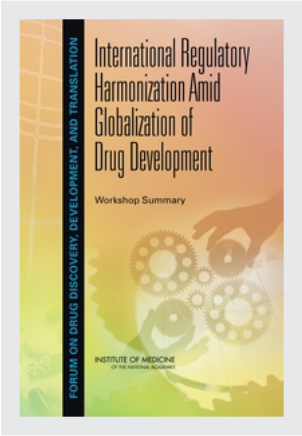

International Regulatory Harmonization Amid Globalization of Drug Development: Workshop Summary

DETAILS

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AUTHORS

Victoria Weisfeld and Tracy A. Lustig, Rapporteurs; Forum on Drug Discovery, Development, and Transition; Board on Health Sciences Policy; Institute of Medicine

International Regulatory Harmonization Amid Globalization of Drug Development

Workshop Summary

Victoria Weisfeld and Tracy A. Lustig, *Rapporteurs*

Forum on Drug Discovery, Development, and Translation

Board on Health Sciences Policy

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OF THE NATIONAL ACADEMIES

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

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ELIZABETH F. C. TYSON, Research Associate
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This workshop summary has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published 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:

Tobias Massa, Bristol-Myers Squibb Company
John Purves, EPCA Ltd
Linda Rosenstock, University of California, Los Angeles
Nathalie Strub Wourgaft, Drugs for Neglected Diseases initiative

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 **Clyde J. Behney,** Institute of Medicine. Appointed by the Institute of Medicine, 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

AMRH	African Medicines Regulatory Harmonization
APEC	Asia-Pacific Economic Cooperation
AU	African Union
AVAREF	African Vaccine Regulatory Forum
BMGF	Bill & Melinda Gates Foundation
CARICOM	Caribbean Community
CDER	Center for Drug Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use (EMA)
CIRS	Centre for Innovation in Regulatory Science
CMC	Chemistry, Manufacturing and Controls
C-Path	Critical Path Institute
DNDi	Drugs for Neglected Diseases initiative
EAC	East African Community
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union

FDA	U.S. Food and Drug Administration
FDASIA	U.S. Food and Drug Administration Safety and Innovation Act
GATT	General Agreement on Tariffs and Trade
GCG	Global Cooperation Group (ICH)
IAEA	International Atomic Energy Agency
ICAO	International Civil Aviation Organization
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IOM	Institute of Medicine
ISO	International Organization for Standardization
JPMA	Japanese Pharmaceutical Manufacturers Association
MERCOSUR	Mercado Común del Sur (the Southern Common Market, South America)
MHLW	Ministry of Health, Labor, and Welfare (Japan)
MS	multiple sclerosis
NAFTA	North American Free Trade Agreement
NDA	new drug application
NEPAD	New Partnership for Africa's Development
NRC	U.S. Nuclear Regulatory Commission
PAHO	Pan American Health Organization
PANDRH	Pan American Network for Drug Regulatory Harmonization
P*h*RMA	Pharmaceutical Research and Manufacturers of America
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
QBD	Quality By Design
RHSC	Regulatory Harmonization Steering Committee (APEC)
SICA	Sistema de la Integración Centroamericana (the Central American Integration System)

TB	tuberculosis
UN	United Nations
VXDS	Voluntary Exploratory Data Submissions
WHO	World Health Organization
WHO PQ	WHO prequalification
WHO PQP	WHO Prequalification of Medicines Programme
WTO	World Trade Organization

1

Introduction[1]

The past several decades have been a time of rapid globalization in the development, manufacture, marketing, and distribution of medical products and technologies. Increasingly, research on the safety and effectiveness of new drugs is being conducted in countries with little experience in research regulation. Additionally, biopharmaceutical companies seeking global markets need to submit applications for approval of a given product to the regulatory authorities of many different countries, each of which could introduce scientific requirements discordant with those of the manufacturer's home market. Differing data requirements across countries may necessitate additional clinical trials and animal studies, increasing the cost of potentially important medicines and slowing patient access to them. In many developing countries, regulatory capacity is insufficient to ensure a smooth process for new drug approval. Even after drugs are approved, international differences in systems to monitor the ongoing safety and quality of approved drugs slow recognition of any safety or manufacturing problems affecting public health. For reasons such as these, demand has been increasing for globally harmonized, science-based standards for the development and evaluation of safety,

[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 Institute of Medicine, and they should not be construed as reflecting any group consensus.

quality, and efficacy of medical products. The goal of such standards is to improve the efficiency and clarity of the drug development and evaluation process and, ultimately, to promote and enhance product quality and the public health.

Since its inception in 2005, the Institute of Medicine's (IOM's) Forum on Drug Discovery, Development, and Translation[2] has focused on the need for strengthening the scientific basis of drug regulation, specifically the development of regulatory science as an essential component of the drug discovery enterprise and translational sciences.[3] Advancing regulatory science is a priority for the U.S. Food and Drug Administration (FDA) and provides an avenue for considering the best tools and approaches for international regulatory authorities to harmonize drug regulations and processes.

In February 2010, the forum sponsored a workshop and subsequently released the workshop summary *Building a National Framework for the Establishment of Regulatory Science for Drug Development: Workshop Summary*, which further defined the field of regulatory science and opportunities to create an infrastructure to support its advancement (IOM, 2011). In September 2011, the forum hosted a workshop and subsequently released the workshop summary *Strengthening a Workforce for Innovative Regulatory Science in Therapeutics Development: Workshop Summary*, which considered opportunities and needs for advancing innovation in the discipline of regulatory science, and examined the development of a workforce within academia, industry, and FDA (IOM, 2012a).

The forum maintains a sustained focus on the need for improving the clinical trials enterprise to support more efficient and effective new drug development, including holding two public workshops exploring approaches to clinical trial transformation; see *Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary* (IOM, 2010) and *Envisioning a Transformed Clinical Trials Enterprise in the United States: Establishing an Agenda for 2020*: *Workshop Summary* (IOM, 2012b).

In addition to the work of the forum, in 2012 the IOM released the report *Ensuring Safe Foods and Medical Products Through Stronger Regulatory Systems Abroad*, which focused on the increasing globalization of the supply chains for foods and medical products (IOM, 2012c). The committee noted that because of international trade, product safety failures in any one country can have ramifications around the world, and there-

[2] Financial support for the forum comes from private foundations, government agencies, industry sponsors, and nonprofit associations.

[3] Regulatory science involves the development and application of scientific tools and methodologies to improve the development, review, and oversight of new therapeutics.

BOX 1-1
Statement of Task for the Workshop

An ad hoc planning committee will plan a 2-day public workshop to address needs for international harmonization of regulatory standards to support the development, evaluation, and surveillance of biomedical products. Specifically, the topics at the workshop will be defined to help identify principles and potential approaches to the development or evolution of more harmonized regulatory standards. Subject-matter experts will be invited to participate in the workshop to discuss and explore principles, approaches, and strategies to support and advance regulatory harmonization. The workshop will feature invited presentations and discussions that will

- provide an overview of the current global regulatory landscape. Identify (a) current organized efforts to promote and evolve harmonized standards, and examples of areas where standards are viewed as adequately harmonized; and (b) areas of need for development or evolution of harmonized standards;
- identify the characteristics of a well-harmonized regulation;
- discuss principles to guide the establishment or evolution of harmonized regulations;
- discuss options and approaches that could facilitate or underlie systemic organizational efforts to develop and/or evolve harmonized standards. Discuss potential structures, methodologies, goals, and outcomes.

The planning committee will develop the agenda for the workshop, select and invite speakers and discussants, and moderate or identify moderators for the discussions. A single individually authored summary of the workshop will be prepared by a designated rapporteur based on the information gathered and the discussions held during the workshop.

fore deemed the regulatory system to be a key factor in public health safety. The committee further noted that the regulatory authorities in low- and middle-income countries often cannot perform all of the necessary responsibilities and asserted "The FDA cannot do its job well without substantive improvements in the capacity of its counterpart agencies in emerging economies." Specifically, the committee called for the sharing of inspection reports as an important first step in mutual recognition and international regulatory harmonization.

To follow on these efforts and to explore the need and prospects for greater international regulatory harmonization for drug development, the IOM assembled an ad hoc committee to plan a workshop that would explore a set of questions, described in the committee's statement of task (see Box 1-1). While harmonization is important in all aspects of interna-

tional biomedical research for drugs, devices, and other technologies, this workshop focused on regulatory harmonization in drug development. Regulatory approaches to approval of medical devices and diagnostics are also amenable to harmonization, but often involve different stakeholders, and so their discussion in this workshop was included when relevant.

OPENING REMARKS[4]

Amid all this globalization, the need for consistent science-based regulations and standards has never been more important.
—Thomas J. Bollyky, Council on Foreign Relations

The co-chair of the IOM's Forum on Drug Discovery, Development, and Translation and workshop co-chair Steven K. Galson, Global Regulatory Vice President, Amgen Inc., emphasized the forum's function as an ongoing neutral place where stakeholders in government, academia, industry, foundations, consumers, and patient groups meet to discuss and confront issues of mutual interest and concern, including the most pressing problems in critical areas of drug development.

Thomas J. Bollyky, Senior Fellow for Global Health, Economics, and Development, Council on Foreign Relations, and workshop co-chair, reviewed the numerous economic and other trends that have provided the impetus for globalization of the research, development, production, and marketing of biomedical products, including

- the quest for lower development costs;
- reduced shipping costs;
- better information and communication technologies;
- lowered tariff barriers;
- rising incomes that create new markets;
- increased government spending on medical care; and the
- growing burden of noncommunicable diseases.

In the midst of these many trends, some concerns remain constant: the need for a science-based approach; support for improvements in the efficiency and clarity of drug development and evaluation; an emphasis on the safety and quality of biomedical products throughout their lifecycle, throughout the world; and increasing access to safe, effective drugs for all who need them.

[4] This section is based on the presentations by Steven K. Galson, Global Regulatory Vice President, Amgen Inc., and Thomas J. Bollyky, Senior Fellow for Global Health, Economics, and Development, Council on Foreign Relations.

INTERNATIONAL HARMONIZATION: AN INDUSTRY PERSPECTIVE[5]

In the pharmaceutical industry, said Peter Honig, Global Vice President, Regulatory Affairs, AstraZeneca, harmonized standards would

- reduce costly duplication of effort;
- encourage sharing of experience and knowledge among regulators and scientists;
- require fewer clinical trials; and
- optimize use of limited resources.

From the industry's perspective, said Honig, harmonization would increase the likelihood that a particular molecule will become a successful drug. Reduced development time, less cumbersome approval processes across countries, and increased speed to market are all important to companies. In addition, Honig stated that harmonization would give patients faster access to new medicines and might lower the costs of drug development, which could lower the price, making new drugs more affordable in many more markets.

The need for harmonization has grown up alongside the trend to globalization. Globalization is a boon to industry, and in particular, Honig stated that it offers companies access to scientific talent "emerging in every nook and cranny of the globe"; enables access to more potential recruits for clinical trials and to lower cost suppliers and operational support; and opens new markets in expanding economies.

Clinical Trials

Until very recently, clinical trial activity has been heavily concentrated in North America and in western and northern Europe. But today, with multiregional clinical trials and global development strategies, the picture is changing. Honig stated that harmonization facilitates the expansion of clinical trial activity. When researchers use clear, shared standards, he said, it is easier for regulators to accept multiregional trial data for their country. Trials can become more efficient. They can better meet the needs of their multinational corporate sponsors.

Honig asserted that an ongoing challenge for industry and regulators is to develop shared expectations regarding the use of adaptive trials, conduct of clinical trials, acceptability of endpoints, and data transpar-

[5] This section is based on the presentation by Peter Honig, Global Vice President, Regulatory Affairs, AstraZeneca.

ency. A major issue in multiregional clinical trials, especially for a novel therapeutic, is obtaining agreement on appropriate endpoints, including patient-reported outcomes. Furthermore, either rules or common expectations may be needed regarding the handling of trial data and when to disclose them.

Recent annual growth rates in clinical trial participation in many non-Western countries have been in the double digits. Notable examples of countries where trial participation is increasing rapidly are Japan, China, South Korea, Russia, and Brazil. By contrast, clinical trial participation in the United States has been shrinking. Countries without adequate human subjects protections may be deemed not desirable recruitment targets.

The European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) has examined the issue of the acceptability of foreign clinical trial data, and FDA reportedly is also considering the issue. At present, said Honig, scientists need a better understanding of the regional differences that show up in trial data and what causes them, particularly whether they indicate fundamental population differences or reflect different patterns of medical practice.

Persistent Barriers

Before clinicians can use a pharmaceutical product in a particular country, it needs to be registered there. Numerous barriers to registration currently exist, said Honig, such as

- China, Korea, and Taiwan require that a new drug be tested in subsets of their population or in separate studies before it can be approved.
- India, Mexico, and Vietnam require that specific numbers of their nationals participate in clinical trials of the proposed drug.

Such requirements can create logistical difficulties in multiregional trials, when researchers are required to allocate a certain number or percentage of trial slots to specific groups of patients. "Eventually those percentages add up, and sometimes they add up to more than 100 percent," said Honig.

As challenging, people in some countries are easier to recruit as trial participants than others. In the United States, said Honig, clinical trial recruitment is often slow. The result is that the trial, which has a fixed number of slots divided into specific categories of predetermined size, may fill certain categories much more quickly than others, and the whole process slows down. The industry aim is, of course, to reduce the time involved in subject recruitment.

The final composition of the trial population can be "guided by scientific insights, proper Phase II dose range, and proper understanding of ethnic sensitivities," said Honig, but harmonized standards and data requirements would greatly facilitate the process.

Before the European harmonization program (see Box 1-2), which has advanced considerably, manufacturers had to seek registration approval for their products in Europe, one country at a time. Now, centralized

BOX 1-2
Selected International Harmonization Efforts[a]

- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Humans (ICH) includes regulators and industry representatives from Europe, Japan, and the United States. ICH has produced guidelines on quality, safety, and efficacy and a common technical document. Although some countries have adopted these standards into law, FDA uses them as guidelines only.
- The European Union (EU) has harmonized the European-regulated market through EMA, which is a decentralized body of the EU, and its Heads of Medicines Agency, a network of the heads of agencies responsible for regulating human and veterinary medicines in the individual countries of the European Economic Area.
- The World Health Organization (WHO) establishes medicinal, clinical, and technical standards and promotes regulatory capacity building, training, and work sharing for regulatory authorities. Notable activities are its Certificate of Pharmaceutical Product initiative and its Prequalification of Medicines Programme (WHO PQP), both intended to increase access to essential medicines in resource-limited countries and ensure that they meet acceptable standards of quality, safety, and efficacy. WHO's International Conference of Drug Regulatory Authorities provides member states with a forum for discussing further collaboration opportunities.
- The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) encourages mutual recognition of manufacturing site inspections.
- The European Medicines Agency-U.S. Food and Drug Administration (EMA-FDA) Quality By Design (QBD) pilot will test a process of parallel review of specific drug development and manufacturing data components, particularly the quality/Chemistry, Manufacturing and Controls (CMC) section of manufacturers' marketing applications.
- Various regional harmonization programs, many of which participate in ICH's Global Cooperation Group (GCG), include initiatives in Africa, the Asia-Pacific area, Latin America, and the Middle East.

[a] Adapted from the presentation by Peter Honig, Global Vice President, Regulatory Affairs, AstraZeneca.

procedures and common labels are all facilitated by harmonized technical requirements. A key underlying factor is having a legal framework in Europe that supports the system, establishing centralized procedures and enabling mutual recognition of each other's data. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use's (ICH's) common technical document and electronic standards for submission of drug approval requests (dossiers) and individual case safety reports for pharmacovigilance is a major step forward for industry, for the regulators, and for information sharing, said Honig.

In addition, Europe has made efforts to facilitate and standardize clinical trial applications. New kinds of therapies, biological products, and dosage forms, and an increased industry focus on lifecycle management—from a product's inception in the laboratory to the end of its patent life—will likely be on the ICH agenda in the future, said Honig.

Challenges for Existing Harmonization Initiatives

A large gap in regulatory capacity and expertise between emerging and developed countries remains, said Honig. Programs, such as those of WHO, help governments in less developed nations to be sure the drugs and medical devices imported into their countries are safe and effective, without requiring them to divert limited resources to replicate more developed nations' regulatory infrastructures. This allows them to focus on the issues of greatest local concern, such as the integrity of the supply chain.

Honig added that many of the regional harmonization initiatives lack key infrastructure pieces that support the European efforts, notably its legal framework, but may be able to build on region-wide economic interests. The regional interests generally take more of a confederation approach, where they adopt guidelines in spirit, but there is no automatic and infrastructural mechanism to make them binding. Eventually, interregional cooperation also may be desirable.

Good practice inspections and reinspections of manufacturing and clinical trial sites can become burdensome, said Honig. A global pharmaceutical company will often have multiple inspectors coming in from different countries and from different regulatory authorities in different regions. "One has to wonder about the incremental value of some of these duplicate inspections," Honig said.

At the same time, industry and regulators alike are vitally concerned with maintaining quality standards, having a common understanding of what those are across agencies, and determine whether regulators can assess quality and ensure supply chain integrity. From an industry

perspective, Honig argued that harmonization efforts ideally need to aim at simultaneous global development, with near-simultaneous product registration around the world.

INTERNATIONAL HARMONIZATION: A REGULATOR'S PERSPECTIVE[6]

Different countries take different approaches to medical products regulation, depending on a number of factors, said Hubert Leufkens, Chair, Dutch Medicines Evaluation Board, and Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University for Pharmaceutical Sciences. This is true even when they are geographically proximate, operate under the same legal framework, and rely on the same scientific processes and the same data to make their decisions. Some regulatory regimes may be more risk-averse, while others may prioritize potential benefits. Whether they emphasize risks or benefits may vary from one instance to another. As a result of these discordant outcomes from regulatory decision making, said Leufkens, patients in one country may have access to medications that others do not have, which regulators may be hard pressed by patients, providers, politicians, and the media to explain.

Leufkens presented an example in FDA's revocation of approval of Avastin for metastatic breast cancer. Although FDA originally approved the drug for this indication, evidence that it did not extend life or improve the quality of life, while increasing the risk of serious side effects, prompted FDA's subsequent decision. Yet, Avastin remains approved for metastatic breast cancer in other countries. Such contradictory situations, some of them widely publicized, can erode public trust in the system. However, Leufkens considers FDA's public report on the reasoning behind its decision a model of balance and perspective. Generally, the way agencies communicate about variance is extremely important and needs greater clarity, he said.

Schellekens and colleagues (2011, p. 175) stated that regulatory systems should be assessed "in terms of their ability to ensure patient safety, enhance public health, and stimulate innovation." Their effectiveness at achieving this latter aim are much in doubt, as the introduction of new and innovative drugs has decreased sharply, despite rapid advances in biomedical research, said Leufkens. Schellekens and colleagues (2011, p. 175) further stated, "Although the reasons for this innovation deficit

[6] This section is based on the presentation by Hubert Leufkens, Chair, Dutch Medicines Evaluation Board, and Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University for Pharmaceutical Sciences.

are not fully understood, many observers see the increasing demands of the regulatory systems as one of the main drivers."

Leufkens asserted that regulators need to answer four important questions in assessing a new pharmacologic product:

1. What is the precise diagnosis it is intended to affect?
2. What endpoints were measured in the research, and are they clinically relevant to the disease or condition at issue?
3. What target population will benefit?
4. What kind of comparison is useful, needed, and feasible?

Although these questions appear straightforward, addressing each of them presents challenges. Leufkens gave examples for each, keyed to the numbers above, including the following:

1. Diagnosis of psychiatric conditions varies from one country to another
2. In oncology, use of overall survival rates versus progression-free survival as endpoints; or in diabetes, the use of blood glucose levels versus or in addition to other measures, with an increasing preference for clinical outcome measures, rather than simple biomarkers
3. Use of biomarkers to identify populations, inasmuch as different nations have different capabilities to conduct a robust biomarker identification effort
4. Divergent views on whether placebo recipients constitute an appropriate comparison group versus active controls (e.g., patients receiving standard treatment), with the trend being for greater emphasis on the latter

Regulators use dossiers prepared by manufacturers in determining whether to approve a new drug. Problems associated with these dossiers are not infrequent. Leufkens said typical problems that can contribute to different regulatory decisions include the following:

- Poor presentation: For example, the dossier presents data in a confusing way or presents too much data, in which case the drug itself often receives a poor assessment.
- Conversely, some dossiers may mask data shortcomings by the strength of their presentations.
- Coping with innovation: It may be difficult for regulators to assess a new concept, so the default is to request more information, but

whether such requests actually produce an improved product is debatable.
- Some advanced therapies, including gene therapies, may appear to regulators as too risky.

In the end, some of the variance in approval decisions across nations arises through the dynamics of their individual review committees and their decision-making styles and processes. Some nations base their processes on precise rules, whereas others base them on principles. The latter approach gives greater flexibility to regulators, said Leufkens, but also reduces the system's predictability.

The labeling of a drug, which includes the indications for which its use is approved, can vary among countries and change over time as new information is compiled. Sometimes the number of indications is expanded and sometimes reduced, particularly if complications arise that suggest use needs to be more tightly controlled. A study of approaches used by FDA and EMA in the evaluation and approval of new anticancer indications found real difference in the regulatory agencies' wording for nearly half (47 percent) of the indications. However, the differences were clinically meaningful in only 10 of these instances (Trotta et al., 2011).

Similarly, a study of differences in regulatory actions by FDA and the European Union related to biologicals appeared at first to suggest these differences were quite large, but further analysis indicated that clinically relevant differences were much smaller (Giezen et al., 2008). The more important feature was the timing in the two entities' actions. FDA was more likely to advise clinicians about potential problems sooner than was the EU, and in some cases even to require a "black box warning" sooner.[7]

Leufkens concluded that there may always be differences in the ways people look at the data, how they weigh the potential benefit or harm of specific products, and how they try to respond to their populations' unmet medical needs.

[7] An FDA "black box warning" is the most stringent notice of potential side effects from a drug; the notices must be carried on the container to allow the drug to stay on the market.

2

Principles and Definitional Considerations

Andreas Seiter, Senior Health Specialist, Pharmaceuticals, Health, Nutrition, and Population, World Bank, introduced the session by noting that pharmaceutical regulation is "the place where hard science meets cognitive complexity," where people of different backgrounds in terms of geography, education, professional training, and habits of mind come together to make vital scientific decisions. Therefore, clarity in definitions is essential, he said, and helps overcome the problem that words may have different meanings in different contexts.

THE TERMINOLOGY LANDSCAPE AND OPTIONS FOR REGULATORS[1]

Mike Ward, Manager, International Programs, Health Canada, began his presentation by emphasizing that the lack of commonly accepted definitions in drug regulation is a stumbling block to harmonization. Lack of clarity exists, he said, even around such deceptively obvious concepts as *regulatory cooperation*. Other examples Ward gave of terms that all countries may not use the same way include

- *International*: Does it mean more than one or two countries, regional, beyond regional?

[1] This section is based on the presentation by Mike Ward, Manager, International Programs, Health Canada.

- *Regulatory* versus *regulation.*
- *Cooperation* versus *collaboration.*

Putting these albeit imprecise notions together, Ward suggested that a working definition of *international regulatory cooperation* could be "inter-country activities carried out with a view to improving national regulatory outcomes and promoting convergence." The current lack of common understandings can lead to confusion and, more important, can set unrealistic or varying expectations in the minds of central agencies, regulators, industries, consumers, and other stakeholders. This working definition could involve any number of countries, is applicable at all stages of the regulatory life cycle, from assessment of new or existing regulations through program implementation, and, finally, to review and evaluate regulatory programs. Inherent in the definition are many potential activities, Ward said, including

- information sharing;
- collaborative scientific work;
- common standards; and
- work sharing.

Ward described the history of international efforts in the harmonization of products. The quest for international harmonization, he said, began with the Industrial Revolution and the need to standardize even humble products like screws so they had identical thread sizes. With the expansion of trade in the 20th century, products crossed borders and many people around the world depended on goods made in other countries. After World War II, the Geneva-based International Organization for Standardization (ISO) was created and the General Agreement on Tariffs and Trade (GATT) was adopted, both of which furthered the push for common standards. GATT was not put in place until 1995, when the World Trade Organization (WTO) began its work. Most recently, the development of the European Union has been an important driver for harmonization of standards not only within Europe, but more broadly, starting with creation of the European Economic Community in 1957, the European Communities a decade later, and, in 1993, the European Union.

In the pharmaceutical field, the leading international body for standards harmonization is the ICH, said Ward. Many drivers led to its creation in 1990—globalization of the pharmaceutical industry; a rapid increase in the diversity of technical requirements; increasing workloads for regulators; the complexity of products, processes, and technology; rising drug development costs; and a more informed and risk-averse public.

Trade agreements and the globalization of many aspects of drug

research and production have pushed regulators to look at the drug approval process as not something confined to their own nations, but rather an activity that requires international regulatory cooperation.

Harmonization or Convergence?

Perhaps most relevant in the current context, said Ward, is the WTO Sanitary and Phytosanitary Agreement related to food safety and animal and plant health. It defines harmonization as "the establishment, recognition and application of common sanitary and phytosanitary measures by different members (jurisdictions)" (WHO, 2010). An example can be seen by looking at pharmacopeial harmonization: The U.S., European, and Japanese pharmacopeias have engaged in harmonization efforts for some time. This does not mean that their texts are exactly the same, but they are harmonized because, when they are tested, they yield the same result. Harmonization applies to work like that of ICH, where people develop together the same standard or even joint processes: one example is the Gulf Cooperative Council's work on joint drug registration and procurement.

Convergence, by contrast, takes a broader outlook and is becoming a more widely used term. Convergence goes beyond the development of common standards and processes to take into account how regulatory authorities actually use them. For example, while review practices are not the same across countries, they often produce the same outcome. Many aspects of regulatory review—templates, operating procedures, competency-based training, and so on—are part of good review practices, but they are not necessarily standardized or harmonized. However, if they produce similar results, they are converging.

Regulatory convergence also considers the disparate capabilities of regulatory authorities across nations. Inherent in the term is the implication that the process is moving forward. Essentially, convergence is dynamic and catalyzed by workload, globalization, technology, and public expectations, said Ward.

Harmonization and Convergence in Action

Operationally, what does harmonization imply? Its benefits are evident, said Ward. It is a key enabler for enhanced international cooperation; it can expand from technical requirements to procedures and processes; then, in certain circumstances, it can evolve into laws and regulations. But while simple in concept, harmonization is difficult in execution.

Key to the success of ICH's operations is the involvement of both regulators and industry, said Ward. Its approach is well managed, sci-

ence based, and consensus driven. Most important, it involves a limited number of players that have comparable regulatory and technical capability, and the regulators are committed to implementing the products of harmonization.

Countries may adopt a harmonized standard or guidance without change or adapt it in any number of ways—good or bad—to meet local circumstances, but true harmonization cannot be measured until the standard's actual implementation is assessed, said Ward. The implementation process may encounter numerous stumbling blocks. A new standard needs to fit into existing laws and regulatory frameworks, which may mean collateral changes are needed with respect to filing documents, policy work, and so on. Regulators may need training to carry out the new standard, or industry may not be prepared to respond to it. Thus, even though a harmonized standard is in place, the implementation phase contains many variables that may result in divergent results. Finally, as explored earlier in the workshop, no matter how well harmonized standards and processes are, different regulatory agencies may reach different conclusions.

Ward noted that the Pan American Network for Drug Regulatory Harmonization (PANDRH), established to promote pharmaceutical regulatory harmonization and capacity building within the Americas, recognized at the outset that asymmetries within the regulatory capacities of the hemisphere's nations might impede implementation. In PANDRH, harmonization connotes a search for common ground within a framework of recognized standards. PANDRH's approach more closely approximates the concept of regulatory convergence, whereby regulatory requirements across economies or countries become more aligned over time as a result of the adoption of internationally recognized technical guidance, standards, and best practices. Importantly, it does not require the harmonization of different countries' laws and regulations.

Where a political and economic directive exists, such as in the European Union and other regions, the issue of different laws is not a problem, asserted Ward. But, worldwide, "if we had to wait for laws to be harmonized, nothing would happen," Ward added. Regulations and technical requirements translate a country's laws into practice and, ideally, these laws would contain some flexibility.

Canada and the United States may not go so far as to harmonize their laws and regulations, but they can adopt good review practices that produce an equivalent result. Two or more systems are said to be equivalent if they produce the same outcomes, regardless of internal system differences. Equivalence can be established and documented through objective means. Examples are mutual recognition agreements related to good manufacturing practices.

Although many nations appear to be on the path to standards harmonization and regulatory convergence, increasingly sophisticated and innovative biopharmaceutical products pose new challenges. Perhaps foremost is that they may require health care settings capable of using them effectively and safely on patients. At present, this final implementation step is not part of the process, except in an after-the-fact way through postmarketing surveillance.

In U.S. medicine today, professional organizations are working to put together standards of care that are consensus driven and evidence based. But the practice of medicine is simply not regulated in the same way as the drug market, and variability in care delivery is outside the domain of drug regulators, Ward argued.

STANDARDS SETTINGS IN THE CONTEXT OF REGULATORY HARMONIZATION[2]

A drug manufacturer today may need to produce multiple versions of the same product to accommodate differences in standards and regulations that exist from one nation to another. The pharmaceutical industry is a global business, and these varying rules cause delays, impede access to needed medicines, and increase the costs of health care. Unless different standards have some scientific justification, they are both medically and ethically suspect, according to Carolyn Compton, President and Chief Executive Officer, Critical Path Institute (C-Path).

Regulatory convergence is a vital strategy for reducing the time and costs required to make new drugs available to patients. Bringing one new drug to market now takes at least a decade and costs more than a billion dollars, said Compton, although one recent analysis estimated the real cost at nearly $11 billion (Herper, 2012).

Streamlining the current process will require collaborative, global approaches to standardization that include the public, regulatory bodies, and the private sectors in industry and academia. That will be difficult because, even within a single company, much less between companies and across countries, there is currently much heterogeneity—a lack of common standards—in the way products are developed, tested, and assessed, said Compton, because

- data to demonstrate efficacy and safety are defined and collected differently;

[2] This section is based on the presentation by Carolyn Compton, President and Chief Executive Officer, Critical Path Institute (C-Path).

- measurements of efficacy and safety are based on different criteria; and
- methods for designing clinical trials for new drugs differ widely.

Conceptually, a good standard is one that saves time, money, and problems in the long run.[3] Compton asserted that standards require certain foci—all of which need to be achieved simultaneously—to ensure that the standard is

- widely accepted;
- freely available (not proprietary or exclusionary);
- applicable cost-effectively;
- endorsed by standards development organizations;
- enforced by regulators; and
- globally applicable.

The ISO defines a standard as "a document that provides requirements, specifications, guidelines or characteristics that can be used consistently to ensure that materials, products, processes and services are fit for their purpose" (ISO, 2013). Among the benefits of international standards cited by ISO are that they ensure products and services are safe, reliable, and of good quality. In the case of drug development, standards are strategic tools and reduce costs by minimizing waste and errors and increasing productivity.

Measurement and Methods Standards

C-Path primarily develops measurement and methods standards. Its multistep, iterative development process brings together the best scientists from industry, academia, and government, including FDA, for precompetitive data sharing. Measurement and methods standards may be distinguished as follows:

- *Measurement standards*, for example, cover use of molecular or imaging biomarkers for efficacy and patient classification, molecular biomarkers for toxicity testing, and patient-, observer-, or clinician-reported outcomes.
- *Methods standards* cover topics like the use of disease models, clinical trial simulation tools, and in vitro models.

[3] Global good standards have been achieved in many other industries. For example, a person possessing a credit card or bank card can visit any ATM anywhere in the world and extract money in the local currency or in U.S. dollars.

FDA, EMA, and PMDA (Pharmaceuticals and Medical Devices Agency [Japan]) have rigorous, formal processes for review and acceptance of proposed standards. Once approved, the new standard can be used by any company to develop drugs with the assurance that the scientific basis of their data collection will be acceptable to these regulators.

C-Path organizes its standards development collaborations into consortiums that are generally focused on a single disease process or on a methodology, such as the generation of patient-reported outcomes instruments. It has established seven consortiums involving more than a thousand scientists and 41 companies around the world.[4] According to Compton, the process of working together on the standards and sharing precompetitive information is improving the culture of drug development. The process also fosters compliance with the standard, she said, as manufacturers develop a sense of ownership that reduces the need for active enforcement.

Meanwhile, the regulatory agencies themselves do not have a harmonized process for qualifying these standards. Some have fees, some do not; FDA has twice the number of minimum steps (24) as EMA and PMDA; and FDA takes about four times as long to decide whether to qualify a new standard, said Compton. So far, only a few standards developed under C-Path's process have been qualified—three by FDA, six by EMA, and one by PMDA.[5] According to Compton, initial conversations are under way between FDA and EMA regarding bringing their tool qualification processes more into alignment. Also, as the process becomes more familiar, she said, the pace of qualification may accelerate.

Data Standards

The challenge of developing data standards is similar to that of developing the scientific standards just described, said Compton. A data standard does not mean a common data element such as the patient's birth date, which can be written many ways: January 20, 1946; 1-20-46; 01/20/46; 20 Jan 46; and so on. This diversity in the ways data are reported creates enormous problems when researchers want to query

[4] The seven consortium and the issues they are working on [in brackets] are coalition against major diseases [understanding diseases of the brain]; critical path to tuberculosis (TB) drug regimens [testing drug combinations]; multiple sclerosis (MS) outcome assessment consortium [drug effectiveness in MS]; polycystic kidney disease consortium [new imaging biomarkers]; patient-reported outcome consortium [drug effectiveness]; electronic patient-reported outcome consortium [drug effectiveness]; predicting safety testing consortium [drug safety].

[5] The review and analytic process for qualifying these drug development tools is separate from that for new product approval.

across datasets, pool and share data, or analyze multiple trials. Adhering to data standards makes clinical trials more efficient; trials that use them can save as much as 60 percent of the time required to analyze and report results and from 70 to 90 percent of the time needed to start up and conduct the trial.

At FDA, the extreme variability and unpredictability of data format and content present major obstacles to performing timely, consistent, and efficient data reviews, said Compton, which ultimately hamper innovation. In order for FDA staff to work efficiently, they need standardized and well-organized data, they need to understand the basis of the data collection, and they need to understand the scientific basis on which those data were collected. According to Compton, data management and review preparation consume about 40 percent of regulatory review time.

Compton argued that implementing data standards would allow FDA to focus on more significant questions relevant to market approval. Its work would be transformed from the "doing steps" of data aggregation and analysis to the "thinking steps" of analysis planning, interpretation, communication, and decision making. Moreover, the sophisticated analytical tools FDA is trying to build cannot be used, at least not efficiently, without these data standards, argued Compton.

According to Compton, C-Path is working collaboratively with the Clinical Data Interchange Standards Consortium to address the 58 therapeutic or disease-specific standards FDA has indicated it urgently needs within the next 5 years. The U.S. Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law in 2012,[6] gives the agency authority to require data standards and electronic submission of market approval applications, which it must do by 2017. Requiring and implementing U.S. data standards through regulation may create efficiencies domestically, but regulatory bodies around the world will have the added challenge of working within this additional set of standards.

Measuring Harmonization

The true extent of global harmonization and convergence is difficult to assess because each country's system also continues to evolve on its own, and major system changes, such as the new U.S. law, periodically occur. Compton suggested that the assessment of progress toward harmonization could be based on achieving standards in a set number of identified technical areas, or specific metrics could be used to assess different aspects of harmonization. Measuring the process improvement in

[6] FDA Safety and Innovation Act of 2012, P.L. 144, 112th Congress, 2nd session (January 3, 2012).

one regulatory system in one country may not require the same yardstick needed in another. Some greater effort to measure the true extent of harmonization would reveal whether only some aspects of drug regulation are harmonizing or converging, while others—and perhaps the whole international system—are becoming more divergent. Citing Lord Kelvin's well-known admonition, Compton said, "If you cannot measure it, you cannot improve it."

3

Overview of the Current Global Regulatory Landscape

The session, introduced by Hans V. Hogerzeil, Professor of Global Health, University of Groningen, the Netherlands, described in more detail several current regulatory harmonization initiatives around the world and what is being learned from them.

ICH[1]

Toshiyoshi Tominaga, Professor and Director, Food and Drug Evaluation Center, Osaka City University Hospital, began by describing ICH, an initiative cosponsored by the drug regulatory agencies and pharmaceutical manufacturing associations of the following organizations:

- Europe (EU/EMA, EFPIA [European Federation of Pharmaceutical Industries and Associations]);
- Japan (MHLW (Ministry of Health, Labor, and Welfare)/PMDA, JPMA [Japanese Pharmaceutical Manufacturers Association]); and
- The United States (FDA, P*h*RMA [Pharmaceutical Research and Manufacturers of America]).

ICH's mission is "to make recommendations towards achieving greater harmonisation in the interpretation and application of techni-

[1] This section is based on the presentation by Toshiyoshi Tominaga, Professor and Director, Food and Drug Evaluation Center, Osaka City University Hospital.

cal guidelines and requirements for pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines" (ICH, 2013).

The governing body of ICH is a steering committee that includes the organizations noted above, with the addition of WHO, Health Canada, and the European Free Trade Association as observers. The International Federation of Pharmaceutical Manufacturers and Associations is a nonvoting member. Additional interested organizations may be invited to participate in expert working group activities, as appropriate.

To produce harmonized guidelines, ICH has a five-step process:

1. Building scientific consensus among members of an expert working group
2. Agreement on draft text
3. Consultation with regional regulatory agencies and solicitation of comments from other regulatory agencies, GCG members, and the public
4. Revision and adoption of harmonized guidelines
5. Implementation guidelines in ICH regions

ICH has produced numerous guidelines in four major categories: quality, safety, efficacy, and multidisciplinary. In addition, it has developed electronic standards, a common technical document for electronic submission of data on new drug applications (NDAs), and other helpful products. The common technical document includes guidance on formatting trial datasets and data elements, which facilitates review and enables industry to submit its data to different regulatory authorities in a single format.

As an example of a completed guideline, Tominaga described guideline Q1A, "Stability Testing of New Drug Substances and Products," which specifies the temperature and humidity conditions under which a drug should be stored in order to demonstrate its stability over different time periods. If this guideline is followed, any of the three ICH regulatory agencies—EMA, PMDA, or FDA—will accept the test data (although sometimes with a requirement for country-specific testing), as will many other regulatory authorities that also have accepted the guideline.

ICH promotes the implementation of guidelines worldwide under its GCG. Involved are the regional harmonization initiatives, as well as individual countries that have implemented ICH guidelines or have major pharmaceutical production and clinical research activities. They are

- **Asia-Pacific Economic Cooperation (APEC)**[2]

[2] The organizations listed in **bold** are discussed later in this chapter.

- Association of Southeast Asian Nations Pharmaceutical Product Working Group
- **East African Community (EAC)**
- Gulf Central Committee for Drug Registration
- **PANDRH**
- Southern African Development Community
- Individual countries, including Australia, Brazil, China, Chinese Taipei, India, Republic of Korea, Russia, and Singapore

As part of its efforts, GCG also coordinates training and capacity building for regulators in non-ICH member countries.

Tominaga asserted that the benefits of ICH adoption for industry are fewer duplicate tests, reports, and submissions. For regulators, he said, data submitted for review are more consistent, which enables more consistent reviews and facilitates cooperation with other regulatory agencies. For the public, he added, the benefits are quicker access to safe and effective new drugs and (as taxpayers and purchasers) lower costs. Speaking specifically about the benefits to his home country of Japan, Tominaga said the ICH experience has helped Japan update and improve its clinical trial system. Furthermore, the pattern of cooperation across countries has laid the groundwork for multinational studies of ethnic factors in drug development.

According to Tominaga, the keys to ICH's success have been its well-defined process and effective management, the commitment on the part of the three founding members to implement ICH guidelines, and its concentration on technical requirements. It does not delve into what regulators need to do or how they develop their decisions. In terms of difficulty, technical guidance is the low-hanging fruit and is an excellent place to start harmonization efforts. Remaining challenges are to achieve mutual recognition of regulations or procedures and mutual recognition of regulatory decisions, with this last the most difficult, said Tominaga.

PANDRH[3]

Drug regulatory harmonization initiatives in Latin America cannot be discussed without reference to broader harmonization initiatives in the Americas and the broader global context. Many regulators in the Latin American region participate in these broader efforts, according to James

[3] This section is based on a presentation by James Fitzgerald, Coordinator, Medicines and Technologies, Area of Health Systems based on Primary Health Care, Pan American Health Organization (PAHO), WHO.

Fitzgerald, Coordinator, Medicines and Technologies, Area of Health Systems based on Primary Health Care, Pan American Health Organization (PAHO), WHO.

PANDRH was established in 2000 by the directing council of PAHO, based on the findings of a conference on harmonization hosted by FDA 2 years earlier. According to Fitzgerald, the agency is working on a number of fronts, including efforts to strengthen national regulatory authorities, improve the capacity for regulating medicines and biologicals, and monitor trends in regional cooperation and collaboration.

At the time of PANDRH's formation, its purpose was to promote "technical agreements on drug regulation among the member states, including multilateral, bilateral, and subregional agreements, with the participation of all sectors and interest groups" (PANDRH, 2000). Since then, the mission has evolved, and the organization now also takes into account some of the asymmetries within the region of the Americas, recognizing that there are many well-established national regulatory authorities and some strongly developing ones, as well as some low-income countries that do not have robust regulatory capacity and are not prioritizing harmonization efforts at present.

The network sets its agenda and promotes technical cooperation under the direction of a Steering Committee that includes members from the subregional economic and trade integration mechanisms of Caribbean Community (CARICOM) (in the Caribbean), Mercado Común del Sur (MERCOSUR) (in the south), Sistema de la Integración Centroamericana (SICA) (in Central America), and the North American Free Trade Agreement (NAFTA) (in North America), as well as representation from industry. The economic development and trade orientation of these bodies is exemplified by one particular instance, where the drug industry harmonization initiative is led by customs officials from the economic ministries, not health officials. While drug regulators and trade officials often have the same objectives, experience has shown that the best outcomes occur when drug regulators, the regulated industry, and academia are in the lead, said Fitzgerald. Once their recommendations are made, they can work through other relevant regional committees, including the trade committees.

PANDRH's technical working groups tackle the requirements and priorities set by the steering committee, which presents the working groups' results to the Pan American Conference. The conference has additional participation by consumers, academics, and professional associations. So far, PANDRH has completed 15 technical documents, including the following 5:

1. Harmonized requirements for the licensing of vaccines

2. Harmonized guidelines for preparation of an NDA
3. Guidelines for good clinical practices
4. Guidelines for clinical trials in pediatrics
5. Considerations about the use of placebos

Additional working group documents are forthcoming.

The impact of this work cannot be truly measured until some years in the future, when the extent to which the guidelines have been adopted, adapted, and implemented can be measured, said Fitzgerald. At present, however, there is some empirical evidence regarding impact. For example, Fitzgerald pointed out that Technical Document 6, which covers self-evaluation of good laboratory practices, has been implemented by 21 countries; 20 countries have adopted the norms in the document covering pharmacovigilance; and the vaccine common technical document is being implemented partially in 14 countries and completely in 7.

The impact of the documents on actual regulatory practice has not been assessed yet, and there is no legal framework within the region to ensure that technical documents are implemented in similar ways. Nevertheless, according to Fitzgerald, PANDRH believes they are having considerable influence. Certainly, they have facilitated capacity building and development of regulatory networks within the region. For example, there is now a regional network of 25 Official Medicine Control Laboratories working together, and a 12-country network for sharing pharmacovigilance information has been formed. The vaccine document specifically has proved to be a useful tool in increasing efficiencies in the vaccine registration process. PANDRH is defining a method to measure and evaluate how countries are implementing these documents to date.

In the discussion period at the end of this panel session, participants focused on how successful implementation depends in large part on a country's approach to policy. Workshop attendee Peter Barton Hutt, Covington & Burling, LLP, described three levels of legal structure: mandatory implementation, guidance, and voluntary convergence. The most stringent, Hutt said, is *mandatory implementation*, which is usually established through statute or, in most countries, regulations. Bilateral or multilateral agreements and treaties can make requirements mandatory across countries and may be essential for true harmonization in the long run, he said. The next strongest level of policy is *guidance*, said Hutt. While guidances, like those developed by ICH, are neither mandatory nor binding on either industry or governments, because industry takes them so seriously, they may be considered de facto mandatory. However, if a manufacturer or regulatory agency diverges from a guideline, there is no enforcement capability. When countries and regions get together and propose *voluntary convergence*, they are using the weakest policy approach, said Hutt. Volun-

tary efforts often are frustrating because they take a long time, and there is no guaranteed outcome. Mike Ward, Health Canada, and Fitzgerald argued that classifications for a country's efforts at harmonization could be simplified further to *mandatory* or *non-mandatory.*

Although voluntary convergence may be slow, negotiations over the legal language in mandatory regulations also can stall. In one case cited by Fitzgerald, legal language was being hashed out over a period of years, but meanwhile, the regulators convened, agreed on basic principles, and moved forward into implementation. Achieving mandatory regulations requires more than the support of the health sector, added Ward. It also needs the backing of political leaders, and it needs to be compatible with economic drivers, such as the thrust toward single-market economies.

The number of entities working on economic integration in the Americas creates a complex situation. The same country may be involved in bilateral and multilateral agreements, each with its distinct political mandates and trade policies. For example, Fitzgerald noted that in recent years, Brazil has signed 13 bilateral agreements among regulators. PANDRH has studied how to move forward with implementation of its harmonization initiatives in this environment and begun a dialog with some of the more well-established national regulatory authorities to that end. These regulators have suggested that PANDRH begin to look at convergence by linking its normative processes, which focus on technical harmonization, while building on established capacity within the national regulatory authorities.

Accordingly, noted Fitzgerald, PAHO member states adopted a resolution in 2010 to strengthen national regulatory authorities for medicine and biologicals. Essentially, member states are to develop regulatory capacity with respect to critical functions within their health systems, and then link into and support the harmonization work of PANDRH. Currently, PANDRH is assessing and evaluating regulatory systems of individual countries, as well as supporting the implementation of institutional development plans of a number of them.

The process has brought countries together to work on joint projects. For example, Fitzgerald recognized that Argentina, Brazil, Colombia, Cuba, and Mexico are meeting biannually and making progress, particularly with respect to sharing reports on good manufacturing process inspections. Cooperation also is increasing between FDA and Health Canada and countries in the southern hemisphere, he said. As drug registration processes are linked, confidence is building among regulators. To ensure regulators have a secure environment for dialog, last year PAHO, with FDA assistance, launched an online platform for access and innovation in health technology.

What PANDRH has learned from all these efforts, said Fitzgerald, is

that regulatory harmonization depends on political, economic, and trade agreements as well as the policies within particular regional initiatives; that implementation of harmonized norms requires well-functioning regulatory systems; that convergence is achievable within short- to mid-term time frames; and that modern communications technologies can facilitate the process.

According to Fitzgerald, in the future, PANDRH will not abandon the normative guidance and technical document development that have been its core work for 15 years, but will move more generally toward good regulatory and review practices and mechanisms to support broadly defined network development.

APEC MEMBER ECONOMIES[4]

APEC was created in 1989 and includes 21 member economies, which account for 40 percent of the world's population, 54 percent of its gross domestic product, and 44 percent of its trade. APEC includes Australia, Canada, China, Japan, Korea, Russia, the United States, and many smaller economies. APEC's goals are to promote trade, sustainable economic growth, and the prosperity of member economies through policy alignment and economic and technical cooperation.

APEC is still relatively new compared to some of the other more well-established regional organizations, but, according to Ward, its experience speaks to how such an organization needs to

- be clear on what it wants to achieve, with whom, and why;
- develop a business case; and
- create a strategy or roadmap describing how it will work toward desired outcomes.

Such a plan needs to be practical and proceed one step at a time, taking into account what is already going on within the region and internationally, said Ward.

According to Ward, APEC's annual work plan is developed around senior officials' meetings, culminating in a leaders' declaration that endorses policy and sets the agenda for the subsequent year. The chairmanship rotates annually among member countries. An understandably complex organization, APEC has more than 40 task forces and committees working on a broad range of issues—from investment banking to food safety. The Life Sciences Innovation Forum, where drug regulatory har-

[4] This section is based on presentation by Mike Ward, Manager, International Programs, Health Canada.

monization fits, has as its underlying premise that a healthy population is necessary to a healthy economy. Thus the forum is concerned with promoting both public and economic health, said Ward, and from its outset, saw regulatory harmonization as a prerequisite to fostering innovation.

Unlike other harmonization initiatives, the forum does not produce harmonized guidances. Rather, it promotes the use of existing international guidelines and best practices. The forum can access APEC funds to undertake projects, although, because country participation is voluntary, only those economies interested in and committed to cooperation participate in a particular activity. Another difference is that APEC has a tripartite structure, with government, industry, and academia playing complementary roles.

Initially, APEC efforts were not sufficiently coordinated or robust and were deemed unlikely to achieve results, said Ward. In 2009, a Regulatory Harmonization Steering Committee (RHSC) and the APEC harmonization center were inaugurated. The RHSC mandate is to promote a more strategic, effective, and sustainable approach to harmonization by

- proactively identifying and prioritizing projects considered to be of greatest value to regulators and regulated industries;
- strengthening linkages with harmonization initiatives both regionally and internationally; and
- persuading key players such as WHO to promote complementary actions and most effective use of resources.

As a result, Ward said, APEC has become a good example of interconnectivity among initiatives. It concerns itself with medical products, notably pharmaceuticals, including biologics, medical devices, and advanced therapies, including cell and tissue therapies.

A growing number of senior regulators from APEC economies participate in the RHSC, as do research-based industry coalitions representing pharmaceuticals, medical devices, generic drugs, and, most recently, the biotech products sector. Also involved is the director of the Seoul-based APEC Harmonization Center, an organization-wide resource to enhance and sustain regulatory convergence and capacity building. APEC is working to establish official liaisons with other international harmonization initiatives, said Ward, because of the belief that it needs to act as a catalyst for international action on issues that demand a global approach, such as supply chain integrity.

APEC's strategic framework outlines a multiyear approach for achieving greater regulatory convergence by 2020; describes guiding principles and the steps necessary to achieve that end; and accommodates different countries' pace. The strategic framework outlines a coordinated

approach to promoting regulatory convergence. From there, APEC moved to identify priority work areas and develop implementation roadmaps that would bring best practices to light. The result is a move from ad hoc, individual country actions to collective efforts. Two examples of the priority work areas in which projects are completed are multiregional clinical trials (led by Japan) and supply chain integrity (United States).

Under way are projects in good review practices, biotech products, pharmacovigilance, good clinical practice inspection, and cellular therapies. Much of this work builds on the standards developed by ICH, using its GCG and ICH Regulators Forum as the interface. APEC plays an enabling role, supporting the uptake and broader understanding of these international standards and best practices, Ward concluded.

HARMONIZATION INITIATIVES IN AFRICA[5]

The African Union (AU) comprises 54 member states, with 900 million people and 8 regional economic communities that undertake most of the continent's economic development activities. AU's New Partnership for Africa's Development (NEPAD) has the mandate to

- facilitate and coordinate implementation of continental and regional programs and projects;
- mobilize resources and partners in support of the implementation of priority programs and projects;
- conduct and coordinate research and knowledge management; and
- advocate for the AU and NEPAD vision, mission, and core principles and values.

Margareth Ndomondo-Sigonda, Pharmaceutical Coordinator, AU-NEPAD Planning and Coordinating Agency, said the African Medicines Regulatory Harmonization (AMRH) initiative has developed as an essential step in reaching the vision of the approximately 6-year-old Pharmaceutical Manufacturing Plan for Africa, developed within the NEPAD framework. The plan's aim is to contribute to a sustainable supply of quality essential medicines to improve public health and promote industrial and economic development on the continent. Regulatory harmonization is seen as a critical factor in facilitating local production of pharmaceuticals, said Ndomondo-Sigonda, ensuring a sound regulatory environment, and encouraging intra- and intercontinental trade.

To this end, Ndomondo-Sigonda asserted that AMRH encourages

[5] This section is based on presentation by Margareth Ndomondo-Sigonda, Pharmaceutical Coordinator, AU-NEPAD Planning and Coordinating Agency.

increased use of harmonized policies and regulatory frameworks by AU member states. It also works to increase the human and institutional capacity for regulating medical products and technologies and to create knowledge assets on medicines regulation at the country, regional, and continental levels. One such activity is the development of a community of practice. In addition, AMRH is planning a scientific conference to bring together regulators, industry, and research organizations to discuss issues of common interest. According to Ndomondo-Sigonda, the first of these will be held in late 2013. The sum of these activities, she said, is creating an enabling environment for harmonization through coordination across regional activities, measurement of impact, and developing an accountability framework.

The consensus of a broad range of stakeholders—funders, international development agencies, United Nations (UN) agencies, and others, as well as regional economic communities—is that the time is right for attempting regulatory harmonization in Africa, said Ndomondo-Sigonda. Setting priorities for action has taken into account that 54 national regulatory agencies are involved in this effort: each of them works independently and may lack adequate medicines policies and laws; have different requirements and formats; vary in regulators' capacity; operate with minimal transparency; have no clear time lines; and make little to no use of reference evaluations conducted by more stringent national medications review authorities.

Because of the severe challenges regulators face, AMRH's first priority for action is to harmonize medicines registration requirements and standards. This activity is seen as not only protecting and improving public health, but also contributing to economic development. To overcome the current fragmented efforts across countries, Ndomondo-Sigonda stated that AMRH hopes to have five to seven regional economic blocks working together to create a single, clear set of guidelines that will drastically limit the number of dossiers that manufacturers need to submit. Achieving more transparent and coordinated regulatory processes will enable pooling of resources and information sharing, and a quality management system will enable more robust research, but will require investments in information management.

In the EAC[6] specifically, a treaty among the partner states provides for cooperation on health issues. Decisions at the ministerial level of the five EAC member nations have enabled their regulatory agencies to develop a proposal for regional harmonization of medicines. The relevant stakeholders have agreed to a governance structure to oversee the project, and

[6] The EAC comprises Burundi, Kenya, Rwanda, Tanzania, and Uganda. It has a population of 133 million and an annual gross domestic product of $79 billion.

technical working groups have been established with different countries having different responsibilities. For example, leadership of the technical working group on registration was assigned to Tanzania, supported by Burundi. By the end of this year, some of this group's guidelines will be ready for review and approval by relevant stakeholders. As another example, the technical working group on good manufacturing processes—led by Uganda, supported by Rwanda—has produced a number of draft documents. Additional technical working groups are focused on information management and quality management systems. EAC's progress is considered a model for other African regions.

At the continental level, AMRH working groups also have formed, for example, around regulatory capacity development, medicines policies, and regulatory reforms. In July 2012, the AU assembly endorsed a roadmap for shared responsibility on key infectious diseases that emphasized the need to accelerate and strengthen harmonization initiatives and, more important, laid the foundation for a single African medicines agency. According to Ndomondo-Sigonda, in 2013 stakeholder consultations are planned to discuss a draft model law for medicines regulation harmonization in Africa.

4

Areas of Need for Harmonized Standards and Barriers to Progress in Addressing the Gaps

Although the morning session of the workshop reviewed the quite extensive harmonization and convergence activities under way around the world, according to Steven K. Galson, Amgen Inc., session chair and workshop co-chair, this session's focus was on the gaps—how they are identified, how they are dealt with, and what the barriers to progress are.

GAPS FROM THE REGULATOR'S PERSPECTIVE[1]

Douglas C. Throckmorton, Deputy Director for Regulatory Programs, Center for Drug Evaluation and Research (CDER), FDA, began his presentation by summarizing the current environment for drug regulatory harmonization. He said harmonization is occurring across a wide range of activities, from regulatory policies to technical standard setting. Multiple parties are involved, each with its own skill sets, resources, needs, and values that affect the pace and success of harmonization efforts. Among these interested parties, regulators have an important role to play.

According to Throckmorton, one of the gaps that regulatory agencies face is acquiring the scientific expertise to regulate the cutting-edge products emerging from many scientific specialties, such as pharmacogenomics, metabolomics, antisense therapies, and the development of nanotechnologies. Regulatory agencies need to be able to evaluate such innovative

[1] This section is based on presentation by Douglas C. Throckmorton, Deputy Director for Regulatory Programs, Center for Drug Evaluation and Research (CDER), FDA.

products so that their first response to them is not overly conservative. FDA has developed the Voluntary Exploratory Data Submissions (VXDS) meeting to address this need. VXDS provides a mechanism for industry and regulators to discuss potential applications of new science to drug development. The meetings are nonregulatory and sponsor driven, and the discussions are not binding. More than half of the 53 VXDS meetings to date have included EMA participation.

Another type of gap has emerged due to improvements in information management, said Throckmorton. These are gaps in interconnectivity among existing knowledge databases. Here, consistent standards of data collection, access, and storage would enable much greater efficiencies, more robust research, and expanded pharmacovigilance.

Gaps in information about how FDA's regulatory structures work are addressed in CDER's Forum for International Drug Authorities. In the past 8 years, the forum has met about 15 times. Throckmorton noted that many of the discussions focus on FDA's perspective on good clinical practices, manufacturing quality, and the like. The educational benefits of this forum also help close the capacity gap, while forging relationships among regulators from around the world, he said.

Harmonization initiatives try to fill different sets of gaps, depending on the level of regulatory development in a given country, said Throckmorton. For example:

- Nations with well-developed regulatory systems will want to ensure their systems support innovation, and, as suggested, they are always playing catch-up with the science.
- Nations with less developed regulatory systems may want to first fill gaps in capacity and bring their system into harmony with other nations (global engagement).
- Regulators in all nations want to minimize any differences between their actions, the expectations of the country's citizens, and the health outcomes they experience. They may ask themselves, "Do our actions result in quality medicines at reasonable costs, efficiently produced? To the extent we are not achieving this, there is a gap."

The role for regulators in closing these gaps, said Throckmorton, is to understand the unique role that regulation pays. It is a legal role in that regulations and laws are applied and enforced, and it is a public health role.

Regulators are in a unique position to see both needs and opportunities and to understand the changes they might make that not only are the

most feasible, but also would have the largest impacts. Throckmorton stated that the five obligations of regulators are to

1. protect the public from harm;
2. preserve maximum individual freedom of choice;
3. promote consistent and dependable rules that are equally applicable to everyone;
4. guarantee meaningful public participation; and
5. provide prompt decisions on all regulatory matters.

These issues are at the heart of harmonization, he concluded.

GAPS FROM THE PERSPECTIVE OF NONGOVERNMENTAL ORGANIZATIONS, FOUNDATIONS, AND PRODUCT DEVELOPMENT PARTNERSHIPS[2]

Based on his experiences, Vincent Ahonkhai, Deputy Director, Regulatory Affairs, Bill & Melinda Gates Foundation (BMGF), has a perspective that combines the views of both the private and public sectors. He identified a number of key gaps in the global health regulatory landscape at different stages of new product introduction: product development, registration, and postregistration. During product development, more timely, effective, ethical, and regulatory approvals for trials are needed, he said. For many reasons it may be difficult to conduct the trials in the countries where products will be used. Ahonkhai said one specific need is for the infrastructure and expertise to support and enforce good laboratory and clinical practices.

For a broad array of products, the public health concern and the registration concern is not focused solely on the expeditious development of innovative medicines, vaccines, or diagnostic tools, but also on making those new products affordable. Thus, the entire end-to-end value chain has to be considered, said Ahonkhai. Ahonkhai stated that the countries he is interested in—among the more than 100 low- and middle-income nations around the world—often use products procured by UN agencies, which makes them affordable. These products undergo initial registration, followed by WHO prequalification (WHO PQ) or some other filter of quality assurance, and finally they need to meet the registration requirements of the purchasing nation. In the postregistration phase, countries need an effective infrastructure to detect and report safety and effectiveness data and then to interpret and act on it, he said.

[2] This section is based on the presentation by Vincent Ahonkhai, Deputy Director, Regulatory Affairs, Bill & Melinda Gates Foundation (BMGF).

In terms of regulatory harmonization challenges, Ahonkhai stated that one gap is in the regulation of vector control products. The only group seriously looking at regulatory standards for public health–focused pesticides, according to Ahonkhai, is the WHO Pesticide Evaluation Scheme.[3] He said there is little innovation in this area, and no new active ingredients have been developed specifically for this use in the past several years. What has happened instead is a repurposing of agricultural pesticides. The Innovative Vector Control Consortium is a not-for-profit product development partnership working on the issue, but very slowly. Many less developed countries have no pathway to regulate these products; in sub-Saharan Africa, some 30 percent do not, said Ahonkhai. Where capacity does exist, it may be found in the Ministry of Agriculture, either alone or in conjunction with the Ministry of Environment or Ministry of Health. As a result, manufacturers and developers face a complex situation when seeking the necessary approvals. By contrast, according to Ahonkhai, the approval process for drugs and vaccines is very clear, in large part because of the work of ICH. Although following ICH standards is not mandatory, its work is widely used.

Ahonkhai described several barriers to closing the gaps in medical product development, including

- the diversity of countries, their health problems, and the variability in their standards, capabilities, and aspirations;
- a lack of sufficient and sustained financing for critical regulatory activities and the staffing to carry them out;
- too few mechanisms for regulators to rely on the work of others—for example, in good manufacturing process inspections; and
- asymmetry among the interests of commercial product developers, public health entities, and nonprofit product development partnerships.

Yet, at each stage in the product development process, Ahonkhai stated that good examples can be found. In clinical trials, he cited the African Vaccine Regulatory Forum (AVAREF), the European and Developing Countries Clinical Trials Partnership, and the Critical Path to Tuberculosis (TB) Drug Regimens. In the registration arena, he said the aforementioned WHO PQ programs and the AMRH initiative stand out. Finally, at the postregistration stage, he noted the WHO Global Vaccine Safety Blueprint and the Safety Surveillance Working Group.

Moving forward, these initiatives and others can build on past successes. One example is the vaccine for meningitis A. Developed with

[3] See http://www.who.int/whopes/en (accessed April 10, 2013).

standards created by the public and private sectors working together, this new vaccine has been registered and is now being administered in Africa's meningitis belt at a very low cost. Ahonkhai concluded that success such as this comes about because of a solid understanding of the landscape of epidemiologic and drug development challenges facing low- and middle-income countries, comprehensive stakeholder engagement, and prioritization of issues where regulatory harmonization can have the most impact.

BREAKOUT SESSION REPORTS

Following presentations by Throckmorton and Ahonkhai, workshop attendees participated in breakout groups in one of five topic areas to further discuss gaps in harmonization:

1. Qualification of innovative development methods/drug development tools
2. Clinical development
3. Evaluation and evidentiary requirements
4. Postmarket safety surveillance
5. Manufacturing standards and process

The groups' assignments were to discuss the high-priority gaps in harmonization for that particular area, barriers to achieving harmonization, and approaches to overcome those barriers. After the breakout sessions, a rapporteur from each group reported back to the larger workshop audience on their observations of the key points of discussion. Several rapporteurs related discussions about the need for greater transparency on how standards for decision making are set and interpreted. Even when consistent standards are used, some said, it is not always clear why specific decisions differ across jurisdictions. At the same time, the breakout group participants identified numerous potential opportunities to move forward in resolving gaps.

Qualification of Innovative Development Methods and Drug Development Tools[4]

Martha A. Brumfield, Director, International and Regulatory Programs, C-Path, identified the following key issues discussed by participants in this breakout group:

[4] This subsection is based on the presentation by Martha A. Brumfield, Director, International and Regulatory Programs, C-Path.

- Organizations or sponsors desiring to qualify a drug development tool, such as an animal model or in vitro test, need to clearly articulate the context of use, including the proposed tool's specific purpose, its sensitivity and specificity, and how it will be used.
- Clinical biomarkers as research tools need special scrutiny and need to be population-specific; researchers need to be clear on whether they are expected to serve as predictive, prognostic, or surrogate endpoints.
- At present, FDA, EMA, and PMDA tool qualification procedures are not harmonized and require differing levels of evidence. The FDA's process requires some degree of predictability about a tool's performance, whereas EMA uses a more principles-based approach. In addition, their legal structures, fee requirements, and time lines are different.

Furthermore, Brumfield noted a willingness among the breakout group participants to consider whether a common technical document might be constructed around areas of agreement in information required by FDA and EMA. From that, she noted, a dossier preparation template could be prepared that would meet the requirements of both agencies, and leave areas of difference to be customized by the respective agencies.

Given the staggering number of potential new drug development tools and methods, setting priorities among them is important, said Brumfield. However, not every group's priorities will be the same. Patients, industry, and regulators may all be deeply interested in different kinds of tools. A prioritization process therefore might start with a gap analysis that would bring to light the priorities of different stakeholder groups, she said.

Tool development and qualification take considerable time and energy. To learn whether they are worth the investment, having not just the priorities, but also a set of publicly available performance indicators would allow developers to learn from both successes and failures, Brumfield added. She noted that the breakout group participants did not agree on which entities should be responsible for collecting and reporting this information.

Under Europe's Marketing Authorization Applications process (equivalent to FDA's NDAs), Brumfield noted that manufacturers may receive scientific advice from the EMA.[5] If this advice pertains to use of

[5] "Scientific advice is when the [EMA] gives advice to a company on the appropriate tests and studies in the development of a medicine. This is designed to facilitate the development and availability of high-quality, effective and acceptably safe medicines, for the benefit of patients." See http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9 (accessed April 10, 2013).

a biomarker, for example, the dossier needs to include information about how the biomarker was used. Brumfield related the group's discussions about how extracting this information through some means (undetermined) could lead to creation of a helpful compendium of effective applications of various product development tools. U.S. NDAs do not necessarily include this information, which means industry would have to divulge it voluntarily for it to be included in a compendium.

She added that the group discussed the fact that stakeholders need to better understand more of the nuances of what qualification means in different jurisdictions and what is known and yet to be learned about specific drug development tools. For example, she noted it would be as educational to learn why specific tools were rejected by the regulatory authorities as it would be to know why others were accepted. Similarly, much might be learned by making available both the regulator's and the industry's perspective on a specific decision. One way to expand this pool of information, she said, would be to offer incentives for researchers to go through the qualification process. Brumfield noted that breakout group participants suggested a variety of incentives, including a priority review voucher, a commitment to a shortened review time frame, or a waiver of a scientific advice fee. Increasing the number of tools evaluated would benefit learning across the product development enterprise, she said.

Evaluation and Evidentiary Requirements[6]

Lawrence E. Liberti, Executive Director, Centre for Innovation in Regulatory Science (CIRS), identified the following key issues discussed by participants in this breakout group:

- Increasing requirements by regulatory authorities of different countries for minimal proportional representation of subjects from the home country in multiregional clinical trials pose difficulties. Liberti said the discussion of the topic centered on whether such requirements reflect real scientific and clinical concerns or whether in some cases they are motivated by political factors or a lack of confidence in other countries' data.
- Development of evidentiary requirements for multiregional clinical research is complicated by a number of additional factors, including inconsistent ethical oversight, noncomparable standards of care and clinical practice, inconsistencies in good manufacturing practices, and differences in risk tolerance.

[6] This subsection is based on the presentation by Lawrence E. Liberti, Executive Director, Centre for Innovation in Regulatory Science (CIRS).

- In studying specific diseases and conditions, the local population needs to be able to provide appropriate controls, an issue that affects study design and the selection of endpoints and comparators.
- Ideally, study populations in different regions would be aligned with respect to patient needs and patient-focused outcomes.

To resolve some of these problems, a way of more effectively communicating benefits and risks associated with a particular product being tested is needed. Transparency about how decisions are made and the uncertainties that were weighed in the decision is essential, said Liberti. He noted that other ways to increase harmonization that were discussed are through capacity building, especially in making good benefit-risk assessments and employing tools that facilitate a simple, structured, and systematic approach to assessing benefits and risks. Among these tools are a common lexicon and a common format for benefit-risk communication. For example, FDA is now publishing on the web the results of its benefit-risk reviews. A well-structured benefit-risk approach that facilitates communication can be used by different stakeholders—developers, regulators, patients, and others, he said.

Liberti noted that if entities communicate well, then the understanding of how to interpret evidentiary standards falls into place, and even smaller regulatory entities can apply systematic, well-developed approaches in their decisions. This makes the agency's position easier to explain in cases where its decision differs (in either accepting or rejecting a product) from those of other regulatory bodies. In this way, said Liberti, local decisions can be informed by global information.

Clinical Development[7]

Leslie Ball, Assistant Commissioner, International Programs, and Deputy Director, Office of International Programs, FDA, stated that the breakout discussion of critical barriers for clinical development focused on two key areas: (1) clinical trials and (2) premarketing safety reporting requirements.

Clinical Trials

In addition to occasional cultural differences and language barriers that impede the smooth operation of multiregional trials, Ball noted the discussion of numerous bureaucratic obstacles, including

[7] This subsection is based on the presentation by Leslie Ball, Assistant Commissioner, International Programs, and Deputy Director, Office of International Programs, FDA.

- difficulty identifying specific regulatory requirements;
- lack of transparency and gaps in regulatory practices, for example, with respect to time lines;
- lack of regulations or organization within regulatory authorities; and
- lack of clarity about the oversight responsibilities of regulatory authorities versus ethics committees, which leads to redundant efforts.

Ball said the breakout group discussed barriers at three levels. At the level of the regulatory authorities, there are differences in the regulations themselves and in the way that regulators work, she said. For example, the European Union and the United States take different approaches to issues such as choosing active comparators, dose finding, determining treatment effects, and dealing with treatment-effect heterogeneity. Nevertheless, expanding ICH beyond the founding members was deemed a positive experience, as were the European Union's centralized procedures and application process.

A second level of barriers arises because of differences from one country to another in how trials are overseen and monitored, said Ball. Third, at the study site level, additional barriers may arise—for example, sites may lack sufficient capacity to carry out the trial, a problem more likely to arise when the trial involves neglected diseases or takes place in developing countries. In addition, she noted there may be specific programmatic complications, such as differing requirements for pediatric drug development, which may encounter barriers at all three levels.

Ball reflected on suggested approaches to reducing these barriers, including an effort to map the regulatory requirements in different countries. For example, the Global Health Technologies Coalition[8] has created a description of the regulatory requirements for 10 developing countries, but frequent changes in requirements make this resource difficult to maintain. As a result, Ball noted one participant suggested that support be offered to countries' regulators so that they could take responsibility for keeping their websites updated.

Joint reviews—particularly for neglected diseases—might be a good place to start in efforts to achieve greater collaboration, noted Ball. Having systems in place that ensure high-quality data would simplify efforts to use trial results across countries.

Ball made two final observations based on the discussions: a good candidate for harmonization is consent requirements for participation in clinical trials, and further development of risk communication in clinical

[8] See http://www.ghtcoalition.org (accessed April 22, 2013).

trials, in the form of a "questions and answers" document, rather than a full guidance, would be desirable.

Premarketing Safety Reporting Requirements

Lack of harmonization between safety reporting requirements—specifically, between the European Union and FDA—is a problem, Ball stated. One of the fundamental differences is in assessing causality. FDA relies on product sponsors to aggregate adverse events and provide their assessment of the causes. The European Union relies on causality assessments by the investigator and by the sponsor. As a result, sponsors have to adapt their reporting to two sets of requirements.

An opportunity for convergence might arise, Ball suggested, if the European Union, within the research protocol, listed certain anticipated events that would not have to be reported, thereby greatly reducing the total number of reports. A clearer threshold focusing on patient safety would lead to reporting only serious and unexpected adverse drug reactions, she said.

Postmarket Safety Surveillance[9]

Andy Stergachis, Professor of Epidemiology and Global Health, Adjunct Professor of Pharmacy, Director, Global Medicines Program, School of Public Health, University of Washington, identified the following key needs discussed by participants in this breakout group:

- Strengthen capacity around postmarket safety surveillance before attempting harmonization and convergence, but with those factors in mind.
- Bring more countries into ICH.
- Decrease variability in individual case safety reports and periodic safety updates because even small differences between country requirements are problematic.
- Decrease variability in (and in some countries create from scratch) benefit-risk frameworks.
- Expand the concept of postmarket safety surveillance to include adverse effects that arise from how medicines are used, as well as product quality (defects, fake products, and substandard manufacturing).

[9] This subsection is based on the presentation by Andy Stergachis, Professor of Epidemiology and Global Health, Adjunct Professor of Pharmacy, Director, Global Medicines Program, School of Public Health, University of Washington.

- Increase evaluation efforts and, correspondingly, develop appropriate metrics.

Stergachis suggested that these challenges result in wasted resources that could be used to increase innovation and access to products. Poor regulatory practices and ineffective postmarket surveillance systems may negatively affect population health, he said. More broadly, inadequate monitoring of marketed products can damage public trust in the regulatory system and threaten public health programs. Regulatory practices that are not evidence based or that lack incremental benefits pose their own risks, he added.

Stergachis noted several solutions suggested by the breakout group participants, including the suggestion for a high-level participatory dialog on a conceptual framework for postmarket surveillance that includes more than adverse events. Achieving greater transparency among regulators requires good working relationships and mutual confidence, so that information about problems, as well as best practices, will be shared. Because some countries' physicians simply do not report adverse events, he noted, the importance of doing so needs to be covered in medical education and facilitated by easy-to-use reporting systems.

Other individual suggestions he noted were to make the case that postmarket surveillance is important to international trade and economies, and to emphasize that low- and middle-income countries have the opportunity to skip some logistical steps in safety reporting and go directly to systems that use mobile technologies.

Finally, Stergachis related that several participants emphasized the importance of sustaining what is already working in harmonization.

Manufacturing Standards and Process[10]

Diane Zezza, Vice President, Global Regulatory CMC, Novartis Pharmaceuticals Corporation, stated that the breakout discussion focused on two key areas: CMC reviews and good manufacturing practices.

CMC Reviews

Zezza stated that members of this breakout group began their identification of challenging areas of non-harmonization for industry, regulators, and patients with the lack of harmonization of dossier content. While the format may be consistent, she said, the content often varies greatly. CMC

[10] This subsection is based on the presentation by Diane Zezza, Vice President, Global Regulatory CMC, Novartis Pharmaceuticals Corporation.

guidances, in particular, are not harmonized, and when this section of the dossier goes through review and approval, many changes need to be incorporated to reflect different regulatory authorities' requirements.

As a result, said Zezza, many variations in specifications and control strategies creep in from the beginning. The complexity only increases in the postapproval phase, in attempting to manage supply chain logistics to meet different specifications or when manufacturing processes evolve. Zezza noted that such challenges increase costs and inhibit continuous improvement overall. For a product with a long lifecycle, especially, these multiple requirements are a significant burden.

Zezza added that even presumably harmonized guidances, like those of ICH, may be implemented inconsistently across countries, and countries may apply additional standards above and beyond the ICH foundation. Some countries require additional import testing, and unexpected results may affect the supply of a product or trigger recalls.

Zezza noted that individual suggestions for ways to tackle these problems, short of a centralized global filing procedure, included

- development of mutual recognition agreements for dossier review and approval of CMC content;
- assessment of whether WHO's Certificate of Pharmaceutical Product process might evolve to include CMC reviews; and
- application of the fundamental principles of the QBD paradigm in an effort to reduce postapproval changes, acknowledging that the QBD approach has not yet achieved its full potential.

Good Manufacturing Practices

The good manufacturing practices standards established by different countries and the way they are interpreted by individual inspectors, even from the same regulatory agency, also are divergent, said Zezza. EU health authorities tend to indicate the significance of their findings, which is deemed helpful, whereas others simply enumerate their observations.

Zezza noted that the multiple preapproval inspections that a company must go through, even for a global product manufactured at a single site, can be quite burdensome. For example, the manufacturer of one recent new product underwent 22 preapproval inspections by various groups, she said.

While many countries appear to agree on the PIC/S standards, it might be possible for PIC/S to add some criteria from the WHO PQ inspection program, which is well accepted in numerous countries, she said, thereby increasing the number of nations that accept PIC/S inspections.

She also noted that significant divergence in regulatory requirements

occurs in the postapproval period. Differences in CMC content rules require different categorizations of change. The timing for review of changes may take 24 to 36 months and, in some countries, is completely undefined. The logistical challenges are enormous, requiring, for example, separating projects before and after change. This burden results in higher manufacturing costs and potential product shortages in certain countries.

One approach to this problem, Zezza said, might be the broader use of global comparability protocols and implementation of QBD principles. She noted potential opportunities to extend ICH's success in the manufacturing arena by persuading all countries to commit to implementing its common data requirements and by linking the ICH guidances to trade agreements.

In the developing countries, the existence of multiple, non-harmonized pharmacopeias creates a persistent challenge. The possibility of a global pharmacopeia and development of good pharmacopeia practices is under active discussion, she said.

Zezza noted that members of the breakout group acknowledged the shortage of health authorities' regulatory infrastructure resources in developing countries. Work-sharing options that would preserve those resources were suggested by participants.

5

Characteristics of Harmonized Regulations and Regulatory Structures

This session, describing harmonized regulations and standards-setting in other sectors, offered two in-depth reports. The first was a look at international harmonization efforts for a completely different field—radiation safety management—to see how that discipline has approached issues similar to those faced in medicines regulation. Session chair James Fitzgerald, PAHO, WHO, noted that important safety standards for radiation protection have been adopted by various international organizations, such as the World Health Assembly and the International Atomic Energy Agency (IAEA). Afterward, the workshop turned to a detailed discussion of WHO's experiences in setting a variety of standards.

RADIATION SAFETY STANDARDS[1]

The U.S. Nuclear Regulatory Commission (NRC) is engaged in ongoing efforts to align its radiation protection regulations with international recommendations, said Cindy Flannery, Senior Health Physicist, Office of Federal and State Materials and Environmental Management Programs, NRC. Much has changed with respect to the amounts of radiation people are exposed to from multiple sources, and scientific knowledge regarding the health harms of radiation because the standards on which U.S.

[1] This section is based on the presentation by Cindy Flannery, Senior Health Physicist, Office of Federal and State Materials and Environmental Management Programs, NRC.

regulations are mostly based originally were adopted several decades ago, she said.

According to Flannery, the NRC's broad mission is to license and regulate the nation's civilian use of byproduct, source, and special nuclear materials to ensure adequate protection of public health and safety, promote the common defense and security, and protect the environment. Its regulations apply to a broad range of activities and sources—nuclear power plants, medical applications, diagnostic and therapeutic applications, industrial radiography, spent fuel, nuclear waste, and so on.

NRC rulemaking is a multistep process of revising current regulations that takes several years to complete. Flannery described the steps:

- *Identify the need for rulemaking*—The request for a change in the rules can come from any source: Congress, the public, professional associations, NRC staff, or others. If this request is approved by the NRC commissioners, staff often begin with a period of seeking input from interested stakeholders.
- *Establish the regulatory basis for the new rule*—A sound regulatory basis reduces the risks for misdirection of licensees; delays or failure of the rulemaking effort; and successful defense of the rule if it is challenged in court.
- *Ongoing stakeholder involvement*—NRC staff may make presentations at meetings of professional organizations and the public, conduct webinars, or use other means to solicit comment on the relevant issues. As the process moves forward, the requests for public input become more detailed and specific.
- *Develop a proposed rule*—The proposed rule is published in the *Federal Register* and other government websites, with a specified comment period.
- *Develop the Final Rule*—The final language of the rule is published in a *Federal Register* notice, which includes a "comment resolution" section providing responses to all the comments on the proposed rule.

In a real-life example, said Flannery, in 2007 the independent International Commission on Radiological Protection announced revised recommendations related to preventing radiation-induced diseases. NRC staff analyzed these recommendations and found that some of the changes warranted similar revision to U.S. rules. The five-member NRC agreed, and staff began the process of engaging stakeholders. That information-gathering process has been under way for 3 years, including three public workshops, presentations at conferences and meetings, and solicitation of comments through the *Federal Register*.

The policy issues they uncovered were addressed in a set of recom-

BOX 5-1
Differing Units of Measurement[a]

The issue of units is one to be addressed in the pharmaceutical arena. In many countries where U.S. firms file drug applications, they are asked to use the International System of Units (SI units)—the modern metric system—but for FDA, applications must be in standard U.S. units. As a result, companies need to maintain two datasets and, essentially, write two applications. ICH's common technical document does not solve this.

The lack of common units affects not just the manufacturers or just the United States; it makes the work of regulators in less-resourced settings more confusing and difficult. Put more broadly, in a globalizing world, what regulators do has impact outside their home jurisdictions. Such problems occur *within* the United States, as well; for example, the root cause of the loss of the Mars Climate Orbiter (total mission cost: more than $655 million[b]) was that the spacecraft team in Colorado used English units and the mission navigation team in California used metric.

Workshop participants were hard pressed to understand how this situation persists in an environment where there is so much interaction among regulators. Common units would be a small step toward harmonization that would have a large impact.

[a] Issues discussed by several individual workshop participants.
[b] See http://mars.jpl.nasa.gov/msp98/orbiter/fact.html (accessed April 22, 2013).

mendations to the commissioners, who, after consideration, asked the staff to move forward with developing the regulatory basis for some of them, said Flannery. For example, staff recommended that NRC update the method required for calculating radiation dose exposures to align with international recommendations, and the commission approved proceeding with this potential change. By contrast, staff recommended reducing occupational dose limits from 5 rem (Roentgen equivalent man) per year to the international standard of, effectively, 2 rem per year, but the commission voted against this change.

In general, the use of different units of measurement around the world is a challenge to harmonization efforts (see Box 5-1). For example, the rest of the world measures radiation exposure and doses in sieverts, but the United States uses rems. The staff recommendation that the NRC align its measurement units with the international standard was denied, and the U.S. units will be retained in the NRC regulations.[2]

[2] It was noted that the first study of the National Academy of Sciences was on the topic of whether the United States should convert its weights and measures systems to be aligned internationally, and the Academy's recommendation was "yes."

In some areas of radiation protection, the United States is moving into alignment with international recommendations, and in some it is not. International recommendations are viewed as a point of reference for developing U.S. regulations and guidance, and, while there likely are benefits to consistency, alignment is not automatic, Flannery explained.

The extensive opportunities that the NRC offers for public input also may move the final outcome away from consistency with international recommendations—a source of divergence not often considered. One workshop participant suggested that proposals to incorporate cost-benefit analysis in rulemaking processes might weaken the impact that public participation currently has in NRC regulation development. Flannery said the NRC recognizes that its decisions will never make everyone happy, but having an open and collaborative process lets stakeholders know they have an opportunity to participate and that their views are being heard.

The benefits of regulatory alignment Flannery described are

- establishing coherence within NRC regulations and updating them to a common basis;
- reflecting a more current estimate of radiation risk and advances in scientific knowledge; and
- consistency with the regulatory schemes of other countries.

REFLECTIONS ON THE EXPERIENCES OF WHO[3]

WHO is the directing and coordinating authority on international health within the UN system, and it is therefore owned by the UN's 193 member states. In addition to the Geneva headquarters, WHO has six regional offices—in Manila, the Philippines; New Delhi, India; Cairo, Egypt; Copenhagen, Denmark; Brazzaville, Republic of the Congo; and Washington, DC, as well as 147 country offices. The country offices vary considerably in size and in the technical sophistication of staff.

According to Lembit Rägo, Coordinator for Quality and Safety of Medicines, WHO, in the field of regulating health products—medicines, biologicals, vaccines, and devices—WHO's role is to set norms and standards and, in a broad sense, to assess national regulatory systems, provide regulatory support to countries building up functional systems, and engage in other capacity-building activities. Many hundreds of people go through WHO's training courses conducted in different part of the world. Regional offices and some country offices may supplement the global training effort. WHO also promotes harmonization and information

[3] This section is based on the presentation by Lembit Rägo, Coordinator for Quality and Safety of Medicines, WHO.

exchange on safety, quality, and best practices. Perhaps most important to developing countries, said Rägo, it ensures the safety and quality of selected products for UN members through its prequalification programs for medicines, vaccines, and diagnostics.

WHO Harmonization Activities

In its constitution, WHO is mandated "to develop, establish, and promote international standards with respect to food, biological, pharmaceutical and similar products" (WHO, 2013). These standards are arrived at through the deliberations of WHO expert committees. For example, Rägo noted:

- The Expert Committee on Specifications for Pharmaceutical Preparations develops standards in many areas, from good manufacturing processes, to finished dosage forms, to bioequivalence, to good distribution practices.
- The Expert Committee on Biological Standardization develops standards for vaccines and biological products.

The expert committees include global experts and may have observers who are representatives from industry and professional organizations. Their process is transparent, with drafts circulated for comment, and everyone may comment on them, he said.

By policy, WHO standards-development efforts do not compete with those of other standard-setting entities, like ICH, but complement them, said Rägo. Some WHO standards have become de facto ICH standards. For example, its good manufacturing practices standard for active pharmaceutical ingredients has become a common standard used by many countries.

Rägo suggested that another important harmonization activity is WHO's project on International Nonproprietary Names. When this initiative began in 1950, numerous nomenclature bodies were issuing similar nonproprietary names; today, few continue this work, and the WHO names are the world standard. This is a huge advance, as these names are used in drug regulation, labeling, prescribing, pharmacopeias, advertising, and the scientific literature.

A biennial WHO conference brings together drug regulators from a hundred or so nations, Rägo said. The conference promotes sharing of information and best practices, international cooperation, and harmonization and convergence. Several major initiatives—including ICH and AMRH—began with discussions at this meeting. Similarly, WHO has taken the lead in convening the few remaining global pharmacopeias.

Rägo concluded that WHO has promoted regulatory collaboration and harmonization for a long time, through various means, and will continue to do so. Its main objective in all such efforts, he said, is to produce measurable public health gains, primarily by improving access to needed medicines.

Challenges

WHO's long and multifaceted experience with international, regional, and national harmonization initiatives demonstrates that these initiatives themselves are not harmonized. They are different in how they are organized, in the entities involved, in their focus, and in how they are implemented. Several workshop participants underscored the importance of harmonizing the functional networks, while in the meantime strengthening the capacity of the smaller countries, in order to facilitate their eventual full participation in one or more networks.

Rägo asserted that countries engaged in successful harmonization initiatives typically have a number of characteristics, including

- an enabling environment and a strong foundation, including effective governance principles—transparency and accountability—and modern legal systems that allow certain flexibilities;
- political will and a common vision;
- socioeconomic development similar to that of other participating countries;
- well-functioning regulatory authorities that have the necessary capacity and resources;
- willingness to invest in harmonization and commit to implementing, updating, and revising guidelines; and
- use of good regulatory practice principles when implementing harmonized guidelines.

Gaps in implementing harmonized standards persist. One gap is the uneven training that regulators receive, which is exacerbated by a lack of consensus on what kinds of training regulators actually need or how to provide it. Even when common technical documents are in use, effective cooperation and work sharing are needed for effective implementation, Rägo argued. Ultimately, a set of good decision-making practices is needed, he said. The regulations may be harmonized and the regulatory practice principles may be in place, but regulators still need time and training to learn how to make good decisions.

Finally, Rägo suggested that the most effective ways to regulate many of the new product groups coming on line have not yet been established.

Countries are still learning how to regulate them, and prospective harmonization has not yet occurred, he said.

Despite these many requirements and various gaps, the EU experience shows harmonization can be successfully achieved. Laws and regulations pertaining to pharmaceuticals in the EU's 27 states are all the same. Implementation variation has been minimized by dividing the tasks. Only a couple of member states take the lead on scientific assessments, for example. The others benefit from that work, they do not duplicate it, and countries that do not take the lead in this area can put their resources elsewhere, he said. No correlation exists between the size of the EU country and its regulatory impact. Countries relatively small in population—like Sweden and the Netherlands—have a relatively high impact in medicines regulation, and the converse is also true.

The WHO PQP has been a success in making treatments affordable. Lower costs are achieved by relying on international-standard-quality generic medications. Competition among generics manufacturers brings costs down further. With fair competition and no artificial trade standards or other double-standard policies, the goal of more affordable medicines is achievable.

Trends Encouraging Harmonization

Joint review of clinical trial applications and products is an emerging trend, which Rägo believes has considerable potential. In this approach, regulators from different countries—even different regions—work on the same products or the same clinical trial applications. AVAREF works in this general way, as does the WHO PQP. The approach is especially promising for products with high public health value, but relative small potential markets.

In both the above examples, the regulators have an incentive to harmonize. Incentives can take many forms: the perceived gains from harmonization may be high and visible, or harmonization may be preferable to the political pressure that inaction would precipitate.

Another trend Rägo noted is to use staff exchanges to promote harmonization and improve regulatory reviews. These exchanges help staff understand other regulators' thinking about the decision-making process. For example, WHO has a 3-month rotation post for assessors from different countries.

As the production of medicines has become global, the era of only locally operating regulators may become increasingly untenable, with the future of medicines regulation more collaborative and networked. Unfortunately, many regulations and regulatory systems operating around the

world are merely unnecessarily redundant. Rägo suggested that ensuring that each regulatory review adds value to the process would require

- taking account one another's work with a view to improving the global system's efficiency;
- committing resources to form cooperative networks based on uniformity of standards and inspections systems; and
- engaging with regional and international initiatives promoting harmonization, information sharing, and use of shared data.

Although some of this is happening, a more structured and efficient approach would move the process along more quickly. "Not all national regulators can fulfill all the functions themselves. National decisions have to be made regarding which areas to focus on, where to build capacity, and in which areas to rely on other regulators' work," Rägo said. If smaller countries aspire to creating regulatory systems akin to those of Europe, the United States, or Japan, the resultant overload of work will delay their people's access to valuable biomedical products.

Next Steps

In the discussion session following this panel, Rägo proposed several specific ways to move forward, including the following:

- Rewrite WHO's guideline for small regulatory authorities based on today's realities and trends. The original version, in its comprehensiveness, was impossible for small agencies to implement.
- Disseminate the best practices of small regulatory agencies that have integrated themselves into collaborative networks for some necessary tasks so they can focus their own work on local value-added tasks.
- Develop a vision and understanding of how to implement good review practices.

6

Finding Solutions: Options and Systemic Approaches[1]

This session, chaired by Michael J. Brennan, Senior Advisor for Global Affairs, Aeras, underscored many of the barriers to harmonization and more efficient operation of biomedical product regulatory authorities and provided potential solutions from the perspective of different stakeholder representatives. The discussion offered additional attention to regulatory strategies promoting development and use of products for tropical diseases.

The discussion and the suggestions that conclude this chapter were directed to the principal challenges facing drug regulatory systems worldwide, including the need to foster collaboration and cooperation, reduce duplication of efforts through mutual trust and recognition, increase regulatory capacity and implementation effectiveness, and make the best uses of limited resources.

LEGAL FRAMEWORK

Numerous times in this workshop the existence of a common legal (and economic) framework in the European Union was cited by par-

[1] This chapter is based on brief presentations made by a reactor panel that included Vincent Ahonkhai, Deputy Director, Regulatory Affairs, BMGF; Raymond Chua, Group Director, Health Products Regulation Group, Singapore Health Sciences Authority; Mary Lou Valdez, Associate Commissioner, International Programs, and Director, Office of International Programs, FDA; David Wood, Coordinator, Quality, Safety and Standards, WHO; and discussions of workshop participants.

ticipants as facilitating the harmonization of drug regulations in member countries. Such frameworks do not exist in all regions, or even in all countries, and their lack is frequently perceived as a stumbling block.

In places where governments lack legal frameworks that would permit them to implement international norms and standards, harmonization becomes difficult. But "different countries have different needs, interests, and expectations from their global engagement," said Mary Lou Valdez, Associate Commissioner, International Programs, and Director, Office of International Programs, FDA. At the very least, she said, a framework can establish minimums for what the country's regulatory system should do, and, if it cannot or does not do them, some accountability mechanism should come into play.

"Regulators should not worry about getting out ahead of their governments," said Peter Barton Hutt, Covington & Burling, LLP, a workshop attendee. "It is the duty of regulators to use creativity and leadership, not to worry about their statutory authority." For example, he noted, some of FDA's most important harmonization efforts were not created by statute or were legislated after the regulators invented them.

COOPERATION AND COLLABORATION

Raymond Chua, Group Director, Health Products Regulation Group, Singapore Health Sciences Authority, noted that in the drug regulatory field, PIC/S[2] has developed an informal cooperation scheme which aims to encourage member states to recognize each others' inspections, harmonize good manufacturing practice requirements, train inspectors, exchange information, and engender mutual confidence.

An area where greater cooperation may be emerging is work sharing. One workshop participant noted that various developed nations' regulatory authorities are looking to work share around issues that arise in the premarket phase of generic drug development. Work sharing plans and joint plans of action also could be useful in expanding the regulatory science base for products going to the least resourced countries.

An area ripe for collaboration is data sharing. Developing secure information platforms where data can remain confidential is a challenge, but are essential to cooperative work, said one workshop participant. Some data-sharing efforts are taking place, but unless there is a collabora-

[2] The mission of PIC/S, which are two international instruments between countries' pharmaceutical inspection authorities, is "to lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products." For more information, see http://www.picscheme.org (accessed April 22, 2013).

tive Memorandum of Understanding across agencies, they can be difficult to accomplish. For example, Lembit Rägo, WHO, noted that WHO has developed a SharePoint platform for exchanging inspection results among a certain set of countries. The hope in developing it, he said, was that shared inspection plans and reports would encourage more risk-based approaches to inspections. However, the countries involved have been slow to add data due to persistent unwillingness to have joint inspections or coordinated inspection plans.

Beyond sharing information across agencies, several workshop participants suggested that increased discussion and collaboration with manufacturers might lead to the industry's better understanding of a country's biomedical product needs, and the regulators' better understanding of the policies and practices that would support the companies that are developing these priority products. One example of a regulatory action supporting industry would be harmonized clinical trial regulations for multinational research.

Collaboration, cooperation, and networking need to be built into institutional structures as someone's job, or the efforts stall out, said Rägo. At the same time, he said, it needs to be recognized that collaborative activities often come on top of a regulator's already-full plate. Collaborating effectively is not necessarily an obvious capacity need or something at which people are naturally good. Time and effort may need to go into figuring out what the best practices are in this arena.

MUTUAL TRUST AND RECOGNITION

Many activities support harmonization, including information sharing, effective communication, and the cooperative work that generates trust and confidence, said Valdez. Convergence will depend on building mutual trust among regulatory authorities so there can be some reliance on the decisions or input from peers.

Mutual trust also is an essential precondition to joint activities. A good example of where that is working (cited by several workshop participants and speakers) is AVAREF, which brings together both regulators and national ethics committees from 19 countries to resolve issues in multinational clinical trials. FDA, EMA, and Health Canada also participate, along with industry, which describes new products in their pipelines. David Wood, Coordinator, Quality, Safety and Standards, WHO, noted that in the forum, participants can hear what the problems are, who is doing what, and come to appreciate the quality of the input from regulators in neighboring countries. In this way, he said, AVAREF is both an information-gathering and trust-building model that might be expanded.

The Singapore Health Sciences Authority uses a mutual recognition

system for its approvals of new drugs, Chua explained. Under its system, manufacturers need to go through a full dossier approval process only for those products that have not been evaluated by any of the Health Sciences Authority's approved reference agencies. If the drug has been approved by one of these agencies, the new drug undergoes an abridged review, which has a shorter time line. If at least two of these agencies have approved the drug, it goes through a verification process, which is the shortest. Both of the latter processes are called confidence-based approaches.

Another challenge to harmonization, often not mentioned, is public trust, said Toshiyoshi Tominaga, Osaka City University Hospital. Even if regulators want to accept the findings of another national or international authority, they also need to satisfy the public, he said. As a consequence, public education and transparency of the decision-making process are essential, and regulators need to balance the need to accommodate the public's concerns with the costs of reinventing the wheel.

CAPACITY BUILDING

Not every country can have the staff and other resources of the world's largest biomedical products regulatory agencies. Although the relatively well-resourced agencies have a different scope of problems than lower income countries, they are reaching out to help build capacity elsewhere. The less well-resourced countries need to determine what level of regulatory activity is sufficient in their particular circumstances, and what their priorities are, so that the help that is available can be directed to the areas of greatest need, said Vincent Ahonkhai, BMGF.

By working together, regulators in a region can allocate priorities across countries, so that across a group of countries, the most important work is being done by the group as a whole. One priority might be filling gaps particular to a region that the larger regulatory authorities have not addressed—such as vaccine stability at higher temperature and humidity levels, said Ahonkhai. Similarly, by not duplicating elements of the drug approval process that other regulatory agencies have completed, a local agency can focus on postmarketing surveillance within its population. Setting priorities will require the lower income countries to make trade-offs, said Ahonkhai; sovereignty is important, but having effective vaccines and access to approved medicines also are important. A need here is to identify the best ways to build capacity that take advantage of networks already in place, in addition to building capacity in the networks themselves.

Wood noted that WHO has found institutional development plans a helpful tool in evaluating local regulatory entities. These plans are devel-

oped based on peer audits that assess the agency's systems, structure, and functions against a set of established criteria, which can be stratified to indicate which functions are appropriate for a given set of circumstances. (Participating on a peer audit team—which comprises both experienced and novice peers—is an educational experience in itself, he said.) The result is an evidence-based plan for further agency development that enables focused capacity-building efforts. For example, the plan identifies what the real training needs are and who needs to be trained to meet them. Ideally, said Wood, an institutional development plan needs the approval of higher governmental authorities in order to obtain the broad support and sustainability needed for capacity-building efforts.

WHO's Global Vaccine Action Plan brought together experts in economic development, health, and immunization, along with other stakeholders.[3] One of the goals of the plan, endorsed by the World Health Assembly's 194 member states in May 2012, is to "introduce new and improved vaccines and spur research and development for the next generation of vaccines and technologies." Its implementation requires a parallel regulatory agenda, which has been developed by a working group and is in publication, reported Wood.

Valdez noted that differential implementation of standards remains a significant barrier to harmonization. Aside from the problem of differences in technical capacity, some countries lack the essential legal and policy platforms that would facilitate implementation and assessment of impact. Thus, the notion of capacity building needs to include scientific capacity, legal capacity, and measurement capacity, she said.

The question of capacity development has no single answer because there is no single motive for it. In a broad sense, the kind of capacity needed is capacity for collaboration, cooperation, and understanding of the global regulatory situation. Capacity building per se does not solve the problems, said Rägo, "You have to know capacities for what and where and when."

BUSINESS CASE

Although the benefits of international harmonization of medical products regulation may be clear to experts in the field, these benefits are not as clear to everyone else, said Wood. Nor is it uniformly evident to policy makers that resources should be devoted to the effort. Wood pointed out that WHO has commissioned some inquiry into how donors feel about supporting harmonization efforts, and learned they do not

[3] See http://www.who.int/immunization/global_vaccine_action_plan/en/index.html (accessed April 10, 2013).

understand why they should support them. They believe the regulatory bodies promoting harmonization are slowing down the process of making medical products accessible. Moreover, many stakeholders believe that ICH is managing these issues, but the workshop's discussions revealed that ICH's efforts, while necessary to the process of harmonization, are not sufficient.

The first step, then, may be to make a stronger case for why harmonization is important. Valdez emphasized the need to develop a business case that demonstrates how key actions discussed at the workshop—such as ensuring supply chain integrity, data transparency, data sharing, pharmacovigilance, and use of science-based standards—would save money and increase the efficiency of regulators and industry alike. While regulators' strength is in leading with the science, she said, they do not do especially well in making an economic argument.

Some solid efficacy cases—examples of how a harmonized system is a good investment—may already exist. For example, James Fitzgerald, PAHO, WHO, noted that Mexico's Federal Commission for the Protection against Sanitary Risks has demonstrated that institutional plans, changed management, and linkages with reference agencies can have an enormous positive economic impact on the pharmaceutical sector and reduce the costs of regulation.

Several speakers agreed that more fundamentally, what is needed is a greater understanding of the importance of regulatory work. Regulators have not been particularly effective in positioning the imperative for regulatory systems in the broader public health dialogue. For example, Valdez noted that recent WHO discussions about the public health workforce did not include the regulatory workforce. "We are also not very good about really positioning the imperative for regulatory systems in even the broader global public health dialog," she added.

TOP-LEVEL SUPPORT

Several workshop participants noted that the highest management level in the regulatory agencies, the level that makes resourcing decisions for projects, need to be involved in discussions about the importance of harmonization. In turn, the business case has to be understood by the government officials to whom these leaders report. Valdez added that ministries of trade and foreign affairs, as well as development assistance agencies, need to understand how these types of investments will expand the strength and the base of a country's economy.

The economic case has to represent advantages not just to the larger markets, but also to leaders in the smaller ones. There is a risk that economic arguments will be interpreted as the larger economies' desire

for access to the smaller markets, said Fitzgerald, with all the economic benefits accruing to the major players. He suggested that WHO and PAHO might serve as honest brokers between the countries with reference systems and those without. At present, for example, El Salvador links to Mexico's registration process; and Mexico links to FDA.

Top-level support can have many benefits, in addition to the obvious potential resource benefits. Political capital is important, as well, and can become advance efforts to promote data sharing, for example. One cautionary note sounded by Chua was that the need for top-down endorsements does not obviate the need for bottom-up assessments of the practicality of a given harmonization effort.

META-HARMONIZATION

A robust area of harmonization is in standards development, with strong engagement by government, industry, and other groups. But because different groups have proposed different standards and guidances, many workshop participants supported the idea of harmonizing these harmonization efforts. Are these standards duplicative or complementary? Are they different enough or adopted differently enough that they create confusion or actual impediments to implementation? Alternatively, do they expand the reach of regulatory science in ways that can build trust and create efficiencies?

Although a great deal of work has gone into creating a large number of harmonized standards, several participants noted that too little attention has been paid to making sure they are implemented effectively, if at all. Wood said the examples built into some standards of how they should be applied are helpful, but do not go far enough. He noted that WHO has developed workshops for people in the field about its new standards. Also, it has worked with industry partners who have contributed real data for case studies about how the standard could be applied. The combination of illustrative case studies and interaction with regulators in the field begins to move implementation along, said Wood, and in a more harmonized way.

Not only are regulators working in silos defined by the different regulatory harmonization issues and organizations, but silos also exist for product lines, such as vaccines, pharmaceuticals, generics, devices, and so on, added Mike Ward, Health Canada.

Considering the role of the regulator in the 21st century, Moheb M. Nasr, Vice President, CMC Regulatory Strategy, GlaxoSmithKline, asked, "Is it to micromanage and evaluate development and manufacturing, or is it to assure quality, safety, and efficacy?" Focusing on the key regulatory functions perhaps needs to precede moving into harmonization, he said,

or all the discussions about capacity building and enhancing activities will focus on very narrow issues.

SUGGESTIONS FOR MOVING FORWARD

One comprehensive suggestion for increasing harmonization was offered by Chua in his presentation, while other presenters and participants made a number of additional suggestions.

Chua proposed development of an international regulatory organization similar to that of the International Civil Aviation Organization (ICAO) or IAEA (see Box 6-1) that would generate the necessary political will from health, trade, and economic reasons and common vision to achieve worldwide adoption. Within the global organization would be smaller working subcommittees that could address specific areas, such as premarketing evaluation, pharmacovigilance, or building on the work PIC/S has done in good manufacturing practices. This three-part approach—premarketing, manufacturing, pharmacovigilance—would cover the whole lifecycle of a pharmaceutical product. The proposed organization would require stable funding, a mechanism for random audits to ensure standards are being met, and ongoing robust governance oversight for sustainability reasons, said Chua.

According to Chua, the governance structure could be based on an expansion of current ICH or WHO platforms, or be housed in a separate organization, although that might best be avoided. Too many overlapping structures, agencies, and organizations have developed over the years that were not well aligned, with much duplication of effort, meetings, and so on. Smaller groups could be formed as needed at the regional or subregional levels or laterally, looking at consistency and alignment across regions.

Compared to regulatory or legislative changes, standards and guidelines would be easier to achieve, as of now, because they do not intrude on national sovereignty rights. ICAO has approached this by setting mandatory global minimum standards, and the biomedical products industry could do the same, with the addition of a second set of standards that responds to any specific local or regional needs. An example of standards that could not be completely harmonized would be those for drugs used in the tropical region, which might require separate stability studies.

The next step would be to adopt implementation plans that move countries toward harmonization and convergence. Harmonization, more or less, refers to synchronization of standards, whereas convergence refers to meetings of practices and process, said Chua. Hence, similar to the operation of PIC/S, the approach might be that if a product is approved by the international organization, it can be used everywhere in the world,

BOX 6-1
Examples from Other Industries[a]

The banking, aviation, and atomic energy industries all achieved harmonization sooner, more quickly, and in a much more coherent manner than has the biomedical products industry.

IAEA—which for historical and political reasons is not a UN specialized agency, but nevertheless reports annually to the UN General Assembly and, as needed, to the Security Council—is charged with several roles that again are roughly parallel to the roles of biomedical products regulation. In broad terms, IAEA resources are directed to promoting sustainable development, catalyzing innovation, building capacity in energy planning and analysis, protecting people from harm, and helping countries improve their scientific and technological capabilities. The agency works across national borders in carrying out these roles, a requirement of which is harmonizing the work of many countries.

ICAO[b] is a UN specialized agency, based in Montréal, Canada, that serves as a global forum for 191 member states that have signed the relevant treaties (the current, 9th edition, of the Convention on International Civil Aviation is referred to as "the statute"). ICAO's purpose is to promote the safe and orderly development of international civil aviation throughout the world. It engages in many activities that parallel those of drug regulatory authorities: determining priorities, developing policies and standards, coordinating global monitoring, delivering targeted assistance, and building capacity.

Its planning work—from the global safety level down to regional and national safety plans—is based on high-level principles accepted by industry stakeholders. It provides a step-by-step guide to help those at the regional or subregional level to implement their safety enhancement plans. Even though the aviation industry is a relatively safe one, ICAO develops precise safety targets aimed at continually strengthening safety programs.

ICAO has a mechanism to ensure that its safety plan is kept updated in a coordinated way. Flight Safety Information Exchange website[c] allows full transparency: Anyone can access its worldwide aviation safety information. Cooperation among member states and the regulators is vital for maintaining these resources.

ICAO standards include "any specification for physical characteristics, configuration, material, performance, personnel or procedure, the uniform application of which is recognized as necessary for the safety or regularity of international air navigation."[d] The governments that contract with ICAO must comply with these standards, in accord with the ICAO Convention, or tell the agency why they cannot. Adherence to the standards is audited by ICAO.

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[a] This box is based on the presentation by Raymond Chua, Group Director, Health Products Regulation Group, Singapore Health Sciences Authority.

[b] See http://www.icao.int/Pages/default.aspx (accessed April 10, 2013).

[c] See http://legacy.icao.int/fsix (accessed April 10, 2013).

[d] See http://legacy.icao.int/icao/en/anb/mais/index.html (accessed April 10, 2013).

again, unless there are distinct regional requirements. Such a system would require the mutual trust and confidence of the regulators, as well as the public.

Chua summarized the steps needed as the six *C*s: commitment, convergence, communication, cooperation, collegiality, and capacity.

In addition to Chua's comments, various individual workshop participants had the following insights about moving forward with harmonization:

- Progress requires two essential preconditions: developing strategic and more structured regulatory frameworks and creating a safe space for discussion.
- To support the business case, people need to be able to demonstrate the importance of harmonization investments and to advocate for them.
- With respect to standards implementation, it would be helpful to create an Internet-based information exchange about ideas that have and have not worked.
- Building in certain incentives for international harmonization is also important, as well as ensuring sustainable ways to measure implementation and update of harmonization.
- Numerous models are being used to increase regulatory capacity, and it would be useful to create an inventory of them that describes their core operating principles and drivers, strengths and weaknesses, and information on their usefulness. Less developed countries could use the inventory to see which models best fit their needs and their environments. Likewise, networks could consider whether to adopt any of the principles used by others.
- An international regulatory cooperative development plan, with perhaps a secretariat at its hub, could support and coordinate various current harmonization initiatives. At present, for example, separate initiatives on generics and biosimilars are addressing the same issues and might productively collaborate.
- Examining best practices from other industries continues to be helpful in sparking new ideas.

7

Tactics and Strategies for a Way Forward[1]

The workshop's final session involved two brief panels and audience discussion led by workshop co-chairs Steven K. Galson, Amgen Inc., and Thomas J. Bollyky, Council on Foreign Relations. The session offered participants an opportunity to make summative comments as well as suggestions for moving toward more harmonized regulations and regulatory structures.

KEY THEMES

Many Paths to Harmonization

There is no "one size fits all."
—Vincent Ahonkhai, BMGF

Harmonization initiatives worldwide have generated a great deal of multicentric leadership, rather than one overarching, hierarchical organization. Hans V. Hogerzeil, University of Groningen, the Netherlands, suggested that what can be learned from the several multinational networks discussed at the workshop—such as ICH, PANDRH, APEC, and

[1] The first panel consisted of chairs of the previous workshop sessions, as described earlier; the second panel involved Deborah Autor, Deputy Commissioner, Global Regulatory Operations and Policy, FDA; Hans-Georg Eichler, Senior Medical Officer, EMA; and Alan Morrison, Vice President, International Regulatory Affairs and Safety, Amgen Inc.

the EAC—is that there are many ways to put networks together. They have independently developed different processes, and they have various scopes. Andreas Seiter, World Bank, added that another commonality is that, although each of these networks exists in a dynamic environment, where many different events and changes occur, similar basic ideas, principles, and terminology are emerging.

While regulators can continue to be encouraged to adopt the broad array of international standards, other initiatives with narrower agendas also have developed and, in some cases, may provide regulatory authorities with an initial demonstration of the usefulness of harmonization. Examples of these more focused activities mentioned by individual workshop participants include the following:

- Harmonization with respect to pharmacovigilance is beginning to happen with the aggregation of postmarketing data and use of standard terminology (Deborah Autor, Deputy Commissioner, Global Regulatory Operations and Policy, FDA).
- Information-sharing platforms, such as shared inspection reports, are being developed and exchanged internationally (Raymond Chua, Singapore Health Sciences Authority; Fitzgerald, PAHO, WHO; Lembit Rägo, WHO).
- Joint review models have developed that have the advantages of pooling capacity, maintaining sovereignty, and moving toward convergence of regulatory approaches. Where these have worked best is with developed country regulators facing a new problem or with regulators in some of the least developed countries where pooling capacity is the most sensible approach (Bollyky; Hans-Georg Eichler, Senior Medical Officer, EMA; Rägo).

There will always be a need for this kind of flexibility, said Bollyky, who believes that a single path to international regulatory harmonization is "an impossibility." All the regulatory issues involved in initial approval, trials, registration, and monitoring cannot be lumped together in the hope of finding a single solution, a participant agreed.

Attributes of Successful Networks

Numerous workshop participants individually identified various attributes of successful networks, including

- a clear vision of what the network wants to achieve, which is vital in establishing a business case that makes sense to stakeholders;

- a dedicated secretariat with dedicated staff (the participating regulatory authorities also may need staff dedicated to the work of harmonization);
- a sufficient budget to support meetings and travel;
- high-level political support; and
- a bottom-up strategy that starts with the scientists, rather than a top-down strategy that starts with the lawyers.

Balancing Competing Regulatory Roles

Regulators have two potentially difficult-to-reconcile goals: protection of the public's health and support for industry. Different metrics would be employed to assess progress toward each goal and to optimize the benefits of regulation for the population and the economy. The drug development and regulation ecosystem is so large and complex that there is enough room to work toward both these goals, as long as the work is prioritized properly, Galson said.

Hogerzeil said the need to work toward both these goals ultimately may put a limit on how far harmonization can go, if individual countries' regulatory systems are sufficiently different in how they balance these two aims. Risk-benefit analysis, done transparently and in a standardized way, can illuminate the balancing process, he said. Such analyses will require both standardized information and standardized ways of presenting it.

Some industry representatives are convinced of the potential benefits of harmonization and want to move forward with it, said Seiter, but they are not the same individuals who travel with trade delegations and negotiate free-trade agreements. The latter group usually includes lobbyists and lawyers with completely different points of view from the scientific community, he said. This suggests the need for some intracompany education about how harmonization is good for business and why it is worth investing in building regulatory capacity in countries that have weak systems, so that product sales can continue to grow in these markets.

Helping the weaker agencies achieve a higher performance level would be a win-win situation, said Seiter. Often, lower-income countries are plagued with tainted, substandard, or fake medications, and if their regulatory agencies were helped to do a more effective job stemming the tide of illegal medicines, the size of the market for legitimate drugs would increase, and the population would not be exposed to worthless or hazardous products. Eichler said it is therefore not just good industrial policy to increase the efficiency and effectiveness of regulatory agencies; it is also good public health policy.

Resource Costs of Harmonization

Harmonization is an investment that may not produce immediate monetary savings, even though the long-term savings from increased efficiency and reduced duplication of effort is inevitably less costly system-wide. Small agencies that do not have the resources to meet all the current demands on them may have the fewest resources to pursue harmonization, but, ironically, would likely see its benefits soonest because it would improve their capacity and performance.

With all the potential benefits in mind, it is hard to understand why more resources are not being devoted to harmonization. However, there is no single answer to the question of the source of financial support for harmonization. It might come from incremental additions to existing work and budgets; it might derive from nonprofit funding for specific projects; it might be obtained through higher fees from sponsor companies. Or, modest resource increases from each of these sectors might be achievable. According to Seiter, for example, industry is willing to pay higher fees for a better regulated system.

Costs of harmonization have to be added to the already strained funding for basic regulatory activities in lower income countries and even some middle-income countries, where sufficient, sustainable funding for training regulators and operating a regulatory agency is a serious and persistent problem.

Governments are increasingly under pressure to figure out how to reduce the costs of regulation and avoid duplication of effort, said Galson, whether it occurs in regulatory tool development, clinical trials, amassing the evidence base, postmarketing safety, or manufacturing processes. What has to be avoided, said Chua, is the temptation of government leaders to assume that, because harmonization is expected to reduce regulatory costs, the workforce and budgets of regulatory agencies can be reduced immediately—before harmonization is achieved. One participant also suggested that some smaller regulatory authorities may rely on inspections as a source of income, which may serve as a disincentive to move toward harmonization which may involve the use of joint inspections or relying on another another's inspection.

To the extent that disharmonization results in duplication and inefficiency, higher industry costs for multiple clinical trials, multiple dossier requirements, or redundant inspections—all of which lead to delays in making effective treatments available—its opportunity costs are high, said Eichler. They are even higher if it means that potential products that will only ever have small markets (e.g., drugs for rare diseases) may not be developed at all. These various opportunity costs are borne by different parties, which make their full impact harder to assess. Regulators bear some; businesses bear others; and patients bear still others, Bollyky noted.

Harmonization and Innovation

Seiter noted that one issue the meeting did not fully explore is whether harmonized regulations actually foster innovation in the biomedical products field, where regulations are often seen as a barrier to developing new products. Yet, innovation is needed in many areas of disease prevention and treatment, and science is on the cusp of enabling many new types of products. With respect to antibiotics, for example, the lack of new products in the face of rising microbial resistance to existing treatments is an increasingly serious problem, he said. Similarly, Seiter added, the current incentive system does not well support development of innovative products related to the neglected tropical diseases (or orphan drugs in general), and there may be opportunities to shift those incentives.

Today's research and development model is simply not delivering, said Alan Morrison, Vice President, International Regulatory Affairs and Safety, Amgen Inc. The number of new drugs approved per billion dollars invested has approximately halved every 9 years since 1950.[2] At present, each new biomedical product costs more than the previous one, and there is a strong imperative to reduce these costs. Harmonization isn't the total solution, said Morrison, but a more predictable regulatory environment worldwide would be a step in the right direction.

Morrison added that harmonization also has to ensure there are no disruptions in the supply chain—a problem of increasing concern. Some of the highly specialized biotechnology products may have a manufacturing run only every 2 or 3 years. The supply chain and storage conditions for these products need to be absolutely reliable, otherwise even developing such projects becomes economically untenable.

Harmonization and Globalization

Harmonization is occurring simultaneously with a homogenization of afflictions facing humanity, said Galson. Although infectious diseases persist, and the biomedical products to prevent and treat them are desperately needed, the global increase in chronic diseases suggests that, over time, much of the same medications will be needed everywhere, he said. Moreover, the slow rise in the global standard of living will enable more and more people to gain access to health care. Finally, the industry itself is becoming more global, said Galson, with many companies operating in dozens of regions and hundreds of countries.

Harmonizing standards for disease-specific entities may be a chal-

[2] See http://www.nature.com/nrd/journal/v11/n3/fig_tab/nrd3681_F1.html (accessed April 10, 2013).

lenge, posited one workshop participant because of differences in clinical practice and accepted endpoints across regions. Galson responded that for many disease areas (e.g., neglected and tropical diseases), the thinking about their treatment is not that different in different nations. He pointed to the osteoporosis guidance developed for the European Union, noting there is not one in the United States.

After a drug is on the market, there are actually two issues, said Eichler: accumulating data on patient experience and deciding whether anything needs to be done about it. The latter depends greatly on the way medicine is practiced locally and the legal systems involved. But with regard to evidence generation for pharmacovigilance, there is much room for harmonization, said Eichler.

Recently FDA reorganized so it could rise to the challenges of globalization, said Autor. Its *Pathway to Global Products Safety and Quality*[3] is built on the themes of forming global coalitions of regulators, developing global data systems, using advanced risk analytics, and leveraging the efforts of public and private third parties. Autor asserted these four fundamental ideas demonstrate FDA's recognition that it needs to work with others, rely on others' work, and create efficiencies.

SUGGESTED PATHS FORWARD

Initial Steps

The steps needed to move harmonization forward can be undertaken by different stakeholders, and they will not be the same for every stakeholder group. More important, no one group or organization can take on all of them. Numerous specific next steps were suggested by individual workshop attendees as being useful both to understanding harmonization and moving it forward. They included the following:

- Articulate the core principles of existing harmonization efforts, which could be used as a framework for developing a common understanding of what harmonization is (Michael J. Brennan, Aeras).
- Examine current harmonization initiatives in detail, perhaps through case studies, to find out what contributes to their successes and failures and how they can be developed further (Bollyky).
- Strategically map the linkages between existing initiatives and countries and work to establish closer links across efforts (Fitzgerald).

[3] See http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/GlobalProductPathway/default.htm (accessed April 10, 2013).

- Invest in economic analysis of the benefits of harmonization (Galson).
- Strengthen the rationale for harmonization in countries that are not now fully participating (Fitzgerald).
- Analyze why two regulatory agencies can look at exactly the same data and arrive at different conclusions (Galson).
- Consider the role of cultural or ethical differences in harmonization efforts (e.g., reporting of adverse events) (Morrison, Toshiyoshi Tominaga, Osaka City University Hospital).
- Identify whether harmonized processes are needed when implementing harmonized norms and, if so, what those processes should be (Fitzgerald).

Workshop participants were divided on the issue of whether to wait until a thorough business case could be developed for harmonization or "just do it." The truth is probably somewhere in between, suggested Autor.

The challenges in harmonization are due to "a combination of inertia and the need for courage and creativity," said Autor. Working with others globally means giving up some control and learning to do some things in another's way. This pulls people outside their comfort zone, said Eichler. One tactic to make people more comfortable is to start with noncommittal meetings that provide what Eichler called the safe harbor. From there, discussions could move to developing a pilot study, still not very threatening. If the pilot succeeds, one or more additional pilots could be tried, as people become comfortable with and accustomed to doing work differently. Ultimately, a new process can be developed.

Postmarketing trials and studies may involve tens of thousands of patients, and many are designed to show that a new treatment is not substantially worse than already available treatments. What is needed in these cases is a better understanding of the criteria by which the study's outcome will be judged.

Ultimately, benefit-risk studies may become useful in facilitating communication across regions and with practitioners and patients.

The Business Case

The conversation about why global convergence is important needs to focus on gains in efficiency, increased coverage and availability, and the complexities of the job that make it impossible to do alone, Autor said. Perhaps the business case should not be written solely by regulators, she said, but by regulators and patients, clinicians, donors, nongovernmental organizations, legislators, consumer groups, and others.

Autor added that a solidly constructed business case can be an important advocacy tool. It can include useful case studies that demonstrate the potential effectiveness of harmonization, discuss the importance of regulatory work, and describe gaps. But what it actually needs to accomplish is to send the message to stakeholders that drug harmonization is important to everyone. It needs to look separately at the opportunities for harmonization in reviews, versus clinical trials, versus inspections, and versus other areas, said Autor. It needs to separately analyze the needs of the developed world versus the developing world.

Business case in hand, the next step is to prepare a proposal and plan for moving to the next level, said Autor, recognizing that this is an evolving field and that continued evaluation of effort will be needed. Bollyky added that focusing on pilot projects in areas where the opportunity costs from different stakeholders line up might be a way to jumpstart efforts, in parallel with building an international secretariat, supporting legal frameworks, and refining the business case. However, he noted that it may be daunting to ask national leaders to make these costly investments in infrastructure before they have seen any benefits from harmonization.

An Evolving Global Regulatory Strategy

Wood said the tools WHO uses to assess national regulatory authorities at present focus on whether systems are in place. The next level of assessment, he said, is to build in performance indicators, but how to do that is not yet clear.

Performance assessment also is needed at the multinational network level. In some cases, going to a regional network may not actually save time in the approval process, but several workshop participants gave examples that review times have been substantially shorter than usual. In one instance, where delays occurred, they were actually on the side of the manufacturer. For example:

- In Latin America, countries sharing inspection schedules and reports are finding that good manufacturing practice inspections by each individual nation are not necessary. Sharing has produced monetary savings, and the quality of the inspections has improved as well (Fitzgerald).
- The prequalification of a new antimalaria drug facilitated its registration in a number of African countries within 2 years—likely much faster than the norm (workshop attendee Nathalie Strub Wourgaft, Drugs for Neglected Diseases initiative [DNDi]).
- DNDi sought a joint ethical review for a new sleeping sickness medication that brought together scientists and people knowledge-

> able about ethics in the relevant countries. Each country's representatives returned to their own institutions' ethics committees for further review. The process facilitated meeting all the requirements for both a scientific and ethical review while maintaining the sovereignty of each country, and also promoted mutually beneficial sharing of information (Strub Wourgaft).

Another topic needing discussion is who should pay for these reviews, said Strub Wourgaft, because she suggested the sponsor may not be the best candidate due to conflicts of interest.

Risk management and risk mitigation strategies also could be harmonized, added one participant. The European Union, for example, has a risk management plan, and the United States uses a risk evaluation and mitigation strategy template. Harmonizing these two approaches would be an improvement.

The many specific ideas put forward provide a starting point for multiple subsequent actions. All told, the meeting projected "an overwhelming sense of optimism" that harmonization can happen and is happening, said Galson, and he closed the meeting by admonishing the group to "go forth and converge."

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Appendix A

Workshop Agenda

International Regulatory Harmonization Amid Globalization of Biomedical Research and Medical Product Development: An Institute of Medicine Workshop

February 13–14, 2013

National Academy of Sciences Building
Lecture Room
2101 Constitution Avenue, NW
Washington, DC 20418

Background and Meeting Objectives:
The past several decades have seen a rapid globalization of commerce, including within the medical product and technology sectors. Investigational studies are increasingly being conducted outside the countries that have a history as hubs for biomedical research, often in countries with limited regulatory capacity. Moreover, biopharmaceutical companies seeking global markets face requirements for regulatory submissions for the same product in numerous international jurisdictions that could introduce scientific requirements that are discordant with standards in their home markets. Discordant data requirements could result in additional clinical trials and animal studies, exposing more patients to experimental drugs and increasing the use of laboratory animals. There is a need for globally harmonized, science-based standards for the development and evaluation of safety, quality, and efficacy of medical products—both to enhance the efficiency and clarity of the drug development and evaluation process, and ultimately to promote and enhance product quality and the public's health. There is also need for harmonization of standards for ongoing safety and quality surveillance of marketed biomedical products.

This public workshop will address needs for international harmonization of regulatory standards to support the development, evaluation, and surveillance of biomedical products. Specifically, the discussions at the workshop will help identify principles, potential approaches, and

strategies to advance the development or evolution of more harmonized regulatory standards.

The workshop objectives are to:

- Provide an overview of the current global regulatory landscape. Identify
  - Current organized efforts to promote and evolve harmonized standards, and examples of areas where standards are viewed as adequately harmonized.
  - Areas of need for development or evolution of harmonized standards.
- Identify the characteristics of a well-harmonized regulation.
- Discuss principles to guide the establishment or evolution of harmonized regulations.
- Discuss options and approaches that could facilitate or underlie systemic organizational efforts to develop and/or evolve harmonized standards.
  - Discuss potential structures, methodologies, goals, and outcomes.

DAY ONE: FEBRUARY 13, 2013

8:30 a.m. Opening Remarks

STEVEN GALSON, *Workshop Co-Chair*
Vice President for Global Regulatory Affairs
Amgen Inc.

TOM BOLLYKY, *Workshop Co-Chair*
Senior Fellow for Global Health, Economics, and Development
Council on Foreign Relations

8:50 a.m. **Plenary Keynotes: Needs from the Perspective of Stakeholders**

Keynote Address: Industry

PETER HONIG
VP and Head, Global Regulatory Affairs
AstraZeneca

Keynote Address: Regulator

HUBERT G. M. LEUFKENS
Chair, Dutch Medicines Evaluation Board;
Member, Committee on Human Medicinal Products,
European Medicines Agency

SESSION I: PRINCIPLES AND DEFINITIONAL CONSIDERATIONS

Session Objectives:

- Examine key definitions and terminology: "harmonization" vs. "convergence" vs. "cooperation" vs. "consensus standards."
- Discuss potential goals for initiatives, including differences arising from terminology.
- Consider potential variations in approach depending on which terminology is adopted and how the desired outcome is defined.

9:35 a.m. Background and Session Objectives

ANDREAS SEITER, *Session Chair*
Senior Health Specialist
Pharmaceuticals, Health, Nutrition, and Population
World Bank

9:40 a.m. **Series of Presentations**

History and Importance of Terminology, the Terminology Landscape, and Options for Regulators

MIKE WARD
Manager, International Programs
Health Canada

Standards-Setting in the Context of Regulatory Harmonization

CAROLYN COMPTON
President and CEO
Critical Path Institute

10:20 a.m. **Discussion with Speakers and Audience**

10:40 a.m. **BREAK**

SESSION II: OVERVIEW OF CURRENT GLOBAL REGULATORY LANDSCAPE

Session Objectives:

- Provide an overview of the current global regulatory landscape.
- Identify current organized efforts to promote and evolve harmonized standards.
- Highlight examples of areas where standards are viewed as adequately harmonized and/or harmonization processes are viewed as well working.

11:00 a.m. Background and Session Objectives

HANS HOGERZEIL, *Session Chair*
Professor of Global Health
University of Groningen, the Netherlands

11:05 a.m. **Series of Presentations**

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

TOSHIYOSHI TOMINAGA
Professor
Osaka City University Hospital

Latin America

JAMES FITZGERALD
Senior Advisor, Essential Medicines and Biologicals
Pan American Health Organization

APEC Regulatory Harmonization Steering Committee (RHSC)

MIKE WARD
Manager, International Programs
Health Canada

East African Community (EAC) Medicines Registration Harmonization Project

MARGARETH NDOMONDO-SIGONDA
Pharmaceutical Coordinator
New Partnership for Africa's Development
African Union

12:05 p.m. **Discussion with Speakers and Audience**

Discussion Topics/Questions

- Description and characterization of existing international standards-setting bodies
- Description and examination of regional harmonization efforts
- Identification and discussion of particular standards that have been developed

12:30 p.m. **LUNCH**

SESSION III: AREAS OF NEED FOR HARMONIZED STANDARDS AND BARRIERS TO PROGRESS IN ADDRESSING THE GAPS

Session Objectives:

- Discuss gaps in the current structures, approaches, and international standards leading to unnecessary discordance among regulatory requirements.
  - Identify top-priority areas where harmonized standards need to be developed or evolved.
  - Consider regulatory requirements and harmonization needs across the full spectrum of medical product development, evaluation, and monitoring/surveillance.
- Discuss how gaps are identified and priorities are set within harmonization efforts.
- Having considered the gaps and areas of need, identify the key barriers that stand in the way of addressing the identified needs.
- Discuss approaches that have been tried and have failed to address the needs.

1:15 p.m. Background and Session Objectives

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

1:20 p.m. **Stakeholder Presentations: Gaps in Current Structures and High-Priority Areas of Need**

Overview: Gaps from the Regulator's Perspective

DOUGLAS THROCKMORTON
Deputy Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Overview: Gaps from the Perspective of NGOs/ Foundations/Product Development Partnerships

VINCENT AHONKHAI
Deputy Director, Regulatory Affairs
Bill & Melinda Gates Foundation

2:00 p.m. **Overview of Charge to Breakout Groups**

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

2:15 p.m. **Breakout Groups Convene Concurrently**

General Discussion Topics/Objectives:

- Identify the key barriers that stand in the way of addressing the identified needs. What are the issues that are the most pressing?
- Discuss approaches that have been tried and have failed to address the needs.
- Deliberate on potential options to address those high-priority needs for consideration at the workshop.

1. ***Qualification of Innovative Development Methods/Drug Development Tools*** **[STAY IN LECTURE ROOM]**
   Richard Meibach, Novartis Pharmaceuticals (*moderator*)
   Martha Brumfield, Critical Path Institute (*rapporteur*)

2. ***Clinical Development*** **[BOARD ROOM]**
   Judith Kramer, Duke University (*moderator*)
   Leslie Ball, U.S. Food and Drug Administration (*rapporteur*)

3. ***Evaluation & Evidentiary Requirements*** **[ROOM 125]**
   Tim Franson, FaegreBD Consulting (*moderator*)
   Lawrence Liberti, Centre for Innovation in Regulatory Science (*rapporteur*)

4. ***Postmarket Safety Surveillance*** **[MEMBERS ROOM]**
   Amrit Ray, Johnson & Johnson (*moderator*)
   Andy Stergachis, University of Washington *(rapporteur*)

5. ***Manufacturing Standards and Process*** **[ROOM 114]**
   Moheb Nasr, GlaxoSmithKline (*moderator*)
   Diane Zezza, Novartis Pharmaceuticals (*rapporteur*)

4:15 p.m. **Breakout Groups Conclude**

4:30 p.m. **Reports from Breakout Groups**

5:20 p.m. **Day One Reflections**

5:30 p.m. **Adjourn Day One**

DAY TWO: FEBRUARY 14, 2013

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

STEVEN GALSON, *Workshop Co-Chair*
Vice President for Global Regulatory Affairs
Amgen Inc.

TOM BOLLYKY, *Workshop Co-Chair*
Senior Fellow for Global Health, Economics, and Development
Council on Foreign Relations

SESSION IV: CHARACTERISTICS OF HARMONIZED REGULATIONS AND REGULATORY STRUCTURES

Session Objectives:

- Consider examples of standards-setting and regulatory harmonization from other sectors and their application to biomedical research and medical product regulation.
- Identify the characteristics of a "well-harmonized regulation" or well-working process.
- Discuss principles to guide the establishment or evolution of harmonized regulations or other desired process and outcomes.

8:35 a.m. Background and Session Objectives

JAMES FITZGERALD, *Session Chair*
Senior Advisor, Essential Medicines and Biologicals
Pan American Health Organization

8:40 a.m. **Series of Presentations**

Radiation Safety Standards
CINDY FLANNERY
Senior Health Physicist
U.S. Nuclear Regulatory Commission

Reflections on the Experiences of the World Health Organization
LEMBIT RÄGO
Coordinator for Quality and Safety of Medicines
World Health Organization

9:10 a.m. **Discussion with Speakers and Audience**

9:40 a.m. **BREAK**

SESSION V: FINDING SOLUTIONS TO THE CHALLENGES OF REGULATORY HARMONIZATION: OPTIONS AND SYSTEMIC APPROACHES

Session Objectives:

- Discuss options and approaches that could facilitate or underlie systemic organizational efforts to develop and/or evolve harmonized standards.

- Discuss potential structures, methodologies, goals, and outcomes.
- Examine these issues with respect both to *development* and *implementation* of desired standards and/or processes.

10:00 a.m. Background and Session Objectives

MICHAEL J. BRENNAN, *Session Chair*
Senior Advisor, Global Affairs
Aeras

10:05 a.m. **Reaction Panel: Potential Solutions from Stakeholder Perspectives**

VINCENT AHONKHAI
Deputy Director, Regulatory Affairs
Bill & Melinda Gates Foundation

RAYMOND CHUA
Group Director, Health Products Regulation Group
Singapore Health Sciences Authority

MARY LOU VALDEZ
Associate Commissioner for International Programs
U.S. Food and Drug Administration

DAVID WOOD
Coordinator of Quality, Safety and Standards:
Immunization, Vaccines and Biologicals
World Health Organization

10:55 a.m. **Discussion with Speakers and Audience**

Discussion Topics/Questions:

- What process or systemic approach holds most promise for supporting *development* of harmonized standards or processes?
- What are the needed structures to support *implementation* of harmonized standards or processes within various systems (e.g., training, capacity building, networks, other needs)?
- How can novel harmonization/convergence strategies, policies, and processes be implemented to facilitate the efficient global introduction of quality products?

- How can we promote and expand on current harmonization/convergence strategies to alleviate regulatory roadblocks?

11:30 a.m. **BREAK FOR LUNCH**

SESSION VI: CONCLUDING STAKEHOLDER DISCUSSION: TACTICS AND STRATEGIES FOR A WAY FORWARD

Session Objectives:

- Discuss key themes from the workshop.
- Based on workshop presentations and discussions, identify tactics and strategies (both short and long term) for addressing the needs for developing and evolving more harmonized regulations and regulatory structures.

12:30 p.m. Closing Discussion with Panelists and Audience: Led by Workshop Co-Chairs

STEVEN GALSON, *Workshop Co-Chair*
Vice President for Global Regulatory Affairs
Amgen Inc.

TOM BOLLYKY, *Workshop Co-Chair*
Senior Fellow for Global Health, Economics, and Development
Council on Foreign Relations

12:35 p.m. **Panel 1: Presentation of Key Themes/Suggested Paths**

HANS HOGERZEIL, *Chair of Session I*
Director for Essential Medicines (former)
World Health Organization

ANDREAS SEITER, *Chair of Session II*
Senior Health Specialist
Pharmaceuticals, Health, Nutrition, and Population
World Bank

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

JAMES FITZGERALD, *Chair of Session IV*
Senior Advisor, Essential Medicines and Biologicals
Pan American Health Organization

MICHAEL J. BRENNAN, *Chair of Session V*
Senior Advisor, Global Affairs
Aeras

1:00 p.m. **Discussion with Speakers and Audience**

1:30 p.m. **Panel 2: Reflecting on Tactics and Strategies for a Way Forward**

DEBORAH AUTOR
Deputy Commissioner for Global Regulatory Operations and Policy
U.S. Food and Drug Administration

HANS-GEORG EICHLER
Senior Medical Officer
European Medicines Agency

ALAN MORRISON
Vice President for International Regulatory Affairs and Safety
Amgen Inc.

2:00 p.m. **Discussion with Speakers and Audience**

2:45 p.m. **ADJOURN**

Appendix B

Participant Biographies

Thomas J. Bollyky, J.D. (*Workshop Co-Chair*), is Senior Fellow for Global Health, Economics, and Development at the Council on Foreign Relations. He is also an adjunct professor of law at Georgetown University and consultant to BMGF. Prior to joinng the Council on Foreign Relations, Mr. Bollyky was a Fellow at the Center for Global Development and director of intellectual property and pharmaceutical policy at the Office of the U.S. Trade Representative, where he led the negotiations for pharmaceuticals, biotechnology, and medical technologies in the U.S.-Republic of Korea Free Trade Agreement and represented the U.S. Trade Representative in the negotiations with China on the safety of food and drug imports. He was also a Fulbright Scholar to South Africa, where he worked as a staff attorney at the AIDS Law Project on treatment access issues related to HIV/AIDS, and an attorney at Debevoise & Plimpton, LLP, where he represented Mexico before the International Court of Justice in Avena and other Mexican Nationals (Mexico versus United States of America) and José Ernesto Medellín before the U.S. Supreme Court in Medellin v. Dretke. Mr. Bollyky is a former law clerk to Chief Judge Edward R. Korman, an International Affairs Fellow at Council on Foreign Relations, an Eesti and Eurasian public service fellow at the Estonian Ministry of Education, and a health policy analyst, through the Outstanding Scholar Program at the U.S. Department of Health and Human Services. His research and writing focuses on trade, legal, and regulatory issues in global health and development, in particular tobacco and noncommunicable diseases, technological innovation and

delivery, clinical trials, and import safety. He has testified before the U.S. Senate on international regulatory issues in global health, and his most recent work has appeared in the *Journal of the American Medical Association*, *Foreign Policy*, *The Atlantic*, *Clinical Trials*, and *Stanford Journal for Law, Science & Policy*. He is a member of the IOM's Committee for Strengthening Food and Drug Regulation in Developing Countries and has served as a temporary legal advisor to WHO. Mr. Bollyky received his B.A. in biology and history at Columbia University and his J.D. at Stanford Law School, where he was the president of the Stanford Law & Policy Review. He is a term member of the Council on Foreign Relations and a member of the New York and U.S. Supreme Court bars and the American Society of International Law.

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

Vincent Ahonkhai, M.D., FAAP, is Deputy Director, Regulatory Affairs for Global Health at BMGF. His role is to provide strategic regulatory oversight for on-time development and registration of foundation health technologies, including vaccines, drugs, diagnostics, and public health pesticide

products. His background is in biopharmaceutical global health research and development (R&D), including clinical development, medical affairs, regulatory affairs, and product safety and pharmacovigilance. His specialty is infectious disease.

Deborah Autor, J.D., is FDA's Deputy Commissioner for Global Regulatory Operations and Policy. Ms. Autor's Directorate, one of four created in July 2011, includes the Office of Regulatory Affairs and the Office of International Programs. The Office of Regulatory Affairs, with a staff of more than 4,000 U.S. employees, is responsible for imports, inspections, and enforcement policy for all FDA-regulated products. The Office of International Programs, with a staff of more than 80 employees around the world, is responsible for maximizing the impact of FDA's global interactions. Ms. Autor leads FDA's strategy for confronting the challenges of globalization and import safety. She co-chaired the group that prepared FDA's 2011 report, *Pathway to Global Product Safety and Quality*, which describes the paradigm shift that FDA must make to face the challenges of globalization today and in the future. Ms. Autor has been with FDA since 2002. Prior to assuming the role of Deputy Commissioner, she served for 5 years as Director of the Office of Compliance of FDA's CDER. In that role, she led policy making and enforcement for key public health programs for drugs, including current good manufacturing practices; human subject protection and bioresearch monitoring; marketing unapproved drugs; pharmaceutical import and export; pharmacy compounding; Internet and health fraud; over-the-counter monograph compliance; adverse event reporting; registration and listing; risk evaluation and mitigation strategies; and drug recalls. Ms. Autor engaged in many international activities in this role, including leading the negotiation of the work plan under the Memorandum of Agreement between the U.S. FDA and China's State FDA. She won the 2011 Meritorious Executive Presidential Rank Award. This award is presented annually to a select group of career civil service senior executives whose integrity, strength, leadership, and relentless commitment to excellence in public service have earned them one of the most prestigious honors in government. Ms. Autor is also a 2011 recipient of the Food and Drug Law Institute's Distinguished Service and Leadership Award in recognition by her peers of remarkable professional achievements and dedicated support to the food and drug law field and community. In addition, Ms. Autor was a 2010 finalist for the prestigious Service to America Medal for the innovative and strategic action that she took to tackle the serious public health issue of marketed unapproved drugs. She has also received 24 awards from FDA, 24 awards from the CDER, 1 award from the U.S. Department of Health and Human Services, and 6 awards from the U.S. Department of Justice. Before joining

FDA, Ms. Autor was a trial attorney for 7 years in the Office of Consumer Litigation of the U.S. Department of Justice, where she litigated civil and criminal cases on behalf of FDA and other federal law enforcement agencies. She began her legal career practicing food and drug law at the firms of Weil, Gotshal & Manges and Buc Levitt & Beardsley.

Leslie Ball, M.D., has served as Assistant Commissioner of International Programs and Deputy Director of FDA's Office of International Programs since September 2012. The Office of International Programs leads FDA's international activities and oversees the operation of FDA's 13 regional and country offices. Prior to this position, Dr. Ball served as Acting Director of the Office of Scientific Investigations, and previously Director of the Division of Scientific Investigations, Office of Compliance, CDER, FDA. While in the Division of Scientific Investigations she was active in developing a risk model for selecting clinical trial sites for inspection, collaborating with EMA and other international regulatory authorities, developing approaches to inspecting electronic data, and instituting process improvements for enforcement actions. Dr. Ball joined FDA in 1996 as a medical officer in the Center of Biologics Evaluation and Research. Dr. Ball graduated with a B.S. in biology from Georgetown University, where she also received her M.D. and completed a residency in pediatrics. She completed a Fellowship in pediatric infectious diseases at the Walter Reed Army Medical Center. She served as a practicing pediatrician at the U.S. Naval Hospital, Subic Bay, Republic of the Philippines, in private practice in Maryland, at the National Naval Medical Center, Bethesda.

Michael Brennan, Ph.D., is the Senior Advisor for Global Affairs at the Aeras Global TB Vaccine Foundation. He develops strategies for the timely introduction of new TB vaccines into low-income countries, and he works closely with National Regulatory Authorities responsible for clinical trial approval and new product licensure. Dr. Brennan also heads projects on the development of correlates and biomarkers for TB vaccines. Prior to joining AERAS, he spent more than 20 years at FDA, where he was an Associate Director at the Office of Vaccines Research and Review, and was also head of the TB vaccine program. In 2001, he worked in Geneva assisting WHO in its development of a new TB Vaccine Initiative. Dr. Brennan has published more than 90 scientific articles on vaccines and infectious diseases, and his early research paved the way for widespread whooping cough immunizations. An authority on vaccine development and regulatory review, he sits on several international advisory committees, including the Stop TB Partnership, WHO, and the U.S. National Institutes of Health (NIH). He received a Ph.D. from Albany Medical College.

Martha A. Brumfield, Ph.D., is Director of International and Regulatory Programs at C-Path. Dr. Brumfield has a consulting practice focusing on concordance in global regulatory initiatives; examining regulatory science qualification programs; and providing educational workshops on these and related topics. Other areas of focus include excellence in clinical trial conduct; facilitation of scientific consortiums; and programs supporting patient access to medicines. At present she is engaged with the nonprofit C-Path as a consultant to guide international program development and to provide regulatory guidance to consortiums. She is also engaged with other nonprofits, Regulatory Harmonization Institute and GlobalMD, to deliver educational workshops on regulatory and clinical trial topics in Asia. She is leading work through C-Path to TB drug regimens toward the identification of regulatory pathways in high-burden TB countries. Dr. Brumfield served on the IOM committee Ensuring Safe Foods and Medical Products Through Stronger Regulatory Systems Abroad. Most recently, Dr. Brumfield was senior vice president, Worldwide Regulatory Affairs and Quality Assurance at Pfizer Inc. She led a global team that supported lifecycle pharmaceutical research, development, and commercialization through creation and implementation of regulatory strategies and quality assurance oversight. Dr. Brumfield also played a key role in managing the broader company relationships with global regulators, trade associations, academics, and others on regulatory policy issues. Dr. Brumfield has been active in several external organizations, including P*h*RMA, CMR, and the APEC Life Sciences Innovation Forum and has worked extensively with the P*h*RMA Simultaneous Global Development program. During 20 years at Pfizer, Dr. Brumfield held a variety of leadership positions in which she led regulatory teams responsible for the U.S., Europe, and emerging markets. Dr. Brumfield also served as the company's head of drug safety surveillance and reporting, and managed global adverse event reporting requirements and the integration of Pharmacia's related safety operations. Dr. Brumfield earned a B.S. and M.S. in chemistry from Virginia Commonwealth University, a Ph.D. in organic chemistry from the University of Maryland, and served as a postdoctoral Fellow at the Rockefeller University.

Raymond Chua, M.B.B.S., M.Sc., DLSHTM, M.B.A., began his medical career after graduating from the Faculty of Medicine in the National University of Singapore (1997). He underwent numerous medical and surgical postings in the public-sector hospitals and Singapore Civil Defence Force until October 2000. Dr. Chua then took up his public health specialist training with the Ministry of Health, Singapore (October 2000 until April 2006), and became certified as a registered public health specialist and Fellow with the Academy of Medicine, Singapore (2007). He was also

awarded a scholarship by the Ministry of Health, Singapore, to earn an M.S. in public health with the London School of Hygiene and Tropical Medicine, University of London (2002–2003). Dr. Chua also holds an M.B.A. with a Merit Pass, from the University of Nottingham, as well as a Graduate Diploma in Change Management, Institute of Public Administration and Management, Singapore (2007). He left the public service to join Eisai Co Ltd in June 2007 as the managing director and regional medical director of Eisai Clinical Research Singapore Pte Ltd, to oversee, execute, and manage the growth, development, and operations of the global and regional clinical research activities within the Asia-Pacific, Oceania, and Middle East countries. In 2010, he joined Shire Pharmaceuticals as international medical director. In July 2011, Dr. Chua joined Health Science Authority as the Deputy Group Director of the Health Products Regulation Group and took over the helm as Group Director in May 2012. He oversees the pre- and postmarketing regulation of all health products, including drugs, medical devices, complementary health products, advanced therapy products, and tobacco in Singapore. He also holds other appointments as council member of the Singapore Medical Council. He is also an appointed member of the International Committee, Faculty of Pharmaceutical Physicians, London as well as a Fellow Physician of the Royal College of Physicians and Surgeons (Glasgow) and a Fellow of the Royal College of Public Health (London).

Carolyn Compton, M.D., Ph.D., is the President and Chief Executive Officer, C-Path. C-Path works with industry, academia, and nonprofit groups to engage in focused collaborative activities that involve prioritization of issues, sharing of data and expertise, consensus building, and publication. Specifically, C-Path drives consensus building to achieve product development tool qualification in order to increase the efficiency and robustness of regulatory approval. Dr. Compton has a broad background in translational research, in the discovery, preclinical, and clinical phases of medical product development. She is board certified in both anatomic and clinical pathology with a track record of leadership in medical innovation and practice. Immediately prior to her leadership of C-Path, she spent 7 years as the director of the Office of Biorepositories and Biospecimen Research in the Office of the Director of the National Cancer Institute. She came to the National Cancer Institute from McGill University, where she had been the Strathcona Professor and Chair of Pathology and the pathologist-in-chief of McGill University Health Center from 2000 to 2005. Prior to this, she had been a professor of pathology at Harvard Medical School, director of gastrointestinal pathology at the Massachusetts General Hospital, and the pathologist-in-chief of the Shriners' Hospital for Crippled Children, Boston Burns Unit for 15 years. She is a professor in the College

of Medicine-Tucson Department of Pathology, and clinical professor in the College of Pharmacy Department of Pharmacy Practice and Science at the University of Arizona. She holds a full professorship at Arizona State University in the School of Life Sciences. She is also an adjunct professor of pathology at the Johns Hopkins School of Medicine. Dr. Compton has held many national and international leadership positions in pathology and cancer-related professional organizations. She is a Fellow of the College of American Pathologists (CAP) and a Fellow of the Royal Society of Medicine. Currently, she is chair of the American Joint Committee on Cancer, serves on the Executive Committee of the Commission on Cancer of the American College of Surgeons, and serves as the pathology section editor for *Cancer*. She is a past chair of the Cancer Committee of CAP and was editor of the first edition of the CAP Cancer Protocols (Reporting on Cancer Specimens) used as standards for COC accreditation. Among her awards are the ISBER Award for Outstanding Achievement in Biobanking, the NIH Director's Award, the NIH Award of Merit, and the CAP Frank W. Hartman Award. She has published more than 500 original scientific papers, reports, review articles, and books.

Hans-Georg Eichler, M.D., M.Sc., is the Senior Medical Officer at EMA in London, United Kingdom, where he is responsible for coordinating activities between the Agency's scientific committees and giving advice on scientific and public health issues. From January until December 2011, Dr. Eichler was the Robert E. Wilhelm Fellow at the Massachusetts Institute of Technology's (MIT's) Center for International Studies, participating in a joint research project under the MIT's NEWDIGS initiative. He divided his time between the MIT and the EMA in London. Prior to joining EMA, Dr. Eichler was at the Medical University of Vienna in Austria for 15 years. He was Vice Rector for Research and International Relations since 2003, and Professor and Chair of the Department of Clinical Pharmacology since 1992. His other previous positions include President of the Vienna School of Clinical Research and Co-chair of the Committee on Reimbursement of Drugs of the Austrian Social Security Association. His industry experience includes time spent at Ciba-Geigy Research Labs, United Kingdom, and Outcomes Research at Merck & Co., in New Jersey. Dr. Eichler graduated with an M.D. from Vienna University Medical School and an M.S. in toxicology from the University of Surrey in Guildford, United Kingdom. He trained in internal medicine and clinical pharmacology at the Vienna University Hospital as well as at Stanford University.

James Fitzgerald, B.Sc. (Pharm), Ph.D., is Coordinator, Medicines and Technologies, Area of Health Systems based on Primary Health Care,

PAHO, WHO. Dr. Fitzgerald is a national of Ireland, and holds a Ph.D. in pharmaceutical sciences from the University of Dublin. He began his career in international public health when he joined PAHO in 1997 working in Haiti until 2002, Washington (2002–2005), and Brazil (2005–2008) as adviser in Medicines, Vaccines, and Health Technologies. In 2008, he assumed the coordination of the regional work program at PAHO in medicines and biologicals, and later health technologies. He is the author and co-author of numerous articles, has presented in numerous international congresses, and is a member of a number of professional societies and advisory groups associated with his profession and area of work.

Cindy Flannery, M.S., is a Senior Health Physicist in the Office of Federal and State Materials and Environmental Management Programs at the U.S. Nuclear Regulatory Commission (NRC). In this position, she serves as office lead for safety culture activities and is also a working group member responsible for revisions to the radiation protection regulations to increase alignment with international recommendations. She joined the NRC in 2004 and served as the Team Leader of the Medical Radiation Safety Team for 5 years. Ms. Flannery has 19 years of experience as a health physicist in the medical industry as well as in military and research organizations. Prior to NRC, she served as Branch Chief and Radiation Safety Officer for the Defense Threat Reduction Agency and as the Radiation Safety Officer/Health Physicist at FDA. Before her employment by the federal government, she worked as a health physics consultant for Krueger-Gilbert Health Physics, Inc., in Maryland and as a nuclear medicine technologist at the Mayo Clinic in Minnesota. Ms. Flannery graduated from Georgetown University with an M.S. in health physics and from the University of Wisconsin with a B.S. in nuclear medicine technology. She was certified by the American Board of Health Physics in 2001. She currently serves as Vice Chair of the American Board of Health Physics Part I Examination Panel, Associate Editor for the *Health Physics News* monthly newsletter, and topic editor for the "Ask the Experts" feature of the Health Physics Society website.

Timothy Franson, B.S.Pharm., M.D., is currently a Principal and Senior Vice President with FaegreBD Consulting in Washington, DC, and Indianapolis, where he leads the regulatory affairs practice; he also serves as President of the U.S. Pharmacopeial Convention (2010–2015). In 2008, Dr. Franson retired from the position of Vice President of Global Regulatory Affairs and Patient Safety after a 21-year career at Eli Lilly. During his time at Lilly, he led a number of industry initiatives, including Co-chair of the Committee for PDUFA (Prescription Drug User Fee Act)-III Renewal, and has testified at several congressional hearings, as well as serving

as Chair of PhRMA's Clinical Steering Committee and FDA Committee Staff Work Group. He also previously served as a member of the AAMC-PhRMA Clinical Trials Forum, member of the Regulatory Advisor Board for the Centre for Medicines Research International, board member of the National Patient Safety Foundation, trustee for Xavier University (Louisiana), member of Auburn University Pharmacy Dean's Advisory Board and civic board leadership roles (Little Red Door Cancer Agency, Indiana State Museum Foundation, Villages Child Welfare Services). Dr. Franson is board certified in internal medicine and infectious diseases. He co-authored a recent chapter in the book *PDUFA and the Expansion of FDA User Fees: Lessons from Negotiators*.

Hans V. Hogerzeil, M.D., Ph.D., FRCP, is Professor of Global Health, University of Groningen. Dr. Hogerzeil qualified as a medical doctor from Leiden University in the Netherlands and received a Ph.D. in public health in 1984. For 5 years he was a mission doctor in India and Ghana and in 1985 he joined the WHO Action Programme of Essential Drugs, first in the Regional Office for the Eastern Mediterranean in Alexandria, and later in WHO's headquarters in Geneva. As a staff member of WHO, he has advised more than 40 developing countries, especially in Africa and Asia, on the formulation of their national medicines policy, essential drugs list, and essential drugs program. As secretary of the WHO Expert Committee on the Selection and Use of Essential Medicines, he initiated the 2002 changes in procedures for updating the Model List of Essential Medicines, with stronger emphasis on evidence-based selections. He established the Web-based WHO Essential Medicines Library and was one of the editors of the WHO Model Formulary in 2006. Under his direction of the Department of Policy and Standards (2004–2008), the WHO PQP was established. From 2008 to 2011, he was Director for Essential Medicines and Pharmaceutical Policies, being responsible for all of WHO's global policies, nomenclature, norms and standards on medicines, the WHO PQP, as well as all technical country support to member states in the field of medicines (currently support programs in more than 100 countries, covering access to essential medicines, quality, and rational use). He was also Chair of the Interagency Pharmaceutical Coordination Group, which coordinates the pharmaceutical policies of WHO, all major UN agencies, the Global Fund, the World Bank, and UNITAID. Dr. Hogerzeil is the editor of several WHO books on essential medicines policies, the quality use of medicines, medicines in emergency situations, and essential medicines for reproductive health. He has published more than 50 scientific papers in peer-reviewed journals and teaches international courses all over the world. In 1996, he was invited to become a Fellow of the Royal College of Physicians in Edinburgh and in 1998, he received

an honorary Doctorate of Science from the Robert Gordon University in Aberdeen, Scotland. His recent interests include essential medicines for reproductive health, access to essential medicines as part of the fulfillment of the right to health, the development of a patent pool for combination therapies for the second-line treatment of HIV/AIDS, and regional regulatory harmonization in Africa.

Peter Honig, M.D., M.P.H., is Global Vice President, Regulatory Affairs, AstraZeneca. Dr. Honig received his baccalaureate, medical, and public health degrees from Columbia University. He has postgraduate training and is board certified in internal medicine and clinical pharmacology and has authored numerous peer-reviewed publications and book chapters. He has held senior leadership positions at FDA and Merck Research Laboratories. He is and has been the P*h*RMA representative to the ICH Steering Committee since 2002 and the current co-chair of the ICH GCG whose mission is to promote regulatory harmonization in non-ICH countries and regions. Dr. Honig has a faculty appointment at the Uniformed Services University of the Health Sciences, is a past president of the American Society for Clinical Pharmacology and Therapeutics, and is an associate editor of *Nature Clinical Pharmacology and Therapeutics.*

Judith M. Kramer, M.D., M.S., is board certified and has practiced both clinical pharmacy and general internal medicine. For the past 27 years she has been engaged in clinical research administration in industry and academia (10 years at Burroughs Wellcome Co., 1 year at Glaxo Wellcome, and 16 years at Duke University). Currently she is Professor of Medicine at Duke University Medical Center, where she is involved full time in research-related activities at Duke Clinical Research Institute. Dr. Kramer was the first Executive Director of the Clinical Trials Transformation Initiative (CTTI), a public–private partnership cofounded by Duke University and FDA with a goal of improving the quality and efficiency of clinical trials. She is now a Senior Scientific Advisor for CTTI. Previously at Duke she served as Chief Medical Officer of the Duke Clinical Research Institute (1997–2006), Principal Investigator for Duke's Center for Education and Research on Cardiovascular Therapeutics (CERTs), focused on cardiovascular disease (2000–2007), and regulatory consultant to the Duke Translational Medicine Institute (2006–2008). From 1999 to 2001, Dr. Kramer developed and was the founding director of the Master's Program in Clinical Research at Campbell University, in Research Triangle Park, North Carolina. She has served on numerous FDA advisory committees as a member of the Drug Safety and Risk Management Advisory Committee from 2006 to 2011 and remains a special government employee. Dr. Kramer received her B.S. and M.S. in pharmacy and M.D.

from the University of North Carolina (UNC) at Chapel Hill. She did her residency in primary care internal medicine at Massachusetts General Hospital, and a senior residency in internal medicine at UNC at Chapel Hill. She is a member of The Rho Chi Society, the academic honor society in pharmacy, and Alpha Omega Alpha Honor Medical Society. Her research interests have focused on developing safe and effective cardiovascular therapies, ensuring persistent use of life-saving medications, and studying how clinical trials are conducted.

Hubert Leufkens, Pharm.D., Ph.D., obtained his Pharm.D. and Ph.D. from Utrecht University. In 1998, he was appointed as full Professor at the Department of Pharmacoepidemiology and Pharmacotherapy of the same university. This is one of the leading groups in pharmacoepidemiology (output included more than 50 publications per year in peer-reviewed press, highly visible profile, resource for innovative methodologies). From 2003 to 2005, he was the Scientific Director of the Utrecht Institute for Pharmaceutical Sciences. During 2006–2007, he was Dean of Pharmaceutical Sciences of the Faculty of Science in Utrecht. Since 2007, he has been appointed as Chair of Dutch Medicines Evaluation Board. Moreover, Dr. Leufkens is one of the co-founders of the SIR Institute for Pharma Practice and Policy in Leiden and active at several (inter)national platforms on pharmacoepidemiology (e.g., since 2009, co-opted member for pharmacoepidemiology of the EMA CHMP, past-President of ISPE), pharmacovigilance (past-member EMA Pharmacovigilance Working Party), orphan drugs (past-Chair of the Dutch Steering Committee on Orphan Drugs), pharma policy (since 2008, Director of the Utrecht WHO Collaborating Centre for Pharmaceutical Policy Analysis and Pharmacoepidemiology), regulatory science, and scenario planning. He is co-author of more than 375 papers in peer-reviewed journals, book chapters, and research reports.

Lawrence E. Liberti, M.Sc., R.Ph., RAC, is Executive Director, CIRS (formerly the CMR International Institute for Regulatory Science). For the past 34 years, Mr. Liberti has worked in and with the pharmaceutical industry, in the fields of regulatory affairs and clinical R&D. He began his career at Wyeth Laboratories working in product development, as a regulatory writer in clinical R&D, and as manager of safety surveillance in medical affairs. He served as the Editorial Director for the North American operations of ADIS International after which he founded PIA Ltd., a company specializing in regulatory writing and consulting. He co-founded Astrolabe Analytica, where he helped develop, patent, and commercialize the Astrolabe Message Mapping System™. Both organizations became part of Thomson Reuters in 2005. Since 2009, he has served as the executive director of CIRS, an independent division of the IP and Science business of

Thomson Reuters. Mr. Liberti has been actively involved in promulgating best practices in the regulatory aspects of medicines development, especially in the emerging markets. He lectures on regulatory issues concerning expediting patient access to medicines, new paradigms of drug development, and ways to improve communications among regulators, HTAs, and sponsors. He serves on the boards of other not-for-profit organizations, including CONTACT Greater Philadelphia (a suicide prevention and elder outreach provider). Mr. Liberti is a pharmacist with a master's degree in pharmacognosy (both from the Philadelphia College of Pharmacy and Science). He is currently undertaking paralegal certification. He was awarded the status of Regulatory Affairs Certified by the Regulatory Affairs Professional Society. He is a Fellow of the American Medical Writers Association and a recipient of its Golden Apple award for excellence in teaching.

Richard C. Meibach, Ph.D., is currently the Global Head of Regulatory Affairs for Neuroscience and Ophthalmology at Novartis Pharmaceuticals. Prior to joining Novartis, Dr. Meibach had been Vice President of Clinical Science at Hoffmann-La Roche Inc., Pharmaceuticals. For 10 years he had global responsibility for central and peripheral nervous system diseases, and urology. He received his Ph.D. in biomedical sciences from the Graduate School of Biomedical Sciences, New Jersey Medical School (1976). Dr. Meibach did a 2-year postdoctoral fellowship in neurology at Albert Einstein College of Medicine, New York. In 1978, he became an assistant professor of pharmacology at Mount Sinai School of Medicine in New York. His research interests were in the anatomical and functional connections of the limbic and extrapyramidal systems in the brain. Major discoveries included the determination of the origin of the fornix system, localization and visualization of serotoninergic type 2 receptors in the brain, and the localization of phencylclidine (angel dust) effects on brain metabolism. Dr. Meibach left basic academic research in 1983 to pursue a clinical research career in the pharmaceutical industry. In addition to Novartis and Roche, he has worked for two other major pharmaceutical companies: Ayerst Laboratories, a division of American Home Products (now Wyeth), and Janssen Pharmaceuticals, a division of Johnson & Johnson. Dr. Meibach has had several successful NDA submissions in his 30 years of industry experience. Of 20 drugs that have achieved more than $2 billion in sales (*MedAd News*, May 2005), Dr. Meibach developed 2 of them (Risperdal for schizophrenia and Duragesic transdermal patch for chronic pain). Dr. Meibach has published 90 research papers and abstracts. His paper on the Phase III study with risperidone, published in 1994, was the number one cited paper of the decade in schizophrenia, with more than 400 citations. Dr. Meibach is called on to review articles for several leading brain research and psychiatric journals.

Alan Morrison, B.Sc., is Vice President, International Regulatory Affairs and Safety, Amgen Inc. Mr. Morrison leads Amgen's International Regulatory Affairs and Safety functions of approximately 300 staff both in the United Kingdom and across more than 30 local affiliate offices worldwide. As well as part of the Global Regulatory Affairs and Safety leadership, he is also a key member of Amgen's cross-functional International Management Committee, which sets and guides the international business overall strategic direction. Mr. Morrison joined Amgen in 2004, having previously held a number of regulatory affairs and safety positions at other companies, including Baxter Bioscience. He is currently Chair of the BioIndustry Association's Regulatory Affairs Group and serves on a number of trade association committees related to biotechnology/biopharmaceuticals.

Moheb M. Nasr, Ph.D., joined GlaxoSmithKline in September 2011 as Vice President for CMC Regulatory Strategy. Prior to joining GlaxoSmithKline, Dr. Nasr served as the Director of the Office of New Drug Quality Assessment (ONDQA), CDER, FDA. Dr. Nasr established and led ONDQA for 8 years. Dr. Nasr represented FDA at ICH and was instrumental in the development of the QBD concept and several quality regulatory guidelines. Dr. Nasr obtained his Ph.D. in chemistry at the University of Minnesota in Minneapolis. Dr. Nasr is an elected Fellow of the American Association of Pharmaceutical Scientists (AAPS), the recipient of the AAPS Regulatory Science Achievement Award, and the University of Wisconsin Pharmaceutical Analysis Excellence Award.

Margareth Ndomondo-Sigonda, M.Sc., M.B.A., is Pharmaceutical Coordinator, African Union-NEPAD Planning and Coordinating Agency. Ms. Ndomondo-Sigonda served as Director General of the Tanzania Food and Drugs Authority for 7 years and Registrar of the Tanzanian Pharmacy Board for 5 years before that. She has been involved in medicines regulation harmonization initiatives in Southern Africa Development Community and EAC. She has consulted for WHO on assessment of medicines regulatory systems in Sudan, Egypt, Kenya, Zambia, CARICOM member states, and the Dominican Republic. Ms. Ndomondo-Sigonda has also been a consultant for assessment of medicines regulatory systems in Zambia, Sudan, Egypt, and Kenya. She now works as a Pharmaceutical Coordinator for the African Union-NEPAD. Ms. Ndomondo-Sigonda is responsible for coordinating the pharmaceutical development programs, including the AMRH initiative. She holds a master's degree in pharmaceutical services from University of Bradford in the United Kingdom, an M.B.A. from Maastricht School of Management in the Netherlands, and a bachelor's degree in pharmacy from the University of Dar es Salaam.

Lembit Rägo, M.D., Ph.D., was a Professor of Clinical Pharmacology (Tartu University) and Founder and first Director General of the Estonian Drug Regulatory Authority, State Agency of Medicines. In December 1999, he joined WHO Headquarters, Geneva, as Coordinator of the Quality Assurance and Safety: Medicines team, which is located in the Department of Essential Medicines and Health Products dealing with medicines regulation and standards. Today the unit is composed of seven interlinked technical programs dealing with International Nonproprietary Names, Quality Assurance, Pharmacovigilance, Regulatory Support, Fighting Falsified Medicines, Prequalification of Medicines, and Blood Products and Related Biologicals. In 2001, he initiated the WHO PQP and has contributed to its development since then. Since 2002, he has organized the WHO biennial International Conference of Drug Regulatory Authorities, bringing together regulators from approximately 100 countries worldwide. His unit publishes the quarterly *WHO Drug Information Journal* and bimonthly *WHO Pharmaceutical Newsletter*. He is the WHO observer to the ICH Steering Committee, ICH Regulators Forum, and ICH GCG. He also serves as vice chair of the Uppsala Monitoring Centre Board, which hosts the WHO Global Database of Individual Case Safety Reports (adverse drug reaction reports). He has numerous international publications on regulatory affairs, medicines quality, and safety issues.

Amrit Ray, M.D., M.B.A., FCMI, serves as Chief Medical Officer for Johnson & Johnson's pharmaceutical division, Janssen Research & Development LLC. In this capacity, Dr. Ray has primary responsibilities for ensuring the safe, effective, and appropriate use of Johnson & Johnson's 1,000-plus pharmaceutical products globally, and for supporting an innovative research pipeline of new medical solutions in areas of unmet patient need. He is chair of the Global Safety Council, the organization's most senior governance body for product safety matters with oversight for identifying, evaluating, and managing medical risk for drugs, biologics, vaccines, and other categories of medicines, across all disease areas from first human exposure through clinical trials and market activity. Dr. Ray leads the Global Medical Organization, including departments for medical safety, development, and medical affairs for established products, and centers of special expertise, such as for pediatric drug development. He has served as Chief Safety Officer since 2009, and was subsequently appointed as Chief Medical Officer in 2012. Dr. Ray is an experienced physician with a U.S., EU, and Asia background in medical leadership across multiple areas of pharmaceutical research. Prior to joining Johnson & Johnson, he served in positions of increasing responsibility at Pfizer Inc. and Bristol-Myers Squibb. His experience includes directing the Phase III-IV development, launch, and commercialization of several new medi-

cines; overseeing departments for medical affairs, safety, and epidemiology; and co-leading Pfizer's acquisition/integration of Pharmacia. At both Pfizer and Bristol-Myers Squibb, Dr. Ray was awarded distinctions for driving the development of medicines in immunology, cardiovascular, and women's health. Dr. Ray earned a B.Sc. (with Honors) in immunology and an M.D. from Edinburgh University Medical School, Scotland. He obtained bench research experience with antibodies at Sir Joseph Lister Laboratories, and clinical medicine training at Edinburgh Royal Infirmary. He began his career serving as a hospital physician delivering patient care in the U.K. National Health Service, and initiated his clinical research experience in obesity at the Mayo Clinic. Dr. Ray also earned an M.B.A. from Dartmouth College and is a former McKinsey management consultant with business experience in valuation, corporate finance, and mergers and acquisitions. Dr. Ray has authored numerous scientific papers and been invited to advise WHO, U.S. Agency for International Development, U.K. Medicines and Healthcare Products Regulatory Agency, Canadian Agency for Drugs and Technologies in Health, China's State FDA, and a number of international expert forums on how medicines can create value and have a positive impact on patient lives.

Andreas Seiter, M.D., is a Senior Health Specialist, Pharmaceuticals, Health, Nutrition, and Population, World Bank. He joined the bank in January 2004 and is responsible for analytical and advisory work in all areas of pharmaceutical policy, such as regulation, governance, quality assurance, financing, purchasing, supply chain, and rational use. He has been working with bank teams, policy makers, and experts on the client side in several countries in Africa, Eastern Europe, the Middle East, Latin America, and South Asia. He is leading the work on medicines regulatory harmonization, with a focus on AMRH. In 2010, he published the book *A Practical Approach to Pharmaceutical Policy*. Dr. Seiter, a German national, is a physician by training and practiced medicine before joining a multinational pharmaceutical company in 1984. He held various positions in medical operations, product management, communications, and stakeholder relations in the industry prior to joining the World Bank.

Andy Stergachis, Ph.D., M.S., is Professor of Epidemiology and Global Health and Adjunct Professor of Pharmacy and Health Services, School of Public Health, University of Washington. His research focus is pharmacoepidemiology, global medicines safety, pharmaceutical outcomes research, and public health systems research. He has served as Chair of the Department of Pharmacy and Department of Pathobiology. He also served as Associate Dean of the School of Public Health. He was Vice President and Chief Pharmacist of drugstore.com. He was Founding Director of

the Pharmaceutical Outcomes Research and Policy Program, University of Washington. A registered pharmacist, he earned his pharmacy degree from Washington State University and his M.S. and Ph.D. from the University of Minnesota. His Postdoctoral Fellowship was from the Health Services Research Center, St. Louis Park Medical Center, Minneapolis. He was the 1990 Burroughs Wellcome-American College of Preventive Medicine Scholar in Pharmacoepidemiology. At the University of Washington he directs the Global Medicines Program, www.globalmedicines.org. He directs the University of Washington components of two projects funded by BMGF, including pharmacovigilance with the Malaria in Pregnancy Consortium. He also directs the University of Washington component of a U.S. Agency for International Development-funded cooperative agreement with Management Sciences for Health on Systems for Improved Access to Pharmaceuticals and Services in developing countries. He is author of more than 100 peer-reviewed publications and has received numerous awards, including the American Pharmaceutical Association Foundation 2002 Pinnacle Award for his career commitment to improving the quality of the medication use process and is a Fellow of the International Society for Pharmacoepidemiology. He served as a professor in residence with the Infectious Diseases Institute, Makerere University, Uganda. He is an elected member of the IOM and has served on several IOM committees, including the Committee on Assessment of the U.S. Drug Safety System and the Committee on Strengthening Regulatory Systems in Developing Countries. He serves as a special government employee for FDA, is a Senior Advisor to the Safety Surveillance Working Group of BMGF, and is a member of the Advisory Group to Global Alert and Response for WHO.

Douglas C. Throckmorton, M.D., is the Deputy Director for Regulatory Programs in the CDER at FDA. In this role, he shares responsibility for overseeing the regulation of research, development, manufacture, and marketing of prescription, over-the-counter, and generic drugs in the United States. From aspirin to cancer treatments, CDER works to ensure that the benefits of approved drug products outweigh their known risks. Dr. Throckmorton is board certified in internal medicine and nephrology, having received his training at the University of Nebraska Medical School, Case Western Reserve University, and Yale University. Prior to joining FDA, he practiced medicine at the Medical College of Georgia.

Toshiyoshi Tominaga, Ph.D., is Professor and Director of the Food and Drug Evaluation Center, Osaka City University Hospital. In his capacity, he supervises all the clinical studies conducted in the hospital. He has been in his current position since August 2012. He joined Japan's Min-

istry of Health, Labor, and Welfare (MHLW), after he acquired his Ph.D. from Faculty of Pharmaceutical Sciences, University of Tokyo (1987). As a carrier official, he worked in narcotics control, NDA review, and drug price setting in the country's health insurance system as well as in several international fronts of MHLW, including a 1-year stint at FDA, and a 3-year stay in Vienna as a diplomat. He also spent 2 years at Harvard School of Public Health. Between 2009 and 2012, as Director of Office of International Programs of PMDA, sister agency to MHLW, he represented PMDA in various bi- and multilateral activities, including ICH in its Steering Committee.

Mary Lou Valdez, M.S.M., is Associate Commissioner for International Programs and Director, Office of International Programs, FDA. Ms. Valdez joined FDA in 2009. The FDA Office of International Programs is the focal point for the agency's international efforts, in close alignment with FDA program centers and offices. Ms. Valdez leads, manages, and coordinates Office of International Programs's staff of about 100 around the world, catalyzing FDA global engagement in collaboration with international health and regulatory partners, ministries of health and agriculture, other U.S. government agencies, industry, academia, multilateral organizations, and other relevant stakeholders. In addition to FDA headquarters, Office of International Programs staff are strategically located in Belgium, Chile, China, Costa Rica, India, Italy, Jordan, Mexico, South Africa, and the United Kingdom. Ms. Valdez has a master of science in management from the University of Maryland University College, and a B.S. in biology from the University of Texas at El Paso. She is proficient in reading, writing, and speaking Spanish. Ms. Valdez came to FDA after serving for 18 years in the Department of Health and Human Services, where she was extensively involved in international health diplomacy. As the Deputy Director of the Office of Global Health Affairs from 2003 to 2008, Ms. Valdez led the development of U.S. policy positions on a wide range of complex public health issues, promulgated them within the governance processes of multilateral organizations, and conducted negotiations with other member governments that resulted in the successful acceptance of many of these positions within the larger international community. Ms. Valdez has extensive experience in hands-on negotiations and diplomacy. She is a member of U.S. government delegations to meetings of the governing bodies of multilateral organizations, including the WHO Executive Board and the World Health Assembly; the Executive Board of the UN Children's Fund, PAHO's Executive Committee, Directing Council, and Pan American Sanitary Conference; the Health Committee of the Organisation for Economic Co-operation and Development and UN special sessions and councils, including the UN Special Session for Children in 2002.

Mike Ward is Manager of the International Programs Division of the Therapeutic Products Directorate of Health Canada. He joined Health Canada in 1986 following 9 years of industrial experience in the QA/QC area. Since then he has held a variety of regulatory positions, including good manufacturing practice specialist, premarket quality reviewer and manager, and senior policy analyst. He served as the Canadian Observer to the ICH Steering Committee and a former regulatory co-chair of the GCG. He chairs the RHSC of the APEC Life Sciences Innovation Forum and is an alternate representative for NAFTA on the Pan American Regulatory Harmonization Steering Committee.

David Wood, Ph.D., is Coordinator, Quality, Safety and Standards, WHO. Dr. Wood holds a Ph.D. in virology from the University of Manchester, United Kingdom (1984). After initial work in diagnostic virology in Manchester, he transferred to the UK National Institute for Biological Standards and Control (NIBSC) (1988) with responsibility for batch release, standardization, and research on poliovirus vaccines, hepatitis A, and yellow fever vaccines. While at NIBSC he became closely involved with WHO activities, working on global standards for biological medicines and with the polio eradication initiative, which is now very close to the goal of eradicating wild-type polioviruses. In February 2001, he transferred to WHO, initially coordinating the research agenda for development of post-certification polio immunization policy and also standardization of virus vaccines. In June 2003, he assumed overall responsibility for all WHO biological standardization activities. He is secretary to the WHO Expert Committee on Biological Standardization. Since January 2006, as Coordinator of the Quality, Safety and Standards Team, he has been responsible for all aspects of regulatory support provided by WHO to countries and UN agencies for biological medicines, including the vaccines prequalification scheme. He is also responsible for a laboratory network of WHO Collaborating Centres for biological standardization.

Diane Zezza, Ph.D., is currently Vice President, Global Regulatory CMC, Novartis Pharmaceuticals Corporation. In this role, Dr. Zezza has global responsibilities for CMC regulatory strategies and activities for all development products and lifecycle management for commercial products for both small molecule and biologics portfolios. This includes global CMC support and regulatory dossier creation for products in all phases of clinical trials, product development through global product registrations, and product lifecycle support and optimization. Prior to joining Novartis, Dr. Zezza was Vice President, Global Regulatory Affairs, CMC, at Merck. Previously, she held several positions and led groups with responsibilities for global Regulatory CMC aspects for small molecules and biologics at

Schering Plough Corporation and at Eli Lilly and Company. Dr. Zezza has been involved in numerous industry and joint FDA-sponsored initiatives that have supported ICH global harmonization efforts for ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management, and ICH Q10 Pharmaceutical Quality Systems efforts. These included co-chairing or organizing joint industry-FDA conferences on Pharmaceutical Quality Assessment, QBD, Regulatory Agreements, and Specification Setting for Small Molecules and Biologics. She has been an active member for many years on several P*h*RMA Committees focused on technical, CMC, quality, and regulatory topics. She holds a B.S. in biology and a Ph.D. in genetics/molecular biology.