Ostroff. To this end, Philbert suggested that regulatory science training curricula integrate the social and behavioral sciences.

TRAINING THE NEXT-GENERATION REGULATORY SCIENTIST

Academic Programs

Speakers discussed difficulties that exist in attracting emerging scientists to the practice of regulatory science. Russ Altman underscored that it is important to adopt a pragmatic approach to accessing universities, medical schools, nursing schools, and Ph.D. programs to attract the next generation of regulatory scientists. Sam Shekar noted that it could prove valuable to emphasize to emerging scientists that the traditional career paths of industry, academia, and government do not necessarily need to be compartmentalized and that collectively the field should look instead toward opportunities for partnerships among these careers, particularly during a scientist's training period.

Several speakers outlined approaches they are taking to address the challenge of adequately training and preparing scientists for careers in regulatory science. Many of these approaches involve partnering with an FDA-established program. Sandy Allerheiligen described a training program at the University of Virginia that allows students to work at FDA while completing their Ph.D. This program gives graduate students the opportunity to gain technical expertise and simultaneously learn how to apply this expertise in a regulatory setting.

The University of Rochester is also developing a certificate training program that would partner students with FDA, and the university is simultaneously exploring the possibility of partnering with government programs such as CERSIs or Clinical and Translational Science Awards (CTSAs). Scott Steele, director of government and academic research alliances and associate professor of public health sciences, University of Rochester, discussed the content and rationale of the university's training programs to workshop attendees. He highlighted the importance of significant and complementary training in academia, industry, and regulation.

Steele noted that one potential way to expand opportunities for regulatory science training is by maximizing the shared missions of the CERSIs and CTSAs to improve medical product development by tapping into the CTSA consortia. To investigate potential areas for collaboration between CERSIs and CTSAs, Steele and colleagues established a working group to share best practices. During the course of their work, Steele and colleagues convened a workshop at which they developed 11 core thematic areas of regulatory science (Adamo et al., 2015) (see Box 4-2). These competency areas could be used to evaluate and prioritize components for developing regulatory science training programs.

BOX 4-2
Examples of Core Thematic Areas of Regulatory Science

- Regulatory Science Research Questions and Priorities
- Regulatory Policies and Process
- Research Ethics
- Drug Discovery and Development
- Medical Device Innovation
- Preclinical
- Clinical Trials
- Postmarketing and Compliance
- Analytical Approaches and Tools
- Communication
- Technology and Innovation

SOURCE: Steele presentation, October 21, 2015.

Industry Programs

Several speakers also discussed industry-driven initiatives to foster the training and career tracks of regulatory scientists. Fields described Pfizer programs, which include internships, temporary assignments, mentoring, and industry–FDA collaborations.

Eileen Cannon, president, P*h*RMA Foundation, noted that the P*h*RMA Foundation is in the process of developing regulatory science rotations between industry and academia, as well as a mechanism that will facilitate FDA access to senior academic scientists to discuss current and specific needs. The goal of these training pathways and collaborations is to make the path to regulatory scientists more intentional and less random, both Fields and Cannon emphasized.

Shekar provided a view from another industry. He noted that Northrop Grumman has developed an internal program to foster career advancement for those working in the discipline of data science, the Future Technical Leaders Program. This program allows recent M.S. and Ph.D. engineering graduates to participate in three 1-year rotations on different projects within Northrop Grumman, training under senior technological mentors. Shekar observed that data scientists are foundational for solving regulatory science problems. The discipline of data science represents a confluence of knowledge in mathematics, computer science, and domain expertise. Data scientists can help uncover new information, optimize processes, improve

precision, make better decisions for the organization, and mature an industry along the continuum of analytic sophistication.

INCENTIVIZING AND FUNDING REGULATORY SCIENCE

Workshop discussions included focused consideration of the following career incentives and pathways in the discipline of regulatory science:

- **Lack of Recognition and Reward.** Bill Potter, senior advisor, National Institute of Mental Health, National Institutes of Health (NIH), noted that many individuals who are actively engaged in regulatory science work are performing it outside of their defined job duties, and it can frequently take nearly a decade to receive recognition in the field. Moreover, in traditional academic research, faculty must publish in high-impact journals to receive promotion or tenure, but publishing regulatory science is very rare, said Martin Landray. The leadership in the regulatory science ecosystem—FDA, NIH, industry—could consider ways to generate rewards and publicize accomplishments outside of the traditional peer-reviewed journal system, said Ostroff.
- **Development of Metrics of Success for Regulatory Science.** Relatedly, many workshop participants argued that it would be beneficial to identify alternative metrics for gauging success that are specific to regulatory science. Alastair Wood observed that regulatory scientists should not be confined to traditional academic standards, and incentives and career advancement benchmarks could instead be designed specifically for the responsibilities of the position. Wood also suggested expanding the questions that regulatory science addresses, such as including mechanistic questions that arise in development of regulatory science applications, and then rewarding accomplishments in answering those questions.
- **Limitations on Funding to Incentivize and Reward Regulatory Science.** Securing funding and resources for research endeavors within any field presents difficulties, and regulatory science is no exception. Weichold noted that there is currently scarce funding to develop or implement successful regulatory science research efforts, especially in academic settings. He and other individual workshop participants noted that increasing and targeting funding for regulatory science research could encourage innovation in the field and the development of career regulatory scientists.

- **Difficulties in Navigating the FDA Hiring Process.** Several participants noted that FDA is required to use the general hiring practices currently approved by the U.S. government, which can present challenges to applicants. Honig referenced the *Mission Possible* report for a deeper analysis of how monetary compensation, which is tied to the governmental hiring system in place, affects FDA's ability to recruit talent (FDA, 2015). Darrell Abernethy, associate director for drug safety, office of Clinical Pharmacology, FDA, suggested that the lengthy time involved with applying for and receiving an FDA position might be a burden for applicants.

5

Challenges and Opportunities in Regulatory Science

Over the course of the workshop, many participants discussed the new sources of information, technology, and techniques that are pushing the boundaries of regulatory science. Many of these new techniques, Stephen Ostroff noted, could be applied not just to help make regulatory decisions, but also to advance the scientific community in other expertise areas, including basic science and translational research. Ultimately, this progress will help make decisions that will serve to advance the health and well-being of the broader population. However, determining when, if, or how new techniques and data should be incorporated into the regulatory science process poses numerous challenges. Alastair Wood touched on a few of these challenges, including organizational acceptance of (or resistance to) a new paradigm, the continuing need to assess the performance of new and traditional data models, and the human capital and infrastructure needed to implement these new information sources. Other key challenges identified by multiple workshop participants involved questions around the data themselves, such as ownership and access or curation and its associated costs. Finally, some participants struggled to fit the tools and the challenges into the overarching principle of improving regulatory science—balancing innovation with rigor to enhance the efficiency, accuracy, and applicability of clinical trials without sacrificing safety to obtain the most efficacious and reliable treatments for disease.

Ultimately, for regulatory science to be improved most effectively, it must evaluate itself in the same manner other scientific disciplines do, said Martin Landray. Despite advances in technology and available tools, Martin Philbert cautioned that precision and scientific understanding can-

not replace good judgment. Many participants thought that regulatory scientists are most efficacious when they remain focused on the public health aspect of their work.

In the closing panel sessions, various workshop participants and speakers outlined the most relevant themes that they identified throughout the workshop and discussed priorities to advance the regulatory science agenda. Statements, recommendations, and opinions expressed in this section are those of individual presenters and participants and are not necessarily endorsed or verified by the Forum or the National Academies of Sciences, Engineering, and Medicine, and they should not be construed as reflecting any group consensus.

REGULATORY SCIENCE LANDSCAPE CONSIDERATIONS

Role of Public Engagement in Regulatory Science

Patients are more empowered and better informed than in the past; both the creation and use of data by patients could ultimately drive clinical or regulatory ecosystem behavior. One workshop participant noted that the regulatory science field should not underestimate the degree to which the most innovative users of data will increasingly be patients; in light of the current progress toward and investment in personalized medicine, there could be a corresponding drive toward patient-level approaches in regulating science applications. For example, a patient's knowledge that he or she has a gene mutation might incentivize the patient to seek participation in a clinical trial.

Data Ownership, Control, and the Precompetitive Space

Many workshop participants also discussed issues of data ownership, patient privacy, and best practices for communicating clinical trial results and disease or treatment risk possibilities. Another challenge addressed by numerous participants was defining the "precompetitive space," or the stages of product development in which competitors collaborate and share information. The quality of the data, as well as its curation, ownership, and control, are still debated and there are many problems and opportunities that could be addressed.

Summary of Individual Participant Remarks

Participants were encouraged to think about the major priorities that influence the regulatory science landscape, and how to incentivize adoption of changes. Their remarks are summarized below.

- *What are the major priorities for advancing the regulatory science landscape?*
  - Defining the precompetitive space so that results from early investigations can be shared and published without compromising intellectual property. (Abernethy, Amur, Philbert, Wagner, Wood)
  - What are the perceived problems in setting the boundaries of the precompetitive space? (Philbert)
  - Deciding who owns and controls the data. (Ostroff, Wood)
  - Deciding how the data are used. (Ostroff)
  - Posing and addressing the right questions will affect the field. (Landray)
- *What investments and incentives are required to encourage consideration or adoption of these priorities?*
  - Consider how regulatory science can be published in high-impact, peer-reviewed journals to increase visibility and reach. (Wood)
  - Obtaining funding for regulatory science research is an obstacle; neither academia nor FDA currently has the means to invest in the research in a comprehensive way. (Weichold)
  - Investment and incentives for undertaking the laborious process of data curation will be necessary to encourage it. (Participant)
  - Articulate, and reward, public health impacts of regulatory research. (Wilson)
- *How can we bridge the gap between regulatory science knowledge and regulation and practice? What approaches could be considered to advance the discipline?*
  - Principles for responsible data sharing are critical; it is unethical to not share clinical trial patient data with collaborators because that necessitates repeating the study for every related question that arises. (Wood)
  - Patients voluntarily contribute their own data for these studies and could considerably add to the data ownership debate.[1] (Participant)
  - Because pharmaceutical companies define their own risk thresholds according to their individual cultures, policies, and legal considerations, they would be key in setting data-sharing policies. (Lavezzari, Sauer)

[1] The Academies recently published a consensus report titled *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk*. More information can be found at: www.nationalacademies.org/hmd/Reports/2015/Sharing-Clinical-Trial-Data.aspx (accessed June 20, 2016).

CONSIDERATIONS FOR APPLICATIONS OF REGULATORY SCIENCE

Biomarkers

There is currently a "confluence of efforts" in developing and characterizing biomarkers, said John Wagner. Government, pharmaceutical companies, nonprofit groups, and consortia are all working to identify and develop biomarkers. One challenge will be to make sure the efforts complement each other and coalesce, rather than compete.

Clinical Trial Data Integration

The plethora of data now available allows for both changes in the way clinical trials are designed and the mechanisms by which treatments are studied postapproval. Ostroff summarized that it is a remarkable time period with regard to the conduct and assessment of clinical trials, particularly due to the computational tools becoming available. The biggest challenge will be in not compromising the ability to find the best, safest, and most effective answer as the methodologies evolve.

Next-Generation Surveillance

The ability to perform rigorous postmarketing surveillance and obtain reliable answers about medical product effectiveness and safety is not new, said Brian Strom. The novel aspect is the size of the databases and the amount of information available for analyses. Given the increasing number of databases and the potential to aggregate them, the shortage is no longer in hypothesis generation, but in exploring hypotheses with rigor. The tools being developed in surveillance may better be considered as ways to generate hypotheses, not as ways of identifying causality.

Modeling

Modeling, like other aspects of regulatory science, is undergoing immense change in response to the availability of big data. Innovative trial design, master trial protocols, Bayesian methods, and using consortia to understand disease are all dependent on the collection and use of data for the creation of knowledge and novel applications, said Darrell Abernethy. A significant opportunity for regulatory science to evolve is now centered on strong pharmacologic and biologic mechanistic approaches to inform population science.

Summary of Individual Participant Remarks

Participants described many obstacles facing the various applications of regulatory science, from considerations for biomarkers to postapproval surveillance. They also discussed the types of investments that could help realize any improvements in regulatory science, and current gaps between knowledge and practice. Their remarks are summarized below.

- *What are the major priorities for furthering innovative applications of regulatory science?*
  - Lack of predictability, a defined evidentiary framework, and a timeline for regulatory decisions for biomarker development. (Wagner)
  - The quality of information available and the ability to curate it, as well as rigorously determined acceptable thresholds for variability. (Ostroff)
  - Determining the correct balance of innovation and rigor for surveillance techniques and the data they can generate. (Strom)
- *What investments and incentives are required to encourage consideration or adoption of these priorities?*
  - Funding, in terms of both time and monetary investment, to allow development of biomarkers. (Several participants)
  - Developing ways to recognize researchers who share specialized software and techniques may encourage more information exchange in the field. (Myers)
  - Identifying current systemic discouragements that lead to a preference for pseudo-efficacy trials in Phase II that may be inappropriate and preclude movement to Phase III, contributing to the high rate of failure to progress to higher trial phases. (Angus, FitzGerald)
  - Removal of barriers to communication of information among sectors (e.g., sharing results with patients in easily understandable terms). (Krall)
- *How can we bridge the gap between regulatory science knowledge and regulation and practice? What approaches could be considered to advance the discipline?*
  - Innovative trial design is the key to good regulatory science, and encouraging those techniques in addition to focusing on biomarkers may bring personalized medicine to realization. (Krall)
  - Properly defining and especially validating biomarkers will be critical in order to use them for trial design without leading to false conclusions or erroneous results. (Wood)

- A consortium approach to developing biomarkers may address key gaps in both development and defining evidentiary standards. (Wagner)
- Cell-based therapies are likely to be the future of medicine, and planning now for how to move basic discovery into robust regulatory systems will be critical. (Greenberg)
- Apparently biased large datasets could be curated to reveal subsets of data that are suitable for scientific discovery; however, this must be considered as a hypothesis-generating rather than a definitive exercise. (Landray)
- Consider the potential applications for artificial intelligence in the future of medicine, given that medicine will become ever more data intensive. (Burch)
- Increased focus on determining personal effects from the application of population effects. (Krall)

INFRASTRUCTURE AND WORKFORCE CONSIDERATIONS

Building a Regulatory Science Workforce

Attracting proficient scientists and recruiting the right expertise to bolster the field's regulatory foundation can be a challenge. Owen Fields expressed concern that the current career path for regulators can all too often be undertaken as a result of a random or unintentional decision. Fields observed that regulatory science is not an encouraged pursuit and by some it is even considered a "dead-end" career. Frank Weichold encouraged participants to consider the needs of existing regulators, especially as new technologies arise. It would be advantageous for current regulatory scientists to have access to ongoing training to be able to use and apply these new tools and stay current in the field, he said. Additionally, several participants thought that encouraging the broader workforce now considered to be regulatory scientists to collaborate synergistically with each other is as critical as it is difficult.

Summary of Individual Participant Remarks

Considerations for building, training, and rewarding an enlightened regulatory workforce generated much discourse and debate among workshop participants. Their remarks are summarized below.

- *What are the major priorities for furthering the development of an innovative regulatory science workforce?*

  - Attracting the best and the brightest to the biomedical sciences in general, and to regulatory science in particular. (Abernethy)
  - Developing a new system to evaluate regulatory scientists on their own terms. (Altman, Landray, Philbert, Ostroff, Wood, and others)
  - Emphasizing that the regulatory portion of the title implies a social obligation and encouraging development of multidisciplinary regulatory scientists. (Rogers and others)
  - Clearly defining expectations and responsibilities for scientists individually and within a group, with an emphasis on leveraging complementary skill sets and encouraging collaboration. (Abernethy)
- *What investments and incentives are required to encourage consideration or adoption of these priorities?*
  - Regulatory science cannot be evaluated fairly using traditional academic metrics, and a reward strategy tailored for the field will be key. (Several participants)
  - Retaining and rewarding data scientists and data curators will become essential, given the juxtaposition of population-based information and personal information now coalescing in the available datasets and medical knowledge base. (Landray)
  - Currently, many regulatory scientists are not recognized or rewarded, and more support for those actively engaged in translational pursuits is necessary. (Potter)
- *How can we bridge the gap between regulatory science knowledge and regulation and practice? What approaches could be considered to advance the discipline?*
  - Use consumer industries as a model for incentivization, with metrics accounting for both quality of work and time to adoption. (Myers)
  - Articulating the broad public health impacts of the work may help draw scientists into the field. (Wilson)
  - Support rotations within industry and academia. (Cannon)
  - Mechanisms for senior academic scientists to support FDA in pharmaceutical research. (Cannon)
  - A broader consideration for partnerships in general, with less emphasis on the differences among government, industry, and academia, combined with aligning the incentives for collaborating parties. (Shekar)
  - First priority should be exceptional scientific training, then teaching scientists to recognize problems with high potential for regulatory impact. (Altman)
  - FDA needs a clear hiring process. (Abernethy)

Appendix A

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[1] This bibliography contains resources provided during presentations by workshop speakers, but not necessarily cited in the workshop summary report. These resources are included here as additional direction for readers interested in further exploration of the topics discussed at the workshop.

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Appendix B

Workshop Agenda

Advancing the Discipline of Regulatory Science for Medical Product Development: An Update on Progress and a Forward-Looking Agenda

An IOM Workshop

October 20–21, 2015
Keck Center
500 Fifth Street, NW Room 100
Washington, DC 20001

Background and Workshop Objectives:

The U.S. Food and Drug Administration (FDA) defines regulatory science as the science of developing new tools, standards, and approaches to assess the safety, effectiveness, quality, toxicity, public health impact, or performance of FDA-regulated products. Since its inception, the Institute of Medicine's Forum on Drug Discovery, Development, and Translation has focused on the need for strengthening the scientific basis of drug regulation. In February 2010, the Forum held a workshop, *Building a National Framework for the Establishment of Regulatory Science for Drug Development*, that examined the state of the science of drug regulation and considered approaches to enhance regulatory science. In September 2011, the Forum held another workshop, *Strengthening a Workforce for Innovative Regulatory Science*

in Therapeutics Development, that considered opportunities and needs for advancing innovative regulatory science through workforce and career development. Over the past several years, models to support the discipline have advanced. FDA's Centers of Excellence in Regulatory Science and Innovation enhance training and educational opportunities for regulatory scientists. Private funders have also established programs: For example, in 2011 the Burroughs Wellcome Fund launched Innovations in Regulatory Science Awards (IRSA), which aim to strengthen regulatory systems capacity by funding regulatory science–based research and collaborations.

This workshop will provide a venue to review progress in building the foundations of regulatory science and to explore a forward-looking agenda for bolstering the field. Participants will examine the current state and scope of the discipline, highlight opportunities to address barriers to success, and explore ways to foster collaboration. The workshop objectives are to:

- Explore current regulatory science priorities and strategies in federal, academic, and private-sector settings.
- Consider the current state of regulatory science as a discipline.
  - Discuss professional training successes.
  - Highlight opportunities to further support training, workforce, and career development.
- Explore the core components of a robust discipline of innovative regulatory science.
  - Consider gaps and key opportunities to address needs to support the discipline of innovative regulatory science.
- Examine needs and barriers to collaboration among, across, and within the public and private sectors.

DAY ONE (October 20, 2015)

8:00 a.m. Breakfast Available

8:30 a.m. Opening Remarks

MARTIN PHILBERT, *Workshop Co-Chair*
Professor and Dean
University of Michigan School of Public Health

ALASTAIR WOOD, *Workshop Co-Chair*
Partner, Symphony Capital
Professor of Medicine and Pharmacology, Weill Cornell School of Medicine

SESSION I: SETTING THE STAGE FOR INNOVATION IN REGULATORY SCIENCE

Session Objectives:

- Introduce and discuss workshop theme.
- Highlight key scientific questions for the field of innovative regulatory science, focusing on the role of information as it is generated across regulatory science domains and ways that it can be better put to use.
- Discuss how new capabilities and access to new information could advance regulatory science for medical product development.
- Highlight operational challenges.

8:40 a.m. Background and Session Objectives

***Session Chair*:** Alastair Wood, Partner, Symphony Capital, Professor of Medicine and Pharmacology, Weill Cornell School of Medicine (*Workshop Co-Chair*)

8:45 a.m. **Workshop Theme and Framework: Innovation in Regulatory Science Through Integration of Information**

Transformation of Our Ability to Generate, Analyze, Integrate, and Share Information Across Regulatory Science Applications

Russ Altman
The Kenneth Fong Professor of Bioengineering, Genetics, Medicine, & (by courtesy) Computer Science
Stanford University

9:00 a.m. *Advancing Regulatory Science Using Information and Information Science: What to Improve and How to Improve It*

Jim Stevens
Distinguished Research Fellow
Eli Lilly

9:15 a.m. *Value of Information to Inform Decision Making Under Uncertainty*

KATHERINE VON STACKELBERG
Research Scientist
Harvard Center for Risk Analysis

9:30 a.m. *Fusing RCTs with EHR "Big Data"*

DEREK ANGUS
Distinguished Professor and Mitchell P. Fink Endowed Chair, Department of Critical Care Medicine
University of Pittsburgh

9:45 a.m. **Panel Discussion and Audience Q&A** (*30 mins*)

10:15 a.m. **BREAK** (*15 mins*)

SESSION II: LEARNING LESSONS THROUGH CONSIDERATION OF REGULATORY SCIENCE APPLICATIONS

Session Objectives:

- Discuss how enhanced approaches to obtaining, accessing, and integrating information could advance the science throughout and across development.
- Through consideration of selected regulatory science applications, discuss current capabilities for regulatory science and strategic priorities in federal, academic, and private sectors.
- Suggest ways forward to address identified gaps and operational challenges.

10:30 a.m. Background and Session Objectives

***Session Chair*:** Stephen Ostroff, Acting Commissioner, U.S. Food and Drug Administration

10:35 a.m. **Identifying and Developing Meaningful Biomarkers**

***Panel Moderator*:** John Wagner, Senior Vice President, Head of Clinical and Translational Sciences, Takeda Pharmaceuticals

10:40 a.m. *Basic Science of Measurement: Metrology Principles for Biomarkers*

Marc Salit
Leader, Genome-Scale Measurements
National Institute of Standards and Technology (NIST)

10:50 a.m. *Opportunities to Develop Meaningful Biomarkers*

Shashi Amur
Scientific Lead, Center for Drug Evaluation and Research's (CDER's) Biomarker Qualification Program
U.S. Food and Drug Administration

11:00 a.m. *Challenges and Opportunities for Qualifying Biomarkers: An Industry Perspective*

Gabriela Lavezzari
Assistant Vice President, Science & Regulatory Advocacy
Pharmaceutical Research and Manufacturers of America (P*h*RMA)

11:10 a.m. *Collaborative Approaches for Developing Kidney Safety Biomarkers*

John Michael Sauer
Executive Director, Predictive Safety Testing Consortium (PSTC)
The Critical Path Institute

11:20 a.m. **Panel Discussion and Audience Q&A** (*30 mins*)

11:50 a.m. **BREAK to Lunch** (*60 mins*)

SESSION II, CONTINUED: CONSIDERATION OF REGULATORY SCIENCE APPLICATIONS

12:50 p.m. **Clinical Trial Data Integration**

***Panel Moderator*:** Rob Califf, Deputy Commissioner for Medical Products and Tobacco, U.S. Food and Drug Administration

12:55 p.m. *Big Data for Randomized Controlled Trials: Opportunities and Challenges for the Reliable Assessment of Treatment Effects*

Martin Landray
Professor of Medicine and Epidemiology, Deputy Director Big Data Institute
University of Oxford

1:05 p.m. *Approaches to Overcoming Variance Due to Heterogeneity: A Case Study in a Rare Disease*

Susan Ward
Founder and Executive Director
The TAP Collaboration

1:15 p.m. *Access to Patient-Level Data from Clinical Trials*

Perry Nisen
Chief Executive Officer
Sanford Burnham

1:25 p.m. *The Role of Open APIs (Application Programming Interfaces) and FHIRs (Fast Healthcare Interoperability Resources) Platform for Integrating Patient Care and Clinical Research Data*

Charles Jaffe
Chief Executive Officer
Health Level Seven International

1:35 p.m. *Data Aggregation Across Diseases and Between Stakeholders*

Enrique Avilés
Chief Technology Officer
The Critical Path Institute

1:45 p.m. **Panel Discussion and Audience Q&A** (*30 mins*)

Panelists:
- *Clinical Trial Data Integration* speakers (above), *and*
- Kyle J. Myers, Director, Division of Imaging, Diagnostics, and Software Reliability (DIDSR), U.S. Food and Drug Administration

2:15 p.m. **BREAK** (*15 mins*)

2:30 p.m. **Next-Generation Surveillance**

***Panel Moderator*:** Brian Strom, Chancellor of Rutgers Biomedical and Health Sciences, Rutgers, the State University of New Jersey

2:35 p.m. *Next-Generation Surveillance: FDA's Sentinel Program*

Richard Platt
Professor and Chair of the Department of Population Medicine
Harvard Pilgrim Health Care Institute

2:45 p.m. *Harnessing Web Search Data as Complementary Signals for Pharmacovigilance*

Eric Horvitz
Distinguished Scientist & Managing Director
Microsoft Research

2:55 p.m. *Online Discussion Forums as Potential Sources of Adverse Drug Event Data*

John H. Holmes
Professor of Medical Informatics
University of Pennsylvania

3:05 p.m. *New Frontiers in Safety Surveillance*

John Brownstein
Associate Professor
Harvard Medical School

3:15 p.m. **Panel Discussion and Audience Q&A** (*30 mins*)

Panelists:
- *Next-Generation Surveillance* speakers (above), *and*
- Danica Marinac-Dabic, Director, Division of Epidemiology, Center for Devices and Radiological Health (CDRH), U.S. Food and Drug Administration

3:45 p.m. **Innovation in Modeling and Integrating Information**

***Panel Moderator*:** Darrell Abernethy, Associate Director for Drug Safety, Office of Clinical Pharmacology, U.S. Food and Drug Administration

3:50 p.m. *Statistical Modeling for Efficient and Adaptive Trial Designs Using Composite Endpoints*

Brian Alexander
Associate Professor of Radiation Oncology
Harvard Medical School

4:00 p.m. *Model Informed Drug Development and Regulatory Decisions Today and Tomorrow*

Sandy Allerheiligen
Vice President, Modeling and Simulation
Merck

4:10 p.m. *Innovation in Modeling and Integrating Information: The CAMD Knowledge Model for Alzheimer's Disease*

Brian Corrigan
Senior Director
Pfizer Inc.

4:20 p.m. *Assessing the Placebo Effect and Drug Efficacy Using Functional MRI*

Ariana Anderson
Assistant Research Statistician
University of California, Los Angeles

4:30 p.m. **Panel Discussion and Audience Q&A** (*30 mins*)

Panelists:
- *Innovation in Modeling and Integrating Information* speakers (above), *and*
- Klaus Romero, Director of Clinical Pharmacology, The Critical Path Institute (C-Path)

5:00 p.m. Wrap-Up of Day One

5:10 p.m. **ADJOURN**

DAY TWO (October 21, 2015)

8:30 a.m. Welcome and Reflections from Day One

Martin Philbert, *Workshop Co-Chair*
Professor and Dean
University of Michigan School of Public Health

Alastair Wood, *Workshop Co-Chair*
Partner, Symphony Capital
Professor of Medicine and Professor of Pharmacology, Weill Cornell School of Medicine

SESSION III: ENVISIONING THE FUTURE OF REGULATORY SCIENCE: A FORWARD-LOOKING AGENDA

Session Objective:

- Discuss opportunities and priorities to advance innovative regulatory science through information.

8:35 a.m. **Disciplinary Components and Infrastructure Needs**

***Panel Moderator*:** Martin Philbert, Professor and Dean, University of Michigan (*Workshop Co-Chair*)

8:40 a.m. *A Workforce to Bridge the Translational and Regulatory Bottlenecks in Drug Development*

GARRET FITZGERALD
Professor of Medicine and Pharmacology
University of Pennsylvania

8:50 a.m. *Core Components of Regulatory Science Curriculum*

SCOTT STEELE
Director of Government and Academic Research Alliances
Associate Professor of Public Health Sciences
University of Rochester

9:00 a.m. *Data Science Workforce Challenges and Solutions: Northrop Grumman Perspectives*

SAM SHEKAR
Chief Medical Officer
Northrop Grumman

9:10 a.m. *Developing the Regulatory Scientist for Medical Product Development: Successful Examples from Pfizer Worldwide R&D*

OWEN FIELDS
Vice President, Regulatory Strategy
Pfizer Inc.

9:20 a.m. **Panel Discussion and Audience Q&A** (*30 mins*)

Panelists:
- *Disciplinary Components and Infrastructure Needs* speakers (above), *and*
- Peter Honig, Senior Vice President and Head of Worldwide Safety and Regulatory, Pfizer Inc.
- Frank Weichold, Director, Science and Innovation, Office of the Chief Scientist/Office of the Commissioner, U.S. Food and Drug Administration

9:50 a.m. **Day Two Keynote** (*15 mins; followed by 5 mins of Q&A*)

The Future of Regulatory Science at FDA

Stephen Ostroff
Acting Commissioner
U.S. Food and Drug Administration

10:10 a.m. **BREAK** (*15 mins*)

10:25 a.m. **Presentation of Key Themes/Suggested Paths from Session II Panel Moderators and Session Chair** (*4 speakers; 10 mins each*)

Panel Introduction

Stephen Ostroff
Acting Commissioner
U.S. Food and Drug Administration

10:30 a.m. *Session II Moderators*

John Wagner (moderator of *Identifying and Developing Meaningful Biomarkers*)
Senior Vice President, Head of Clinical and Translational Sciences
Takeda Pharmaceuticals

Brian Strom (moderator of *Next-Generation Surveillance*)
Chancellor of Rutgers Biomedical and Health Sciences
Rutgers, the State University of New Jersey

Darrell Abernethy (moderator of *Innovation in Modeling and Integrating Information*)
Associate Director for Drug Safety, Office of Clinical Pharmacology
U.S. Food and Drug Administration

11:10 a.m. **Reflecting and Envisioning the Regulatory Science Discipline of 2020: Panel Discussion with Session Chairs, Panel Moderators, Panelists, and Audience**

***Panel Moderators*:** Martin Philbert and Alastair Wood (*Workshop Co-Chairs*)

Panelists:
- Session II moderators (above), *and*
- Eileen Cannon, President, P*h*RMA Foundation
- Mark C. Rogers, Board Chairman, Reagan-Udall Foundation

Discussion Questions:

- What are the three to five priorities that could advance regulatory science domains?
- Do we have a cohesive approach to advancing the discipline of regulatory science? Are the strategic priorities that have been articulated and adopted by the key players aligned with, and positioned to advance, innovative regulatory science?
- What investments and incentives are needed to get us there?
- How to bridge the gap from regulatory science knowledge to regulation and practice?

12:10 p.m. **ADJOURN**

Appendix C

Participant Biographies

CO-CHAIRS

Martin Philbert, Ph.D., is professor of toxicology and dean of the University of Michigan School of Public Health. He earned his B.S. from the College of Arts and Technology at Cambridge, and his doctorate from the London University Royal Postgraduate Medical School. He was awarded a postdoctoral fellowship in the Neurotoxicology Laboratories at Rutgers University. Dr. Philbert served as a research assistant professor at Rutgers' Neurotoxicology Laboratories until he joined the faculty at the University of Michigan School of Public Health as an assistant professor of toxicology. He was promoted to associate professor in 2000 and to professor in 2004. He served as associate chair for research and development in the Department of Environmental Health Sciences from 2000 to 2003. In 2004, Dr. Philbert was appointed senior associate dean for research of the School of Public Health, a position he held through 2010 when he was appointed as dean. He also served as interim director of the Center for Risk Science and Communication. Dr. Philbert has maintained a continuously federally funded portfolio of basic research activities throughout his career. His research focuses on the development of flexible polymer nanoplatforms for optical sensing of ions and small molecules and the early detection and treatment of brain tumors. Other research interests include the mitochondrial mechanisms of chemically induced neuropathic states. Most recently his work has been funded by the National Institutes of Health, the U.S. Department of the Air Force, and the National Cancer Institute. He is the author of more than 150 peer-reviewed scholarly manuscripts, abstracts,

and book chapters. Dr. Philbert is the chair of the newly formed U.S. Environmental Protection Agency (EPA) Chemical Assessment Advisory Committee, which provides peer review of risk assessments produced under the auspices of EPA's Integrated Risk Information System and a standing member of the Agency's Science Advisory Board. He also served a 4-year term on the National Advisory Environmental Health Sciences Council of the National Institute of Environmental Health Sciences and provides consultation to the federal agencies on a variety of issues surrounding emerging nanotechnologies, nanomedicine, health, and safety. Dr. Philbert is an elected member of the National Academy of Medicine, a Fellow of the Royal Society of Chemistry (UK), a Fellow of the Academy of Toxicological Sciences, and a member of the Division on Earth and Life Studies of the National Academies of Sciences, Engineering, and Medicine.

Alastair Wood, M.D., was professor of both medicine and pharmacology at Vanderbilt University Medical School and served as assistant vice chancellor for clinical research and associate dean, 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. He is a partner at Symphony Capital LLC, a private equity company investing in the clinical development of novel biopharmaceutical products. Dr. Wood is a member of many societies, including the National Academy of Medicine, American Association of Physicians, American Society for Clinical Investigation, Honorary Fellow, American Gynecological and Obstetrical Society, Fellowship of the American College of Physicians, Fellowship of the Royal College of Physicians of London, and Fellowship of the Royal College of Physicians of Edinburgh. He was the 2005 recipient of the Rawls-Palmer Award and in 2008 received the honorary degree of Doctor of Laws, honoris causa, from the University of Dundee. Dr. Wood has served on a number of editorial boards, including the *New England Journal of Medicine* Editorial Board and was the Drug Therapy Editor of the *New England Journal of Medicine* from 1985 to 2004. His research has resulted in more than 300 articles, reviews, and editorials.

PLANNING COMMITTEE

Russ Altman, M.D., Ph.D., is a professor of bioengineering, genetics, and medicine (and of computer science, by courtesy) and past chair of the Bioengineering Department at Stanford University. His primary research interests are in the application of computing and informatics technologies to problems relevant to medicine. He is particularly interested in methods for understanding drug action at molecular, cellular, organism, and population levels.

His lab studies how human genetic variation impacts drug response (e.g., http://www.pharmgkb.org). Other work focuses on the analysis of biological molecules to understand the action, interaction, and adverse events of drugs (http://features.stanford.edu). Dr. Altman holds an A.B. from Harvard College, an M.D. from Stanford Medical School, and a Ph.D. in Medical Information Sciences from Stanford. He received the U.S. Presidential Early Career Award for Scientists and Engineers and a National Science Foundation CAREER Award. He is a fellow of the American College of Physicians, American College of Medical Informatics, American Institute of Medical and Biological Engineering, and American Association for the Advancement of Science. He is a member of the National Academy of Medicine. He is a past president, founding board member, and a fellow of the International Society for Computational Biology, and a past president of the American Society for Clinical Pharmacology & Therapeutics. He has chaired the Science Board advising the U.S. Food and Drug Administration commissioner. He currently serves on the advisory committee to the National Institutes of Health director. Dr. Altman is board certified in internal medicine, and has recently been certified in the first class of diplomates in clinical informatics. He is an organizer of the annual Pacific Symposium on Biocomputing (http://psb.stanford.edu), and a founder of Personalis, Inc. He received the Stanford Medical School graduate teaching award in 2000 and the mentorship award in 2014.

Sharon Hesterlee, Ph.D., is the new chief science officer for the Myotonic Dystrophy Foundation. Previously, she has been the vice president of research for Parent Project Muscular Dystrophy (PPMD), where she oversaw research investments in Duchenne muscular dystrophy (DMD), began the DMD Research Round Table, and participated in the development of the first quantitative benefit–risk study in a rare disease and in the first patient organization–generated U.S. Food and Drug Administration draft guidance. Before PPMD, she spent 11 years with the Muscular Dystrophy Association (MDA), where as a senior vice president she established MDA Venture Philanthropy and MDA's Translational Research program, brokering and managing more than $30M in drug development contracts with industry and other partners. She has also served as part-time scientific director for the Association for Frontotemporal Degeneration (FTD), where she managed the FTD Treatment Study Group. She has been involved in the planning of numerous meetings to identify and remove barriers to therapy development for rare disease and she has served on several advisory boards, such as the U.S. Department of Health and Human Services Federal Advisory Committee for muscular dystrophy and the NINDS (National Institute of Neurological Diseases and Stroke) Council. Dr. Hesterlee received her Ph.D. in Neuroscience from the University of Arizona in 1999. She currently serves on the board of directors of the Health Research Alliance and

the advisory board to the University of Arizona's School of Mind, Brain and Behavior.

Rusty Kelley, Ph.D., joined the Burroughs Wellcome Fund (BWF) as a program officer in 2013 and directs the Fund's Scientific Interfaces and Regulatory Science initiatives. Prior to his position at BWF, Dr. Kelley was the director of preclinical and translational medicine at Tengion, Inc., a regenerative and tissue engineering company originating from Boston Children's Hospital and Wake Forest University. As a senior scientist and then as a director at Tengion, Dr. Kelley was responsible for stewarding a broad-based intellectual property (IP) portfolio, designing and executing good laboratory practice (GLP) efficacy and safety studies, authoring the pharm-tox and risk–benefit analysis sections of U.S. and European regulatory filings, and developing early-phase clinical trials for the renal and bladder franchises. Prior to Tengion, Dr. Kelley was a postdoctoral fellow at the University of North Carolina at Chapel Hill, where he was awarded an American Heart Association fellowship under Dr. Cam Patterson, a BWF Translational Science awardee. In Patterson's translational genomics group, Dr. Kelley published in vascular biology using genetic BMP and VEGF mouse models of cardiovascular disease that included a faculty of 1,000 *Journal of Cell Biology* (JCB) manuscript describing a novel endocytic mechanism for regulating BMP signaling. Prior to his postdoc, Dr. Kelley was awarded a Stanley Scott Cancer Center graduate fellowship at Louisiana State University's (LSU's) Health Sciences Center, where he studied and published in Phase I, Cyp450-mediated drug metabolism. Before attending graduate school, Dr. Kelley worked in clinical development at PPD, Inc., of Wilmington, North Carolina, where he helped oversee multiple Phase I–III clinical trials (including for then Glaxo-Wellcome) in the United States and overseas in the divisions of General Medicine, National Institutes of Health (NIH)-sponsored trials, and Infectious Disease. Prior to joining PPD, Inc. in 1995, he worked for AAIPharma, also of Wilmington, North Carolina, in the formulation and development group of their Pharmaceutics Division following a wet chemistry bench position in their Analytical Division. He received a bachelor's degree in chemistry from the University of North Carolina at Chapel Hill and earned his Ph.D. from LSU in pharmacology and experimental therapeutics.

Emma Meagher, M.D., serves as associate professor of medicine and pharmacology at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia. Dr. Meagher graduated cum laude with her M.D. from the Royal College of Surgeons in Dublin, Ireland, and completed postgraduate training in internal medicine, cardiology, and pharmacology. In her role as senior associate dean and chief clinical research officer,

Dr. Meagher is responsible for the institution's clinical research infrastructure and its portfolio. Dr. Meagher's research interest is the development of novel therapeutics for dyslipidemia. Her educational interests are in the fields of translational research methodology and career development for clinical and translational scientists and novel modalities for education in pharmacology to undergraduate medical students. She currently serves on the Association for Clinical and Translational Science board of directors and chairs its education committee.

Robert Meyer, M.D., is the inaugural director of the Virginia Center for Translational and Regulatory Sciences at the University of Virginia's (UVA's) School of Medicine, as well as being an associate professor of public health sciences. In this position, he is heading a group that will develop a regulatory science educational track, as well as provide regulatory and translational knowledge resources to university and external entities who seek to move basic science discoveries to the bedside. He is a member of the U.S. Pharmacopeia Expert Panel revising the Medicare Model Guidelines and on the Benefit–Risk Advisory Council for FasterCures. Prior to joining the faculty at UVA, Dr. Meyer was vice president and head, Global Regulatory Strategy, Policy and Safety at Merck Research Laboratories, where he was responsible for leading an organization of more than 1,000 individuals in the oversight of all regulatory strategy and operations, global regulatory policy and intelligence, and global product safety and pharmacovigilance. At Merck, Dr. Meyer served on the Early and Late Stage Development Review Committees and the Safety Review Committee and chaired the Development Policy Committee. Externally, Dr. Meyer chaired the Regulatory Affairs Coordinating Committee for Pharmaceutical Research and Manufacturers of America (P*h*RMA) from 2012 to 2013, and served as a key P*h*RMA negotiator on PDUFA V. Prior to Merck, Dr. Meyer worked for the U.S. Food and Drug Administration (FDA) from 1994 to 2007. In his final 5 years at FDA, Dr. Meyer was the director for the Office of Drug Evaluation II within the Center for Drug Evaluation and Research (CDER), with responsibilities for pulmonary and allergy, metabolic and endocrine, and analgesics, anesthetics and rheumatologic drug products. Dr. Meyer was involved in several CDER initiatives, amongst them chairing the development of the Pre-Market Risk Assessment guidance. Additionally, he participated with the FDA negotiation team for PDUFA III and IV. While at FDA, Dr. Meyer served as a technical expert to the Medical Aerosols Technical Options Committee to the Montreal Protocol on the Protection of the Ozone Layer, work for which he was recognized by both the United Nations Environmental Programme and the U.S. Environmental Protection Agency. He also served on the third expert panel for the National Heart, Lung, and Blood Institute's National Asthma Education and Prevention

Program (NAEPP EPR3). Prior to joining FDA, Dr. Meyer was a practicing pulmonologist and critical care specialist on the faculty of the Oregon Health & Science University, where he helped create the medical service for the Lung/Heart-Lung Transplantation service. Dr. Meyer received his M.D. from the University of Connecticut School of Medicine and his bachelor's degree in Natural Science from Lehigh University.

Stephen Ostroff, M.D., served as acting commissioner of the U.S. Food and Drug Administration (FDA) from April 2015 to February 2016. Previously, he was FDA's chief scientist, responsible for leading and coordinating FDA's crosscutting scientific and public health efforts. The Office of the Chief Scientist works closely with FDA's product centers, providing strategic leadership and support for FDA's regulatory science and innovation initiatives. Dr. Ostroff joined FDA in 2013 as chief medical officer in the Center for Food Safety and Applied Nutrition and senior public health advisor to FDA's Office of Foods and Veterinary Medicine. Prior to that, he served as deputy director of the National Center for Infectious Diseases at the Centers for Disease Control and Prevention (CDC). He retired from the Commissioned Corps of the U.S. Public Health Service at the rank of Rear Admiral (Assistant Surgeon General). Dr. Ostroff was the director of the Bureau of Epidemiology and acting physician general for the Commonwealth of Pennsylvania and has consulted for the World Bank on public health projects in South Asia and Latin America. Dr. Ostroff graduated from the University of Pennsylvania School of Medicine and completed residencies in internal medicine at the University of Colorado Health Sciences Center and Preventive Medicine at CDC. He is a fellow of the Infectious Diseases Society of America and the American College of Physicians. Prior to assuming the role of FDA's acting commissioner, he chaired the Public Health Committee of the American Society for Microbiology's Public and Scientific Affairs Board.

Paul Seligman, M.D., M.P.H., is executive director for global regulatory policy at Amgen. Prior to joining Amgen in 2012, he had a public health career of nearly 30 years in the federal government. At the U.S. Food and Drug Administration (FDA), he served as the director of FDA's Latin America Regional Office, as associate director for safety policy and communication in the Center for Drug Evaluation and Research (CDER), and as the director of the Office of Pharmacoepidemiology and Statistical Science. Before joining FDA in 2001, Dr. Seligman served for 7 years as the deputy assistant secretary for health studies at the Department of Energy. He began his Public Health Service (PHS) career in 1983 at the Centers for Disease Control and Prevention (CDC) as an Epidemic Intelligence Service officer. He completed a primary care internal medicine residency at The Cambridge Hospital in Cambridge, Massachusetts, prior to join-

ing CDC. From 1974 to 1976, he was a Peace Corps volunteer in Kenya. Dr. Seligman holds an M.D. from the University of California, Davis; an M.P.H. in industrial health from the University of Michigan; and a B.S. in Chemistry from Yale University. He is board certified in internal medicine, occupational medicine, and public health and general preventive medicine. He is a retired commissioned Oofficer from the PHS, having attained the rank of Rear Admiral.

Brian Strom, M.D., M.P.H., is the recently appointed inaugural chancellor of Rutgers Biomedical and Health Sciences (RBHS) and the executive vice president for Health Affairs at Rutgers University. RBHS has nine schools and five centers/institutes, and includes academic, patient care, and research facilities. Dr. Strom was formerly the executive vice dean of institutional affairs, founding chair of the Department of Biostatistics and Epidemiology, founding director of the Center for Clinical Epidemiology and Biostatistics, and founding director of the Graduate Program in Epidemiology and Biostatistics, all at the Perelman School of Medicine of the University of Pennsylvania (Penn). Dr. Strom earned a B.S. in molecular biophysics and biochemistry from Yale University in 1971, and then an M.D. from the Johns Hopkins University School of Medicine in 1975. From 1975 to 1978, he was an intern and resident in internal medicine, and from 1978 to 1980, he was a National Institutes of Health (NIH) fellow in clinical pharmacology at the University of California, San Francisco. He simultaneously earned an M.P.H. in epidemiology at the University of California, Berkeley. He has been on the faculty of the University of Pennsylvania School of Medicine since 1980. The Center for Clinical Epidemiology and Biostatistics (CCEB) that he created at Penn includes more than 550 faculty, research and support staff, and trainees. At the time Dr. Strom stepped down, CCEB research received nearly $49 million/year in extramural support. Its total budget was approximately $67 million. Although Dr. Strom's interests span many areas of clinical epidemiology, his major research interest is in the field of pharmacoepidemiology, that is, the application of epidemiologic methods to the study of drug use and effects. He is recognized as a founder of this field and for his pioneer work in using large automated databases for research. He is editor of the field's major text and editor-in-chief of *Pharmacoepidemiology and Drug Safety*, the official journal of the International Society for Pharmacoepidemiology. In addition to writing more than 580 papers and 14 books, he has been principal investigator (PI) for more than 275 grants, including more than $115 million in direct costs alone. Dr. Strom has been invited to give more than 400 talks outside his local area, including presentations as the keynote speaker for numerous international meetings. He has been a consultant to NIH, the U.S. Food and Drug Administration (FDA), Centers for Disease

Control and Prevention (CDC), United States Pharmacopeial Convention (USP), Association of American Medical Colleges (AAMC), Joint Commission on Accreditation of Healthcare Organizations (JCAHO), foreign governments, most major pharmaceutical manufacturers, and many law firms. Dr. Strom is also a nationally recognized leader in clinical research training. At the Perelman School of Medicine, Dr. Strom developed graduate training programs in epidemiology and biostatistics. Dr. Strom was PI or Co-PI of 11 different NIH-funded training grants, each of which supported clinical epidemiology trainees in funded training grants and in different specialties and subspecialties, and has been the primary mentor for more than 40 former and current clinical research trainees and numerous junior faculty members. Internationally, Dr. Strom was a key contributor to the conceptualization and planning that led to the development of the International Clinical Epidemiology Network (INCLEN), created in 1979 with support provided by the Rockefeller Foundation to provide clinical research training to clinicians from selected developing country sites. Dr. Strom was a member of the board of regents of the American College of Physicians, the board of directors of the American Society for Clinical Pharmacology and Therapeutics, and the board of directors for the American College of Epidemiology, and is currently a member of the board of directors for the Association for Patient-Oriented Research. He was previously president of the International Society for Pharmacoepidemiology and the Association for Clinical Research Training. Dr. Strom was on the Drug Utilization Review Committee and the Gerontology Committee of USP, served on the Drug Safety and Risk Management Advisory Committee for FDA, and chaired or was a member of a number of Institute of Medicine committees. He is an elected member of the National Academy of Medicine. Dr. Strom is a member of the American Epidemiology Society, and is one of a handful of clinical epidemiologists ever elected to the American Society of Clinical Investigation and American Association of Physicians. He has been awarded a multitude of awards, including the John Phillips Memorial Award for Outstanding Work in Clinical Medicine, an award from the American College of Physicians that is considered to be one of the highest awards in internal medicine. Dr. Strom also received the 2013 Association for Clinical and Translational Science/American Federation for Medical Research National Award for Career Achievement and Contribution to Clinical and Translational Science for translation from clinical use into public benefit and policy. Penn awards that Dr. Strom received include the Class of 1992 Class Teaching Award and the Samuel Martin Health Evaluation Sciences Research Award. Dr. Strom received the 2004 Christian R. and Mary F. Lindback Award, the University's most prestigious teaching award, in recognition of the contribution he has made in his career to clinical research teaching.

SPEAKERS/PANELISTS

Darrell Abernethy, M.D., Ph.D., is the lead for the biosimilars program in the Office of Clinical Pharmacology. In addition, he is responsible for leading the development of a pharmacological mechanism–based safety program in the Office of Clinical Pharmacology to work in synergy with efforts in the Office of Surveillance and Epidemiology and other offices and centers at the U.S. Food and Drug Administration (FDA). Dr. Abernethy brings more than 25 years of experience in medicine and pharmacology, including positions in academia, practice, and research. Prior to joining FDA, he served as chief science officer at United States Pharmacopeial Convention (USP). Dr. Abernethy earned his M.D. and Ph.D. from the University of Kansas School of Medicine. In addition to his work at FDA, he is currently a professor of medicine (geriatrics) and of pharmacology and molecular science (part-time) at the Johns Hopkins University School of Medicine. Dr. Abernethy's training in internal medicine was at the University of Miami/Jackson Memorial Hospital, and postdoctoral training in clinical pharmacology at Massachusetts General Hospital followed this. He is board certified in internal medicine and clinical pharmacology. He joined the faculty at Tufts–New England Medical Center as an assistant professor. Following this he was at Baylor College of Medicine, where he became associate professor of medicine. Dr. Abernethy then moved to Brown University School of Medicine as chief of the Division of Clinical Pharmacology and became a professor of medicine at that institution. He then moved to Georgetown University School of Medicine as Francis Cabell Brown Professor of Medicine and Pharmacology and director of the Division of Clinical Pharmacology. Dr. Abernethy then joined the National Institute of Aging as chief of the Laboratory of Clinical Investigation in the intramural research program. Following that he served as chief science officer at USP. Dr. Abernethy's studies of mechanisms of peripheral distribution of drugs and drug disposition and effect in obesity and pharmacokinetic/pharmacodynamic relationships of cardiovascular drugs in aging have been well received and led to his being named to the Institute for Scientific Information's Most Highly Cited Researchers in Pharmacology. He has received the Rawls-Palmer Award from the American Society for Clinical Pharmacology and Therapeutics, the Nathaniel Kwit Award from the American College of Clinical Pharmacology, and the Abrams Award in Geriatric Clinical Pharmacology from the American Society for Clinical Pharmacology and Therapeutics. As an educator, he has served on the National Board of Medical Examiners (NBME) Pharmacology Test Committee (1992–1996; chair 2009–present), chair of the NBME (now called the United States Medical Licensing Examination [USMLE]) Applied Pharmacology Committee (1997–2000), the USMLE biostatistics task force and Step 1 Test Committee (2000–2006),

the USMLE International Foundations of Medicine Task Force (2010–2012), and the Evidence-Based Medicine Committee (2013–present). As an extramural investigator, he served on the National Institute of General Medical Sciences Pharmacological Sciences study section (1988–1992), the FDA generic drugs (1990–1992) and cardiorenal (1992–1996) advisory committees, and as chair of the U.S. Department of Veterans Affairs merit review geriatrics subcommittee (1998–2000). Dr. Abernethy's professional affiliations include serving as president of the American Society of Clinical Pharmacology and Therapeutics (1991–1992). In addition, he has served as a member of the editorial boards of the *Journal of the American Geriatrics Society*, *Biopharmaceutics and Drug Disposition*, and *Molecular Interventions*, and as editor-in-chief of *Pharmacological Reviews*. He is currently on the editorial boards of *Clinical Pharmacology and Therapeutics*, the *Journal of Clinical Psychopharmacology*, *Drugs*, and *Drugs and Therapy Perspectives*; is associate editor of the *Journal of Pharmacology and Experimental Therapeutics*; and is deputy editor of *Pharmacology Research & Perspectives*.

Brian Alexander, M.D., M.P.H., is a radiation oncologist specializing in research and clinical care for patients with tumors of the central nervous system. He is the disease center leader for radiation oncology at the Center for Neuro-Oncology, Dana-Farber Cancer Institute. His research interests include the characterization of the radiation responsiveness of glioma stem cells, preclinical evaluation of novel therapeutics, and innovative designs for early-phase clinical trials. Dr. Alexander's work has been pioneering in the area of biomarker-based and Bayesian clinical trial designs in neuro-oncology. Dr. Alexander previously served as a White House fellow and special assistant to the Secretary of Veterans Affairs. Under Secretary Peake, he helped prepare the U.S. Department of Veterans Affairs (VA) for the transition of administrations and worked to develop a public reporting system for quality performance indicators that formed the foundation for VA ASPIRE. During the transition and the early part of the Obama administration, Dr. Alexander served as a health policy advisor to Secretary Shinseki. In addition to advising on daily operations, he led the department's effort to organize the International Roundtable on Clinical Quality and Patient Safety, coordinated the VA's preparation for the Obama administration's Health Care Summit, and organized the stand-up and directed the activities of the VA's Coordinating Council on National Health Reform. Dr. Alexander was a member of the Institute of Medicine's Committee on the Governance and Financing of Graduate Medical Education. He is a graduate of Kalamazoo College, the University of Michigan Medical School, and the Harvard School of Public Health.

Sandy Allerheiligen, Ph.D., is vice president of quantitative pharmacology and pharmacometrics, Merck Research Laboratories, and previously led the modeling and simulation department at Merck. Prior to joining Merck in 2010, she held positions at Eli Lilly & Company, including global senior director of Pharmacokinetics, Pharmacodynamics (PK/PD) & Trial Simulation; senior director, Drug Disposition; and distinguished fellow and chief scientific officer of Quantitative Pharmacology. Her research focuses on study design and application of mathematical methods to enable quantitative decisions for nonclinical and clinical development. She has applied PK/PD modeling to oncolytic and endocrine agents. Her recent work is on the integration of biomarkers, PK/PD modeling, and trial simulation in nonclinical and clinical drug development, drug disease models, and use of quantitative and systems pharmacology approaches. Dr. Allerheiligen received a doctorate in PK/PD from the University of Texas, Austin; completed postdoctoral fellowships at the University of Texas Health Center, San Antonio; and was a clinical assistant professor of Clinical Pharmacology. Through her involvement in American Association of Pharmaceutical Scientists, American Association of Clinical Pharmacology and Therapeutics, International Society of Pharmacometrics, and National Institutes of Health working groups, she has worked to expand the use of PK/PD modeling and quantitative and systems pharmacology methodologies in academia, regulatory agencies, and across the industry. She is a fellow of the American Association of Pharmaceutical Sciences and frequently lectures on modeling and simulation topics.

Shashi Amur, Ph.D., is currently the scientific lead for the Biomarker Qualification Program housed in the Office of Translational Sciences (OTS) in the Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration. She received her Ph.D. in biochemistry from the Indian Institute of Science, India, and completed postdoctoral fellowships at Temple University and at the University of California, Los Angeles. She then gained experience in diagnostic and biotech sectors (Specialty Laboratories in Santa Monica, California; Applied Biosystems in Foster City, California; and Neotropix, Inc., in Pennsylvania) before joining CDER as a senior genomics reviewer in the Office of Clinical Pharmacology (OCP). Dr. Amur has been an invited speaker at national and international conferences and is the author of several scientific publications. Her current research interest areas include pharmacogenomics, human leukocyte antigen–associated adverse events, and biomarkers in autoimmune diseases and in Alzheimer's disease. Dr. Amur has served as chair of the Pharmacogenomics Science Interest Group and chair of the OCP Science Day Committee, and has organized seminars and workshops at CDER. She is currently the chair of

the Pharmacogenomics Focus Group at American Association of Pharmaceutical Scientists.

Ariana Anderson, Ph.D., is an assistant research statistician at the University of California, Los Angeles (UCLA), a recent recipient of the Burroughs Wellcome Fund 2014 Career Award at the Scientific Interface, and a trainee of Dr. Robert M. Bilder. She received her B.S in mathematics and her Ph.D. in statistics from UCLA, followed by a postdoctoral fellowship in neuroimaging with Dr. Mark S. Cohen. She was a featured speaker at the Institute for Pure and Applied Mathematics' Multimodal Neuroimaging conference, the Neuroimaging Training Program, and worked with Dr. Karl Friston at University College London on approaches to relaxing Bayesian priors in dynamic causal models. Dr. Anderson's research focuses on measuring the impact of pharmaceutical interventions in neuropsychiatric and related disorders. This includes measuring how the placebo effect changes brain activity measured through functional magnetic resonance imaging, and how best to measure psychiatric disorders for which no objective laboratory test exists.

Derek Angus, M.D., M.P.H., FRCP, is a physician and researcher focusing on optimal care of the critically ill. He currently holds the title of Distinguished Professor and Chair of the Department of Critical Care Medicine at the University of Pittsburgh, where he is also the founder and director of the CRISMA (Clinical Research, Investigation, and Systems Modeling of Acute Illness) Center. CRISMA is a large, National Institutes of Health–funded multidisciplinary research center with a broad portfolio of clinical, translational, and health services research studies of sepsis, trauma, and acute respiratory failure. Dr. Angus has published several hundred papers, is the section editor for "Caring for the Critically Ill" at *JAMA*, and is the recipient of numerous national and international awards and honors in his field.

Enrique Avilés, joined the Critical Path Institute in 2010 as director of data standards, management, and technology. In 2012, Mr. Avilés was appointed chief technology officer. He has more than 30 years of experience in information technology (IT) product development, data storage, and program management, and has led numerous projects to support large IT clients with a special focus on health care and banking IT systems. Since 2001, Mr. Avilés served as an executive at IBM in roles such as data storage product program management, storage product development, client technical support, and marketing. His executive experience also includes a 2-year assignment working as the IBM technical advocate for a major health care provider in the United States in support of its electronic health record (EHR) system, one of the largest deployments of an EHR system.

In this role, his responsibility was to ensure that IBM hardware, software, and services used for the client's EHR system operated reliably on a 24/7 basis. Additionally, Mr. Avilés was the IBM executive data storage advocate for one of the largest banks in Japan, traveling there multiple times each year to review product quality and new product development status with senior bank executives. Mr. Avilés received his Bachelor of Science degree in Mechanical Engineering from the Georgia Institute of Technology. He also received graduate certificates from the University of Arizona for an executive M.B.A. program and from George Washington University for Project Management.

John Brownstein, Ph.D., is an associate professor at Harvard Medical School and is the chief innovation officer of Boston Children's Hospital. He also directs the Computational Epidemiology Group at the Children's Hospital Informatics Program in Boston. He was trained as an epidemiologist at Yale University. Overall, his research agenda aims to have translation impact on the surveillance, control, and prevention of disease. He has been at the forefront of the development and application of public health surveillance, including HealthMap.org, an Internet-based global infectious disease intelligence system. The system is in use by millions each year, including the Centers for Disease Control and Prevention, World Health Organization (WHO), U.S. Department of Homeland Security, U.S. Department of Defense, U.S. Department of Health and Human Services (HHS), and European Union, and has been recognized by the National Library of Congress and the Smithsonian. Dr. Brownstein has advised WHO, the Institute of Medicine, HHS, and the White House on real-time public health surveillance. He was awarded the Presidential Early Career Award for Scientists and Engineers, the highest honor bestowed by the U.S. government to outstanding scientists and engineers. Dr. Brownstein is also co-founder of UberHEALTH, a collaboration between the Vaccine Finder project, also co-founded by Dr. Brownstein, and logistics company Uber. He has authored more than 150 peer-reviewed articles on epidemiology and public health. This work has been widely reported in media outlets, including the *New England Journal of Medicine*, *Science*, *Nature*, *The New York Times*, *The Wall Street Journal*, CNN, National Public Radio, and the BBC.

Robert Califf, M.D., MACC, was confirmed as commissioner of the U.S. Food and Drug Administration (FDA) in February 2016. Previously, Dr. Califf served as the FDA's Deputy Commissioner for Medical Products and Tobacco from February 2015 until his appointment as commissioner. In that capacity, Dr. Califf provided executive leadership to the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, and the Cen-

ter for Tobacco Products. He also oversaw the Office of Special Medical Programs and provided direction for crosscutting clinical, scientific, and regulatory initiatives, including precision medicine, combination products, orphan drugs, pediatric therapeutics, and the advisory committee system. Prior to joining FDA, Dr. Califf was a professor of medicine and vice chancellor for clinical and translational research at Duke University. He also served as director of the Duke Translational Medicine Institute and founding director of the Duke Clinical Research Institute. A nationally and internationally recognized expert in cardiovascular medicine, health outcomes research, health care quality, and clinical research, Dr. Califf has led many landmark clinical trials and is one of the most frequently cited authors in biomedical science, with more than 1,200 publications in the peer-reviewed literature. Dr. Califf served on the Institute of Medicine (IOM) committees that recommended Medicare coverage of clinical trials and the removal of ephedra from the market, as well as on the IOM Committee on Identifying and Preventing Medication Errors and the National Academies of Sciences, Engineering, and Medicine's Health Sciences Policy Board. He has served as a member of the FDA Cardiorenal Advisory Panel and the FDA Science Board's Subcommittee on Science and Technology. Dr. Califf has also served on the Board of Scientific Counselors for the National Institutes of Health and the National Library of Medicine, as well as on advisory committees for the National Cancer Institute; the National Heart, Lung, and Blood Institute; the National Institute of Environmental Health Sciences; and the Council of the National Institute on Aging. While at Duke, Dr. Califf led major initiatives aimed at improving methods and infrastructure for clinical research, including the Clinical Trials Transformation Initiative, a public–private partnership co-founded by FDA and Duke. He also served as the principal investigator for Duke's Clinical and Translational Science Award and the NIH (National Institutes of Health) Health Care Systems Research Collaboratory coordinating center. Dr. Califf is a graduate of Duke University School of Medicine. He completed a residency in internal medicine at the University of California, San Francisco, and a fellowship in cardiology at Duke.

Eileen Cannon, B.S., is president of the P*h*RMA Foundation, which provides competitive grants and fellowships—funded by pharmaceutical company contributions—to young scientists beginning careers in research and teaching related to drug discovery. P*h*RMA currently provides more than $3.4 million annually in awards. They have supported more than 2,200 scientists through more than $80 million in the past 50 years. Its programs are geared toward young scientists to help them build connections that have encouraged them to dedicate their careers to research that benefits the lives of patients globally. Ms. Cannon is responsible for program develop-

ment, fund raising, review committee meeting planning, budgeting and financial operations, and the administration of the Foundation programs. Ms. Cannon joined the P*h*RMA Foundation in 1999 as the director of development and became executive director of the Foundation in 2005. In 2015 she was promoted to the position of president. Previously, she spent several years at P*h*RMA in Washington, DC, in the Meetings and Conference Department as a meeting planner and hotel specialist. In her years prior to P*h*RMA/P*h*RMA Foundation, she held positions as director of sales and sales manager for Wyndham Hotel and Resorts in Washington, DC, and Annapolis, Maryland. She received a B.S. in human resources and education from the University of Delaware. She is a member of the American Association of Pharmaceutical Scientists and the Association Foundation Group in Washington, DC.

Brian Corrigan, Ph.D., received his B.Sc. in pharmacy from the University of Alberta, Canada, and Ph.D. in pharmacokinetics from the University of Alberta. He is currently an executive director within Clinical Pharmacology at Pfizer, in Groton, Connecticut. Dr. Corrigan's work has focused on application of clinical pharmacology and pharmacometric approaches to facilitate decision making in all stages of drug development for compounds in the neuroscience and pain therapeutic areas. Dr. Corrigan is an advocate for the discipline of pharmacometrics. He served as treasurer of the Midwest Users Forum for Population Approaches in Data Analysis (MUFPADA), and was a co-organizer of multiple MUFPADA meetings. He served on the editorial advisory board for the *Journal of Pharmacokinetics and Pharmacodynamics*. He was programming chair for the American Conference on Pharmacometrics in 2013. He served as a member on the American Society for Clinical Pharmacology and Therapeutics Pharmacometrics Task Force. He is the current president of the International Society of Pharmacometrics.

Owen Fields, Ph.D., received a B.S. in Biochemistry with a minor in Mathematics from Wichita State University. He earned his Ph.D. from the Department of Molecular and Cellular Biology at the University of California, Berkeley. He then served in the Policy Development Branch, Center for Food Safety, U.S. Food and Drug Administration (FDA), where he helped develop the initial U.S. policy on agricultural biotechnology, led the team that developed the review procedure that applies to such products, and served as the lead reviewer for three of the first seven products FDA approved. He then moved to Regulatory Affairs at Wyeth, where he worked on both late- and early-stage products, worked on the initial and supplemental approvals of Rapamune and BMP2, and worked extensively in inflammation and tissue growth and repair. At the time of the merger with Pfizer he became vice president of regulatory strategy for the Biothera-

peutics Research Unit. Subsequently Dr. Fields assumed the same title for the consolidated Pfizer Research and Development.

Garret FitzGerald, M.D., is the McNeil Professor in Translational Medicine and Therapeutics at the University of Pennsylvania in Philadelphia, where he chairs the Department of Pharmacology and directs the Institute for Translational Medicine and Therapeutics. Dr. FitzGerald's research has been characterized by an integrative approach to elucidating the mechanisms of drug action, drawing on work in cells, model organisms, and humans. His work contributed substantially to the development of low-dose aspirin for cardioprotection. Dr. FitzGerald's group was the first to predict and then mechanistically explain the cardiovascular hazard from nonsteroidal anti-inflammatory drugs. He has also discovered many products of lipid peroxidation and established their utility as indexes of oxidant stress in vivo. His laboratory was the first to discover a molecular clock in the cardiovascular system and has studied the importance of peripheral clocks in the regulation of cardiovascular and metabolic function. Dr. FitzGerald has received the Boyle, Coakley, Harvey, and St. Patrick's Day medals; the Lucian, Scheele, and Hunter Awards; and the Cameron, Taylor, Herz, Lefoulon-Delalande, and Schottstein Prizes. He is a member of the National Academy of Medicine and a fellow of the American Academy of the Arts and Sciences and of the Royal Society.

John H. Holmes, Ph.D., is a professor of medical informatics in epidemiology at the University of Pennsylvania Perelman School of Medicine. He is the interim director of the Penn Institute for Biomedical Informatics and is chair of the Graduate Group in Epidemiology and Biostatistics at Penn. He has been recognized nationally and internationally for his work on developing and applying new approaches to mining epidemiologic surveillance data, as well as his efforts at furthering educational initiatives in biomedical informatics. Dr. Holmes's research interests are focused on several areas in medical informatics, including evolutionary computation and machine learning approaches to knowledge discovery in clinical databases (data mining), interoperable information systems infrastructures for epidemiologic surveillance, regulatory science as it applies to health information and information systems, clinical decision support systems, semantic analysis, shared decision making and patient–physician communication, and information systems user behavior. Dr. Holmes is a principal or co-investigator on projects funded by the National Cancer Institute, the National Library of Medicine, and the Agency for Healthcare Research and Quality, and he is the Penn Principal Investigator of the National Institutes of Health-funded Penn Center of Excellence in Prostate Cancer Disparities. Dr. Holmes is engaged with the Botswana–UPenn Partnership, assisting in building infor-

matics education and clinical research capacity in Botswana. Dr. Holmes sits on the board of directors of the American Medical Informatics Association (AMIA), and is chair of the International Affairs Committee of AMIA and the AMIA representative to the International Medical Informatics Association (IMIA). Internationally, he serves as vice president of IMIA for North America, and in the past was vice chair of the IMIA Working Group on Data Mining and Big Data Analytics and on the board of directors of the Artificial Intelligence in Medicine Society (Europe). Dr. Holmes is an elected fellow of the American College of Medical Informatics and the American College of Epidemiology.

Peter Honig, M.D., M.P.H., is senior vice president and head of Worldwide Safety and Regulatory at Pfizer. In this role, Dr. Honig leads Pfizer's commitment to patient safety by working across the organization to ensure regulatory efficiency, quality control, and compliance throughout all stages of product development and once marketed.

Eric Horvitz, M.D., Ph.D., is a technical fellow at Microsoft and director of the Microsoft Research lab at Redmond. His contributions in biomedical informatics include efforts to build and field predictive models of clinical outcomes from electronic health record data and the use of anonymized logs of online behavioral data for public health, including projects in pharmacovigilance, mental health, and health care use. Dr. Horvitz has been elected a fellow of the National Academy of Engineering, the Association for Computing Machinery, the Association for the Advancement of Artificial Intelligence (AAAI), the American Association for the Advancement of Science, and the American Academy of Arts and Sciences. He was recently awarded the AAAI Feigenbaum Prize for his contributions to advances in artificial intelligence. He has served on the National Library Working Group Advisory Committee to the National Institutes of Health Director, on the National Science Foundation Computer and Information Science and Engineering Advisory Board, and as president of AAAI. He received his Ph.D. and M.D. at Stanford University.

Charles Jaffe, M.D., Ph.D., is the chief executive officer of Health Level Seven International. He completed his medical training at Johns Hopkins and Duke Universities and postdoctoral training at the National Institutes of Health and the Lombardi Cancer Center at Georgetown University. He has served in various academic positions in the Departments of Medicine and Pathology as well as in the School of Engineering.

Martin Landray, Ph.D., FRCP, FBPhS, is a professor of medicine and epidemiology within the Nuffield Department of Population Health and

deputy director of Oxford's Big Data Institute within the Li Ka Shing Centre for Health Information and Discovery at the University of Oxford. His work seeks to further understanding of the determinants of common life-threatening and disabling diseases through the design, conduct, and analysis of efficient, large-scale epidemiological studies (including clinical trials) and the widespread dissemination of both the results and the scientific methods used to generate them. His previous and ongoing international trials have enrolled more than 65,000 individuals with cardiovascular or kidney disease from 18 countries across four continents. The results of completed studies have changed regulatory drug approvals, influenced clinical guidelines, and changed prescribing practice to the benefit of patients. He also oversees the development of systems for recruitment, data collection (including integrated measurement devices and record linkage), analysis, and data sharing for U.K. Biobank, a prospective cohort study of 500,000 middle-aged men and women. In addition to leading his own research, he is heavily involved in efforts to streamline clinical trials, working with national and international organizations (including the U.S. Food and Drug Administration [FDA], European Medicines Agency, Medicines & Healthcare products Regulatory Agency [MHRA], and Medical Research Council [MRC]) to ensure high-quality research is efficient in providing robust information for health care decision making. He is a member of the Steering Committee of the Clinical Trial Transformation Initiative (CTTI, an FDA initiative, coordinated by Duke University) and a leader of the CTTI Monitoring and Quality by Design Projects. He was previously an advisor to the U.S. FDA initiative to develop standardized definitions for cardiovascular endpoints in clinical trials, a member of the National Institute for Health Research Commissioning Board, and a member of a U.K. Department of Health/MRC/MHRA project to promote risk-based monitoring of clinical trials. Dr. Landray completed medical training at University of Birmingham (UK) and specialist training in Clinical Pharmacology and Therapeutics and General Internal Medicine at the University of Birmingham. He continues to practice clinical medicine as an Honorary Consultant Physician in the Cardiology, Cardiac and Thoracic Surgery Directorate at Oxford University Hospitals National Health Service Trust. He is a fellow of the Royal College of Physicians of London, the Higher Education Academy, the American Society of Nephrology, and the British Pharmacological Society.

Gabriela Lavezzari, Ph.D., M.B.A., joined P*h*RMA in 2012 as assistant vice president, Science and Regulatory Advocacy. In this role, Dr. Lavezzari is the primary staff lead for a variety of strategic initiatives aimed at establishing P*h*RMA as a valuable source of scientific expertise in innovative biopharmaceutical research and development within the Scientific and Regulatory Affairs division of P*h*RMA. Dr. Lavezzari brings to P*h*RMA

more than 10 years of combined research experience in the government and industry, with multidisciplinary expertise in Personalized Medicine and Regulatory Science. Prior to joining P*h*RMA, Dr. Lavezzari served as director of extramural development at the Medco Research Institute, a subsidiary of Medco Health Solutions, where she led clinical utility and cost-effectiveness research to create value-based reimbursement decisions for a variety of diagnostics products across different therapeutic areas. Prior to Medco, Dr. Lavezzari spent 2 years at Theranostics Health, a proteomic-based diagnostics company, where she led the laboratory operations and the oncology product development. Prior to Theranostics, Dr. Lavezzari worked at Social Scientific Systems, where she provided scientific support to and managed multiple Adult Clinical Trial Groups (HIV/AIDS) and laboratory science, laboratory technical, and specialty laboratory committees, subcommittees, and working groups. In addition to her experience in the industry, Dr. Lavezzari performed research at the National Institutes of Health, National Institute of Neurological Disorders and Stroke, and Georgetown University, where she completed her postdoctoral training in neuroscience. Dr. Lavezzari received her Ph.D. in biological sciences from the University of Milano (Italy) and her M.B.A. from the New York Institute of Technology.

Danica Marinac-Dabic, M.D., Ph.D., is director of the Division of Epidemiology at the U.S. Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH). She has more than 20 years of experience in obstetrics, gynecology, perinatal epidemiology, and regulatory science and surveillance settings. A physician and an epidemiologist by training, Dr. Marinac-Dabic is in charge of scientific oversight of all device postmarket studies mandated by FDA either as a condition of approval or anytime postmarket. Dr. Marinac-Dabic also oversees CDRH's Epidemiologic Regulatory Science Program, charged with advancing the methodologies and infrastructure for evidence development and appraisal with application to medical device regulatory science. Under Dr. Marinac-Dabic's leadership, in 2010 FDA launched its Medical Device Epidemiology Network (MDEpiNet) Initiative to develop national/international infrastructure and innovative methodological approaches for conducting robust studies and surveillance to improve medical device safety and effectiveness understanding throughout the device lifecycle through public–private partnerships with academia and other stakeholders. Dr. Marinac-Dabic also leads FDA's International Consortium of Orthopedic Registries Initiative (launched in 2011) focusing on innovative approaches to regulatory science and surveillance for orthopedic medical devices/procedures through through a distributed model of more than 30 national and international orthopedic registries capturing information on more than 3.5 million ortho-

pedic procedures worldwide. Under her leadership, in 2013 FDA launched its International Consortium of Cardiac Registries and in 2014 International Consortium of Vascular Registries Initiatives designed to expand collaborative work among international cardiovascular registries and integrate it into medical device regulatory science, active surveillance, and comparative effectiveness and safety research. Dr. Marinac-Dabic served as a chair of the Medical Device Special Interest Group at the International Society for Pharmacoepidemiology and Therapeutic Risk Management. She also serves as the FDA principal and member of the executive committee of the MDEpiNet Public–Partnership, member of the Steering Committee of the STS/ACC Transcatheher Valve Therapies Registry, TJ FORCE Registry, National Breast Implants Registry, and Oxford-based IDEAL Collaborative. Dr. Marinac-Dabic authored several book chapters, several dozens of manuscripts, and invited presentations on various topics in the fields of medical device epidemiology and surveillance, registry development and use for medical device research, innovative methods for evidence synthesis, and comparative effectiveness and safety research. Prior to coming to FDA, Dr. Marinac-Dabic garnered experience in obstetrics, gynecology, and epidemiology in the academic and hospital settings as well as teaching experience in the academic environment.

Kyle J. Myers, Ph.D., received bachelor's degrees in mathematics and physics from Occidental College and a Ph.D. in optical sciences from the University of Arizona. Following a postdoc at the University of Arizona, she worked in the research labs of Corning Inc. Since 1987 she has worked for the Center for Devices and Radiological Health (CDRH) of the U.S. Food and Drug Administration (FDA), where she is currently director of the Division of Imaging, Diagnostics, and Software Reliability in CDRH's Office of Science and Engineering Laboratories. In this capacity she serves as the director for CDRH research programs in medical imaging systems and software tools, including 3D breast imaging systems and computerized tomography devices, digital pathology systems, medical display devices, computer-aided diagnostics, biomarkers (measures of disease state, risk, prognosis, etc., from images as well as other assays and array technologies), and assessment strategies for imaging and other high-dimensional dataset medical devices. She holds adjunct faculty positions at the University of Arizona and Georgetown University. Dr. Myers is a fellow of the Optical Society (OSA), SPIE, and the American Institute for Medical and Biological and a member of the National Academy of Engineering. Along with Harrison H. Barrett, she is the co-author of *Foundations of Image Science*, published by John Wiley and Sons in 2004 and winner of the First Biennial J. W. Goodman Book Writing Award from OSA and SPIE. She is the FDA principal investigator on the Medical Device Innovation Consortium

Computer Modeling and Simulation Project. She is an associate editor for the *Journal of Medical Imaging* and *Medical Physics*.

Perry Nisen, M.D., Ph.D., is a physician scientist whose expertise spans fundamental research, clinical practice, and drug discovery and development. He was appointed as CEO of Sanford Burnham Prebys Medical Discovery Institute in August 2014, and holds the Donald Bren Chief Executive Chair. He oversees execution of the Institute's strategic vision to accelerate the translation of basic research discoveries into innovative therapeutics that have a tangible impact on people's lives. Before joining Sanford Burnham Prebys, Dr. Nisen was senior vice president of science and innovation at GlaxoSmithKline (GSK). In that role, he facilitated innovation and integration of research and development across GSK's global organization; facilitated the discovery, development, and commercialization of a large portfolio of medicines; and was a champion for clinical trial data transparency. Earlier in his career at GSK, he held various key positions, including interim chief medical officer, senior vice president and oncology therapy area head, senior vice president of cancer research, and senior vice president of clinical pharmacology and discovery medicine. Previously, Dr. Nisen was divisional vice president of cancer research and oncology development at Abbott Laboratories, where he helped build a Cancer Discovery organization and created a pipeline of clinical candidates. Dr. Nisen holds a B.S. from Stanford University and an M.D. and a Ph.D. from the Albert Einstein College of Medicine. Formerly, he was the Lowe Foundation Professor of Neuro-Oncology at the University of Texas Southwestern Medical Center.

Richard Platt, M.D., is professor and chair of the Harvard Medical School Department of Population Medicine at the Harvard Pilgrim Health Care Institute. He is principal investigator of the U.S. Food and Drug Administration Sentinel System, which performs postmarketing safety surveillance using electronic health data from more than 175 million people. Dr. Platt is also principal investigator of the Patient-Centered Outcomes Research Institute's PCORnet coordinating center, a consortium of 34 networks that will use electronic health data to conduct comparative effectiveness research. He co-leads the coordinating center of the National Institutes of Health Care System Research Collaboratory and leads a Centers for Disease Control Prevention Epicenter. He co-chairs the Clinical Effectiveness Research Innovation Collaborative of the National Academy of Medicine's Leadership Consortium for Value & Science-Driven Health Care, and is a member of the Association of American Medical Colleges Advisory Panel on Research.

Mark C. Rogers, M.D., M.B.A., was trained at Harvard and Duke in pediatrics, cardiology, anesthesiology, and critical care medicine, then arrived at Johns Hopkins to become the first director of the Pediatric Intensive Care Unit. He was later named professor and chair of the Department of Anesthesiology and Critical Care Medicine. For 14 years, Dr. Rogers led both the Department and the Pediatric Intensive Care Unit to leadership positions in medicine, both nationally and internationally. During this time, he was awarded a Fulbright and was elected to the National Academy of Medicine. He was author of 125 publications and author or senior editor of 12 books translated into many languages. His *Textbook of Pediatric Intensive Care*, now named for him in its fifth edition, is the international standard in the field. He became associate dean at Hopkins and also received an M.B.A. from the Wharton School of the University of Pennsylvania during his tenure at Hopkins. When Dr. Rogers left Hopkins, the Medical School named the Endowed Professorship for the Chair of the Department after him. Beginning in 1992, Dr. Rogers served as CEO of Duke Hospital and Health Network and vice chancellor for health affairs at Duke University. The work he did was highlighted in *The New York Times*, in a case study at Harvard Business and Public Health Schools, and in a featured article on him in *The Wall Street Journal*. He next became the senior vice president for the New York Stock Exchange company that sequenced the human genome. From there, he became president of a major biotech investment bank in what was then the new field of biotechnology. In that role and subsequently on his own, he has been the founder of multiple biopharmaceutical companies, including several that have gone public on NASDAQ and on the Toronto Stock exchange. In addition, he has significant roles in the public service sector and is presently chair of the Reagan-Udall Foundation, which was set up by the U.S. Congress as the civilians advisory group for the U.S. Food and Drug Administration.

Klaus Romero, M.D., is a clinical pharmacologist and epidemiologist by training with 15 years of combined experience in academic clinical research. He is a fellow of the American College of Clinical Pharmacology and the American Society for Clinical Pharmacology and Therapeutics. He has conducted research on endemic channels for non-steroidal anti-inflammatory drug-related gastropathy, antibiotic-related dysglycemia, drug-induced QT prolongation, pharmaco-epidemiology, and patient education. Dr. Romero has been with Critical Path since 2008. He has helped to lead clinical pharmacology, pharmacoepidemiology, and modeling and simulation projects for the Coalition Against Major Diseases, the Polycystic Kidney Disease Outcomes Consortium, and the Critical Path to Tuberculosis Drug Regimens Consortium, achieving major milestones such as the first regulatory endorsement by the U.S. Food and Drug Administration and Euro-

pean Medicines Agency of a clinical trial simulation tool for mild and moderate Alzheimer's disease. He is fluent in English, Spanish, German, and Portuguese, and has published in the areas of clinical pharmacology, pharmacometrics, cardiovascular drug safety, and pharmacoepidemiology.

Marc Salit, Ph.D., and his team in the Material Measurement Lab at the National Institute of Standards and Technology (NIST) are dedicated to technology development and measurement infrastructure supporting biology and biotechnology, including standards, reference data, predictive models, genome-scale measurement methods, and the engineering of living matter. He has worked extensively in measurement science in chemistry and physics, with emphasis on precision measurements, lab automation, algorithm development, measurement uncertainty, traceability, and standards development. His research is now focused on bringing experience from the chemical metrology community to the emerging biometrology community. Most recently, Dr. Salit's team is best known for convening and hosting the Genome in a Bottle Consortium, and development of the first whole human genome reference materials to support regulated applications of NextGen DNA sequencing. Earlier work led to the development of standards from the External RNA Control Consortium, the widely used External RNA Controls Consortium spike-in RNA controls. Dr. Salit now leads the NIST team in Palo Alto, California, embedded full-time on the Stanford main campus. He is working together with faculty from the School of Engineering and School of Medicine to build a new Joint Initiative for Metrology in Biology, a public–private–academic collaboration platform to develop the critical measurement science and standards for the 21st century of biology.

John-Michael Sauer, Ph.D., is the executive director of the Predictive Safety Testing Consortium at the Critical Path Institute (C-Path) and an adjunct professor in the Department of Pharmacology at the University of Arizona College of Medicine. He received his undergraduate and master's degrees in biomedical science at Western Michigan University and his doctorate degree in pharmacology and toxicology from the University of Arizona. Dr. Sauer is a toxicologist by training with more than 15 years of experience in drug discovery and development. He has been responsible for leading multiple functional areas across several pharmaceutical companies. He is dedicated to bringing quantitative translational science approaches to safety assessment, as well as transforming the way we use nonclinical safety data to drive clinical study design and data interpretation. Prior to joining C-Path in 2013, Dr. Sauer had the opportunity to play an individual contributor role at Eli Lilly in the toxicology and ADME (absorption, distribution, metabolism, and excretion) department, where he participated in the devel-

opment, registration, and commercialization of the drug Strattera for the treatment of attention deficit hyperactivity disorder in children and adults. In addition, he supported many other discovery and development teams across multiple therapeutic areas. He also played a pivotal leadership role in the transformation of Elan Pharmaceutical's discovery and development strategies, including the incorporation of several translational science approaches. Dr. Sauer gained operational and management experience in the Contract Research Organization environment as the Site Scientific Head for Covance Chandler in Arizona. Dr. Sauer has more than 100 scientific publications in the areas of toxicology, drug metabolism, clinical pharmacology, pharmacokinetics, and pharmacology.

Sam Shekar, M.D., M.P.H., is the chief medical officer within Northrop Grumman's Information Systems Sector. He provides strategic direction for the Health Division and serves as an adviser to health care and public health organizations, customers, and partners on technology and policy issues in the medical and public health fields. He also directs the Life Sciences Program and its bioinformatics, genomic analytics, and medical ontology programs within the Health Division.

Scott Steele, Ph.D., M.A., serves as the director of government and academic research alliances at the University of Rochester, where he facilitates strategic research and educational partnerships between the university and government agencies and laboratories, industry, and other academic institutions. He is an associate professor in the Department of Public Health Sciences, where his academic interests are focused on a range of science and technology policy issues, including translational research and regulatory science, public health preparedness, and national security. He also serves as the deputy director of the Goergen Institute for Data Science. He is actively involved in regulatory science educational programs at its Clinical and Translational Science Institute and coordinating national Clinical and Translational Science Award initiatives, including recently co-leading the development of a set of regulatory science competences to guide training and education in this area. Dr. Steele currently chairs a subcommittee of the U.S. Food and Drug Administration (FDA) Science Board evaluating the FDA Centers of Excellence in Regulatory Science and Innovation. Prior to joining the University of Rochester, Dr. Steele served in the White House Office of Science and Technology Policy (OSTP), initially as a policy analyst and later as the executive director of the President's Council of Advisors on Science and Technology (PCAST). Dr. Steele coordinated PCAST studies addressing issues in personalized medicine, information technology, nanotechnology, energy technologies, and approaches to enhance university–private-sector research partnerships. At OSTP, he also led several programs

related to biosecurity, medical countermeasures development, biotechnology, and science education. Dr. Steele received his B.S. with honors in biology from Union College in Schenectady, New York. Following this, he performed research at the General Electric Center for Research and Development and was a fellow at the National Institutes of Health. Dr. Steele completed his M.A. and Ph.D. in molecular biology at Princeton University.

James L. Stevens, Ph.D., is a Distinguished Research Fellow at Lilly Research Laboratories. For more than four decades in the government, academic, and industry sectors, he has studied molecular and cellular responses to the metabolism and toxicity of drugs and xenobiotics. His current research focuses on application of systems biology to improving drug safety assessment and elucidating mechanisms of drug toxicity. Prior to joining Lilly Research Laboratory in 2000, Dr. Stevens held positions at the National Institutes of Health, the U.S. Food and Drug Administration, the University of Vermont, and the W. Alton Jones Cell Science Center, where he was executive director. He has served on a variety of national advisory committees, including the Health Education Systems Incorporated Board of Trustees, National Advisory General Medical Sciences, National Toxicology Program Board of Scientific Counselors, Environmental Protection Agency Board of Scientific Counselors Subcommittee on Chemical Safety for Sustainability, as well as the boards of directors for Argonex Pharmaceuticals, Inc., and Upstate Biotechnology, Inc. He has received the Achievement Award from the Society of Toxicology and was elected a fellow of the American Association for the Advancement of Science.

Katherine von Stackelberg, Sc.M., Sc.D., is a research scientist at the Harvard Center for Global Health and the Environment and an affiliate at the Harvard Center for Risk Analysis. She is also co-leader of the Biogeochemistry of Global Contaminants Group at Harvard University and a principal at NEK Associates Ltd. For the past several years, she has served as leader of the Research Translation Core of a Superfund Research Program grant at Harvard University. Dr. von Stackelberg has nearly 30 years' experience designing and implementing human health and ecological risk assessments, focused on integrated, risk-based modeling approaches to support sustainable environmental decision making. She has published on the use of uncertainty analysis in decision making, bioaccumulation modeling, and the use of decision analytic approaches to integrate ecosystem services and risk assessment for more effective decision making. Dr. von Stackelberg is the area editor for ecological risk assessment for the journal *Risk Analysis* and serves on the editorial boards of *Human and Ecological Risk Assessment* and *Risk Analysis*. She is a frequent peer reviewer for several additional journals. Dr. von Stackelberg served on the Board of Scientific Counselors

at the U.S. Environmental Protection Agency (EPA) for 6 years and was chair for the past 3 years. She led the effort to explore the use of decision analytic tools and methods to support environmental decision making within the EPA Office of Research and Development. She is a member of the Scientific Advisors on Risk Assessment for the European Commission in Brussels, and serves on several technical committees of the Interstate Technology and Regulatory Council, including complex sites, contaminated sediments, and risk assessment. Dr. von Stackelberg was elected treasurer of the Society for Risk Analysis, and was recently elected to the board of directors for the Society for Environmental Toxicology and Chemistry, where she also serves on the Global Science Committee (chair from 2012 to 2015) and on the steering committee for the Ecosystem Services Advisory Group. She has served on several EPA funding and grant program peer review panels. She was an invited participant to a recent Society of Environmental Toxicology and Chemistry Pellston workshop on ecosystem services, and a National Institute for Mathematical and Biological Sciences workshop on population modeling in ecological risk assessment. Dr. von Stackelberg received an A.B. cum laude from Harvard College, and an Sc.M. and an Sc.D. from the Harvard School of Public Health in Environmental Science and Risk Management.

John Wagner, M.D., Ph.D., received his M.D. from Stanford University School of Medicine and Ph.D. from the Johns Hopkins University School of Medicine. Postgraduate training included an internal medicine internship and residency, as well as molecular and clinical pharmacology postdoctoral fellowships at Stanford. He began his professional career in academic research on cystic fibrosis and has continued in the pharmaceutical industry, largely in the context of drug development as well as biomarkers. Currently, Dr. Wagner is senior vice president and head, Clinical and Translational Sciences, Takeda Pharmaceutical International. He is also president of the American Society for Clinical Pharmacology and Therapeutics, a premier translational medicine and clinical pharmacology scientific association. Dr. Wagner is also on the adjunct faculty at Harvard–Massachusetts Institute of Technology. Previously, he was a senior consultant to the Institute of Medicine (IOM); vice president and head, Early Development Pipeline, and projects and head, Global Project Management at Merck & Co., Inc.; co-chair of Merck's early development governance committee; vice president and head, Clinical Pharmacology, at Merck; and acting modeling and simulation integrator, Strategically Integrated Modeling and Simulation. He is the past chair of the P*h*RMA Clinical Pharmacology Technical Group; past chair of the adiponectin work group for the Biomarkers Consortium; past committee member of the IOM Committee on Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease; and current member

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Susan Ward, Ph.D., is an experienced strategist, helping large and small companies transition technology into products. Dr. Ward earned her bachelor's, master's, and Ph.D. degrees in pharmacology from the University of Manchester, United Kingdom. She has more than 50 articles in peer-reviewed journals, holds 9 patents, and is a frequent invited speaker. Dr. Ward is the independent director for Provasculon Inc., is a mentor for M.B.A. students at Boston University, and recently completed 6 years as a trustee, treasurer, and executive committee member at the Cambridge School of Weston, a leader in progressive education. Dr. Ward has held prominent positions at Sterling Drug, Wyeth Research, and Millennium Pharmaceuticals. Since 2004, Dr. Ward has built a consulting practice crafting the initial research and development strategy for Alnlyam Pharmaceutical, establishing a global program that markedly enhanced quality of development candidates for Novartis Institutes for BioMedical Research (NIBR), and delivering value-based commercialization strategies for software companies focused on life sciences, including Definiens, Conformia (acquired by Oracle), and GNS Biotech. Most recently, Dr. Ward has extended her practice to rare disease foundations engaged in sponsorship and venture investment in drug-focused programs and biotechnology companies.

Frank Weichold, M.D., Ph.D., is director, Office of Critical Path and Regulatory Science Initiatives in the Office of the Chief Scientist at the U.S. Food and Drug Administration (FDA). He also chairs the FDA Senior Science Council and represents FDA at the Maryland Life Science Advisory Board. The expertise and leadership he brings to the regulatory agency build on his clinical, academic, and industrial medical product development experiences. With his team and in partnership with other stakeholders, he leverages creative ability to advance, coordinate, and integrate scientific innovation and resources for FDA to address mission-critical health science and regulatory responsibilities in a global environment.