Global Health Risk Framework: Research and Development of Medical Products: Workshop Summary

DETAILS

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GLOBAL HEALTH RISK FRAMEWORK

Research and Development of Medical Products

WORKSHOP SUMMARY

Theresa Wizemann, Michelle A. Mancher, and Anne B. Claiborne,
Rapporteurs

Board on Health Sciences Policy

Institute of Medicine

The National Academies of
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[1] The National Academies of Sciences, Engineering, and Medicine's boards do not review or approve individual products. The responsibility for the content of the workshop summary rests with the workshop rapporteurs and the institution.

Reviewers

This workshop summary has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published workshop summary as sound as possible and to ensure that the workshop summary meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this workshop summary:

GARY NABEL, Sanofi
BERNARD PECOUL, Drugs for Neglected Diseases Initiative
BT SLINGSBY, Global Health Innovative Technology Fund
SAMBA SOW, Center for Vaccine Development–Mali
RAJEEV VENKAYYA, Takeda Pharmaceuticals

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 **ROBERT LAWRENCE,** Johns Hopkins University. He was responsible for making certain that an independent examination of this workshop summary was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this workshop summary rests entirely with the rapporteurs and the institution.

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Contents

Acronyms and Abbreviations

AAV	adeno-associated viruses
AVAREF	African Vaccine Regulatory Forum
BARDA	Biomedical Advanced Research and Development Authority
BMGF	The Bill & Melinda Gates Foundation
BPO	Biopreparedness Organization
CDC	Centers for Disease Control and Prevention (U.S.)
CHAI	Clinton Health Access Initiative
DNDi	Drugs for Neglected Diseases initiative
DoD	U.S. Department of Defense
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
FDA	U.S. Food and Drug Administration
GAAS	Ghana Academy of Arts and Sciences
GDP	good distribution practice
GHIT	Global Health Innovative Technology Fund
GHRF	Global Health Risk Framework

GSK	GlaxoSmithKline
HHS	U.S. Department of Health and Human Services
HIV	human immunodeficiency virus
ICMRA	International Coalition of Medicines Regulatory Authorities
IHR	International Health Regulations
IOM	Institute of Medicine
IP	intellectual property
IRB	institutional review board
MCM	medical countermeasure
MERS	Middle East respiratory syndrome
MMV	Medicines for Malaria Venture
MSF	Médecins Sans Frontières (Doctors Without Borders)
MTA	Material Transfer Agreement
NAM	National Academy of Medicine (U.S.)
NGO	nongovernmental organization
NIH	National Institutes of Health (U.S.)
PCR	polymerase chain reaction
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
PPE	personal protective equipment
PREP	Public Readiness and Emergency Preparedness
RCT	randomized controlled trial
SAMRC	South African Medical Research Council
SARS	severe acute respiratory syndrome
SNS	Strategic National Stockpile (U.S.)
TB	tuberculosis
UBMTA	Uniform Biological Materials Transfer Agreement
UN	United Nations
UNICEF	United Nations Children's Fund
WHO	World Health Organization

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Introduction[1]

Outbreaks of emerging infectious diseases in the 21st century, from the emergence of severe acute respiratory syndrome (SARS) in 2003 to the recent reemergence of Ebola virus disease, continue to demonstrate that the international community does not have adequate systems in place to reliably prepare for, detect, and rapidly respond to large-scale public health emergencies. Countless lives have been lost, and billions of dollars have been spent responding to and recovering from these outbreaks. What and where will the next outbreak, pandemic, or epidemic be; how far will it spread and how quickly; and how much human and economic loss will be sustained before it is brought under control? The time is now, said Victor Dzau, President of the U.S. National Academy of Medicine (NAM), in his opening remarks, before the next outbreak, to define and implement an effective global architecture for recognizing and mitigating the threat of epidemic infectious diseases.

[1] The planning committee's role was limited to planning the workshop. This workshop summary has been prepared by the 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 National Academies of Sciences, Engineering, and Medicine, and should not be construed as reflecting any group consensus.

THE GLOBAL HEALTH RISK FRAMEWORK INITIATIVE[2]

Since the 2014 Ebola outbreak many public- and private-sector leaders have seen a need for improved management of global public health emergencies. The effects of the Ebola epidemic go well beyond the three hardest-hit countries and beyond the health sector. Education, child protection, commerce, transportation, and human rights have all suffered. The consequences and lethality of Ebola have increased interest in coordinated global response to infectious threats, many of which could disrupt global health and commerce far more than the recent outbreak.

With encouragement and input from the World Bank; the World Health Organization (WHO); and the governments of the United Kingdom, United States, and West African countries; and support from various international and national organizations (Ford, Gates, Moore, Paul G. Allen Family, and Rockefeller Foundations; Dr. Ming Wai Lau; the U.S. Agency for International Development; and the Wellcome Trust), the NAM agreed to manage an international, independent, evidence-based, authoritative, multistakeholder expert Commission[3] on improving international management and response to outbreaks. As part of this effort, the Institute of Medicine (IOM) convened four workshops in the summer of 2015 to inform the Commission report. These workshops examined questions of ***governance for global health, pandemic financing, resilient health systems***, and ***research and development of medical products***. Each workshop gathered diverse perspectives on a range of policies, operations, and options for collaboration to improve the global health system. A published summary from each of the workshops has been independently written and reviewed, and their release will be coordinated.[4]

THE WORKSHOP ON RESEARCH AND DEVELOPMENT OF MEDICAL PRODUCTS

The Workshop on Research and Development of Medical Products is one of the four workstream activities of the Global Health Risk Framework Initiative. An independent planning committee was charged with developing the workshop to consider strategies, systems, and policies needed to foster communication and create partnerships to advance the development

[2] For more information see http://nam.edu/initiatives/global-health-risk-framework (accessed October 30, 2015).

[3] For more information on the Commission see http://nam.edu/initiatives/global-health-risk-framework (accessed October 20, 2015).

[4] Summaries from the other three workshops can be found at http://iom.nationalacademies.org/reports/2016/GHRF-Governance; http://iom.nationalacademies.org/reports/2016/GHRF-Finance; http://iom.nationalacademies.org/reports/2016/GHRF-Health-Systems.

of vaccines, diagnostics, therapeutics, and personal protective equipment (PPE) for emerging infectious diseases (see Box 1-1). The workshop was co-hosted by the IOM and The University of Hong Kong, in Hong Kong, on August 19-21, 2015. Invited experts and participants from academia, industry, U.S. and other government organizations, and civil society were welcomed by Victor Dzau and Gabriel Leung, Dean of the Li Ka Shing Faculty of Medicine at The University of Hong Kong. The workshop, co-chaired by Tachi Yamada, Managing Partner at Mountain Field, LLC, and

BOX 1-1
Statement of Task

An ad hoc committee will plan and conduct a 3-day public workshop that will provide a forum for relevant stakeholders to describe and provide input on the core needs and strategies to facilitate development of medical products to prevent, diagnose, treat, and protect from emerging threats such as global infectious diseases. The committee will define the specific workshop topics to be addressed, develop the agenda, select and invite speakers, and moderate workshop discussions.

The overarching objectives for the workshop include

- Gathering diverse perspectives of informed stakeholders to foster constructive discussion and facilitate the formation of collaborative solutions;
- Characterizing needs and gaps in current approaches to addressing global infectious disease outbreaks and other public health threats, and describing barriers to addressing those needs;
- Highlighting opportunities and potential approaches to improve the global system for addressing emerging threats;
- Documenting key successes and lessons learned from past global infectious disease outbreaks and other public health emergencies and how they may inform preparation and response to future outbreaks and emergencies; and
- Considering indicators and metrics that may be used to guide and assess the resilience of the global health infrastructure to future outbreaks and emergencies.

Speakers and workshop participants will be invited to describe and examine systems and approaches to discover and develop medical products to address emerging threats. The focus of the workshop will be on global systems and policy needs to foster communication, partnerships, and other strategies to advance medical product development. Workshop discussions will describe and examine the current state of approaches and infrastructure for research and development; barriers to the effective and efficient development of medical products; and potential strategies to address impediments to the research or development processes. The scope of medical products under consideration at the workshop will include

BOX 1-1 Continued

therapeutics, vaccines, diagnostics and other medical devices, and personal protective equipment. Key areas for consideration may include

- **Product development:** Describe current product development platforms; explore science and research needs, including needs for development of appropriate and effective regulatory science and evaluation tools.
- **Clinical development:** Discuss clinical trials approaches, including clinical trial methods and ethics considerations around enrollment and access to developing products in an emergency.
- **Optimization for development:** Explore incentives and infrastructure for product development, and conditions and needs for effective public–private partnerships and global/intergovernmental partnerships.
- **Regulatory review standards and systems:** Address regulatory considerations, including approaches to global regulatory harmonization and regulatory systems capacity.
- **Manufacturing:** Describe issues pertaining to supply chain management and product quality and integrity, and deployment of medical products.
- **Legal issues:** Highlight key legal considerations, including developer/manufacturer liability, distribution/sharing of biological samples, other patent/data exclusivity considerations, and sharing of preclinical and clinical trial data.
- **Indicators:** Explore indicators to facilitate and measure success and advances in the face of new and emerging threats.

Maria Freire, President and Executive Director of the Foundation for the National Institutes of Health (NIH), consisted of keynote lectures followed by panel discussions on the topics of models and incentives for engagement of product developers; discovery research; product development; regulatory review and approval; manufacturing and stockpiling; and supply chain and distribution. Participants then discussed top priorities and crosscutting themes from the discussions (see Appendix C for the full agenda). The following report summarizes the presentations from expert speakers and the discussions among workshop participants. Highlights and main points identified by individual participants during each major topic of discussion are summarized in a box at the start of each section.

WHO PERSPECTIVE ON THE GLOBAL HEALTH RISK FRAMEWORK

In her keynote address to open the workshop, WHO Director-General Margaret Chan said that the world missed its first wakeup call, the 2009-2010 H1N1 influenza pandemic, perhaps because it was milder than expected. Ebola was thus a second wakeup call, she said, and she shared her perspective on the four pillars of the Global Health Risk Framework. (Highlights of Dr. Chan's address are summarized in the box below.)

Highlights of WHO Director-General Chan's Keynote Address[a]

- Experience shows that, during a crisis, the traditional research and development model can be adapted, partnerships that are otherwise unlikely can be formed, and time frames can be compressed from years to months.
- The flexibility and collaboration that happens during a crisis needs to be moved upstream. Planning and agreement need to happen in advance of a crisis regarding rules of engagement, protocols and regulatory pathways, gaps in research and development, financing, liability, and other issues.
- A smarter approach is needed for funding and advancing research and development of medical products for emerging threats. Expecting the pharmaceutical industry to repeatedly redirect its research investments toward emerging crises with little to no return on investment is not a sustainable model.
- Coordination of efforts is essential. Affected countries are often inundated by partners and overwhelmed by multiple demands. When these partners cannot come together in a coordinated way, they are dissipating their collective energy. WHO has a range of mechanisms for fulfilling this coordination function.
- Governments must understand that if they do not pay attention to health and human security, their economic achievement could be eroded.

[a] This list is the rapporteurs' summary of the main points made by Dr. Chan during her presentation and does not reflect any consensus among workshop participants.

Governance

A challenge when discussing governance in global health is who is governing whom. Global governance starts with national and subnational

governance, Chan said. In countries with highly decentralized political systems, the federal government often cannot get information from the state or provincial government. Every government should have a mechanism to ensure it can meet its responsibilities as a global citizen under the International Health Regulations (IHR), Chan said. She cautioned, however, that there often are disincentives for countries to report outbreaks quickly. Upon timely reporting, many have suffered rapidly instituted trade bans and travel bans (e.g., canceled flights and closed borders).

Health Systems Strengthening

With regard to health systems strengthening, Chan noted that many countries and states do not have any health system to start with. Although 194 countries have signed on to the IHR, only 64 countries actually have the core capacities to be able to implement them. Clinics and hospitals are lacking, doctors and nurses are few, and isolation wards are nonexistent. In Liberia, for example, there is one doctor per 100,000 population. Countries without the capacity to prevent, detect, notify, and respond need to be transparent and inform WHO, so that global assets can be brought to bear, Chan said. For example, during the Ebola outbreak, France, the United Kingdom, and the United States, mobilized military assets to build treatment centers to isolate people who were exposed. This was important, she explained, because people in that environment often cannot stay home for the 21-day isolation period (e.g., they do not have enough food for more than a few days). Quality of care is also important, Chan continued, and while many African leaders are prepared to invest in overall infrastructure, health clinics and hospitals are not considered infrastructure. The global conversation needs to include financing instruments for health infrastructure, including human resources and health information systems. Resilient health systems include both the public health elements as well as the primary health care elements. She suggested that one of the mistakes of the past was the approach of developing parallel systems (i.e., a system for HIV, another for malaria, and a separate system maternal and child health), which fragmented the government instead of bringing the systems together to provide quality care. Chan pointed out that 8.6 million people travel by air every day, with many more crossing borders on foot and by train, ship, or other means. In this highly connected world, mechanisms and systems are needed for early warning and national, as well as regional and global, response when required. The weakest links are the countries that have no capability.

Financing

Chan explained that WHO does not have funds set aside to respond; indeed, in an outbreak situation, WHO cannot mobilize funds without writing a proposal, appealing to governments, and waiting for them to give funds. In many cases, the donor imposes conditions (e.g., if the money given is to be used for immunization, WHO has no authority to use it for another area as needs change). It took almost 4 months before any funds were flowing in for the Ebola response, she said. To address this, WHO member states are discussing how to establish a contingency fund to support early stage mobilization so that WHO can respond before an outbreak gets out of control. The World Bank is also considering a pandemic financing mechanism.

Financing is needed not just for health system strengthening and crisis response, but also for research and development of medical products for emerging threats, Chan said. Every time there is a crisis, industry is asked to stop their normal research and production and make substantial investments with little or no expectation of a return. A mechanism must be developed in advance of the next crisis that establishes how to bring together the experts and identifies the financial and other resources that can be brought to bear for the research and development of diagnostics, vaccines, and therapeutics. Chan also noted that liability remains an unresolved issue for companies developing products for use in a crisis.

During the discussion, John Rex, Senior Vice President in Global Medicines Development at AstraZeneca, emphasized the importance of bringing the treasury, finance, and economics communities into the conversation. Chan agreed and pointed out that, in many governments, the Minister of Health might have no access to the Minister of Finance or the heads of state. Leaders must come to understand that if they do not pay attention to health and human security, their economic achievement could be eroded, she said. She noted that some presidents are beginning to realize that a health crisis of this nature cannot be handled by the health ministry alone.

Research and Development

Pharmaceutical companies decisively shape the global research and development agenda and, as private-sector entities, they invest primarily where profitable markets exist. The system inherently tends to neglect innovation for diseases that disproportionately affect poor populations. Although the need may be great, Chan said, the demand fails because of an inability of these people to pay (i.e., there is a market failure). WHO's position is that no person should be denied access to lifesaving or health-promoting interventions for unfair reasons (including an inability to pay)

and, correspondingly, people should not suffer from diseases simply because market forces have failed to advance the development of vaccines or therapeutic options. Chan reminded the workshop participants of a 2006 independent commission report on intellectual property (IP) rights, innovation, and public health, which she said presented a wealth of evidence that the current system of pharmaceutical development is fundamentally flawed, leaving significant health needs unmet because of its reliance on patents and commercial incentives for priority setting and financing of medical research and development.[5] A global strategy and plan of action to address the IP concerns raised was approved by consensus at the World Health Assembly in 2008. Countries now need new proposals for financing and coordinating needs-driven research and development. Chan acknowledged that the need to stimulate research and development for diseases impacting the poor differs from the need to ensure tools are available for new and emerging infections; however, they share more similarities than differences and there are the lessons from the past to draw from.

Since the emergence of the recent Ebola outbreak, WHO has been exercising its convening role and organizing a series of stakeholder meetings. Chan pointed out that chief executive officers (CEOs) of the large pharmaceutical companies have been openly sharing information on their research protocols, clinical trial designs, and production capacity. She challenged participants to move this flexibility and collaboration upstream, and find ways to plan and agree in advance to rules of engagement, define acceptable protocols and regulatory pathways, identify gaps in research and development for emerging pathogens, and identify opportunities for governments and foundations to promote this research and development. In this regard she urged participants to make use of WHO as a coordinating body to bring stakeholders together. Experience shows that the traditional research and development model can be adapted, partnerships that are otherwise unlikely can be formed, and time frames can be compressed from years to months.

During the discussion, Yamada highlighted the importance of having a "team captain" to deal with the multitude of issues that need to be coordinated. Chan agreed and noted that the three countries affected by the recent Ebola outbreak were inundated by partners and overwhelmed by multiple demands. When these partners cannot come together in a coordinated way, they dissipate their collective energy. Per its constitution, WHO is the United Nations (UN) agency for health and is the coordinating and directing authority for all health matters. However, WHO must balance this role with a country's desire to have visibility and credibility in responding to

[5] See http://www.who.int/intellectualproperty/documents/thereport/ENPublicHealthReport.pdf?ua=1 (accessed October 30, 2015).

an issue. Chan remarked that there need to be incentives for governments to take (and to receive credit for taking) action, instead of being forced into action by WHO or other partners. In this regard, what is the duty and responsibility of a country after it signs on to the IHR? She referred participants to the external reviews of the global responses to Ebola and pandemic H1N1 influenza outbreak, which note that member states have largely failed to implement core IHR capacities[6] (Fineberg, 2015). When the WHO Director-General is informed in a timely manner of all outbreaks, an assessment can be made about the scale and complexity of the outbreak, what type of response is appropriate, and what role WHO will play. A lesson learned, she said, is that a lot can be accomplished on an informal basis as a result of discussions and relationship building.

[6] See *Report of the Ebola Interim Assessment Panel—July 2015*, http://www.who.int/csr/resources/publications/ebola/ebola-panel-report/en (accessed October 30, 2015), and *Alert, Response, and Capacity Building Under the International Health Regulations (IHR)*, http://www.who.int/ihr/review_committee/en (accessed October 30, 2015).

2

Models and Incentives for Engagement

Vaccines and medicines are best made by industry, and without industry being an active participant nothing will happen, Yamada said. If the Ebola outbreak is thought of as a health issue, then it fits the fundamental model of the pharmaceutical industry, which is to make medicines and vaccines at a profit and share the profit with shareholders. However, if the Ebola outbreak is thought of as a national or human security issue, then the responsibility of industry expands beyond the profit model to helping the world overcome a health crisis. In this context, he said, industry would be unlikely to self-finance an Ebola vaccine development program; there should be other participants at the table. Invited speakers and participants discussed partnership approaches, sustainable and effective business models, and existing and promising incentives that support the research and development of medical products for emerging infectious diseases (highlights and main points are summarized in the box below).

Highlights and Main Points Made by Individual Speakers and Participants[a]

- Many pharmaceutical companies are self-driven to participate in research and development of medical products for emerging infectious diseases, even in the absence of a clear economic return on investment. However, industry should not be asked to bear the entire financial burden of developing products for responding to public health crises. (Slingsby, Yamada)

- There are successful models to address market failures and spur development of products to address unmet needs. Among the models discussed were public–private partnerships, product development partnerships, prizes, and insurance models. Early research is primarily funded by foundations and government grants. Government also has a role as funder and partner in advancing development. (Marks, Outterson, Reddy, Slingsby, Venkayya, Yamada)
- Elements of success for public–private partnerships include establishing trust among stakeholders, relevance of the partnership to each stakeholder's mission, clear communication, transparent organizational structure and clearly defined roles for partners, and management of conflicts of interest. (Marks, Slingsby, Spigelman, Venkayya)
- The Global Health Innovative Technology (GHIT) Fund in Japan is a case example of government partnering with industry and foundations to develop products for emerging infectious diseases. (Slingsby, Spigelman)
- A product development partnership (a particular type of public–private partnership) takes a portfolio approach to developing tools to address a specific threat (rather than a single product-specific approach). A product development partnership acts as a facilitator, taking responsibility for the portfolio and ensuring accountability (i.e., that a product is developed). (Reddy, Venkayya)
- Incentives for pharmaceutical research and development are needed that delink return on investment from sales/reimbursement-derived revenues (e.g., prizes and priority review vouchers). (Marks, Outterson)
- There is no one best approach for motivating companies to invest in development. A blend of push and pull incentives will likely be needed. (Marks, Outterson, Venkayya)

[a] This list is the rapporteurs' summary of the main points made by individual speakers and participants and does not reflect any consensus among workshop participants.

PUBLIC–PRIVATE PARTNERSHIPS AS THE ESSENTIAL OPERATING MODEL

The Global Health Innovative Technology (GHIT) Fund

BT Slingsby, CEO and Executive Director of the Global Health Innovative Technology (GHIT) Fund, described the GHIT Fund as a case example of how incentives can be aligned to bring different funders and partners together in order to drive forward product development for global health.[1] Slingsby concurred with Chan that the lack of innovations and products to eliminate and control neglected diseases is a failure of market incentives. He cited a recent study showing that, of 336 new drugs approved in 2000-2011, only 1 percent (four) were for neglected diseases (Pedrique et al., 2013). This failure of market incentives is due, in large part, to the inability to demonstrate a return on investment. A solution to address this market failure, he said, is public–private partnerships.

The GHIT Fund is a unique Japanese partnership to drive forward global health product development using Japanese innovation, technology, and capabilities. Twenty-five percent of the funding comes from the private sector (Japan's leading pharmaceutical companies); 25 percent comes from the civil sector, The Bill & Melinda Gates Foundation (BMGF), and the Wellcome Trust (WT); and the Japanese government matches the private sector and philanthropic contributions, making up the remaining 50 percent. Slingsby pointed out that there is no link between the cash donated by the private sector and any funds awarded to those companies for product development.

Each GHIT Fund investment, regardless of the size of the investment, is awarded to an international partnership between a Japanese entity and a non-Japanese entity. In its first 2 years, the GHIT Fund invested roughly $43 million in product development, which has been leveraged through a co-funding strategy into a $73 million product portfolio. The current portfolio includes 39 partnerships, with targeted development platforms spanning discovery through clinical development for drugs, vaccines, and diagnostics targeted to malaria, tuberculosis (TB), and neglected tropical diseases.

The foundation of the GHIT Fund's success is its clean and transparent governance structure, Slingsby said. There is a council comprising the funders, an independent board of directors, a selection committee, an advisory panel, and a management team. This structure was specifically designed to overcome the conflicts of interest that could occur with having

[1] For further information about the GHIT Fund see https://www.ghitfund.org (accessed October 30, 2015).

pharmaceutical companies as both funders and beneficiaries of the fund. The council of funders meets yearly, and its decision making is limited to business oversight activities such as approving audited financial statements and changes in the articles of incorporation. This firewall between the council and the rest of the organization precludes the private sector from any of the organizational decision making, including investment decisions.

The success of this unique public–private partnership is further based on the alignment of self-driven incentives, Slingsby explained. The foundation partners, both BMGF and WT, are interested in harnessing the technological prowess of Japanese drug developers and deploying it for global health. Japanese pharmaceutical companies who want to be competitive in the developing world and on the global stage understand the importance of being engaged in access issues pertinent to emerging and frontier markets. Complementary capabilities of the international development sector that act as incentives for companies to partner with the GHIT Fund include localizing their portfolio mix, branding, and building partnerships across sectors. GHIT is also aligned with the global health policies of the government of Japan, including the Japan Revitalization Strategy, the Healthcare and Medical Strategy, and Japan's Strategy for Global Health Diplomacy. Slingsby noted that each strategy sits within a different ministry of the government (the Cabinet; the Ministry of Health, Welfare, and Labor; and the Ministry of Foreign Affairs). The Japan Revitalization Strategy is an economic policy, and the number one industry taxpayer in Japan is the pharmaceutical sector. From an economic perspective, the government needs these companies to continue to grow and to be competitive on the global stage. The Healthcare and Medical Strategy is focused on bringing innovation from Japan to the global market. Japan's Strategy for Global Health Diplomacy calls for working with the private sector and funding initiatives to make new and innovative health care technologies more accessible in the developing world (Abe, 2013). Each of the funders has self-driven incentives, Slingsby concluded, and if those self-driven incentives can be aligned, it is not difficult to bring everyone to the same table and discuss how to create an initiative.

The Medicines for Malaria Venture (MMV)

David Reddy, CEO of the Medicines for Malaria Venture (MMV), described MMV as an example of a product development partnership to develop a portfolio of interventions to counter neglected and emerging threats.[2] MMV is a not-for-profit organization focused on the discovery,

[2] For further information about MMV see http://www.mmv.org (accessed October 30, 2015).

development, and delivery of new, effective, and affordable antimalarial drugs. The MMV operating model is to take syndicated investments from governments and philanthropic organizations and work in partnership with those funders, industry, academia, the National Malaria Control Programs, and other agencies to build a virtual drug pipeline. MMV uses independent expert scientific review to guide clinical candidate selection and works within a strong contractual framework with its partners to increase access and good governance. MMV is an integrated global effort with about 250 partners, including 28 pharmaceutical companies, 13 biotechnology companies, and a large number of universities, research institutes, clinical sites, and government agencies. Reddy explained that partners are aligned around common target product profiles, which he said become the guiding principles for the partnerships. The target product profiles are published and become the subject of calls for proposals.

A strength of the product development partnership model is that, in working with its partners, MMV has been able to assemble a network of assays that cover the entire life cycle of the malaria parasite, which can be used to compare candidates in a portfolio of drugs. One key approach to de-risking and accelerating early development has been through the use of translational platforms, in particular, animal models and an induced human subclinical infection challenge model. Working with its partners, MMV has also established a network of clinical trial sites in malaria-endemic countries. Thus far, 12 novel candidates have been identified against 6 new biological targets in the parasite life cycle. This is the type of deep portfolio that is necessary when development of drug resistance is a concern, Reddy said.

Open innovation is also an aspect of the MMV model. With support from BMGF, the Wellcome Trust, and others, MMV has developed the "Malaria Box" containing 400 diverse compounds with antimalarial activity, distilled from 20,000 hits generated from screening of 4 million compounds suspected of antimalarial activity from partners' compound libraries. The compounds, along with structural and pharmacokinetic information, are available free of charge to researchers, under the condition that they publish their results and place any data in the public domain. To date, around 200 of these boxes have been dispatched across 30 countries. Active compounds have been identified against sleeping sickness, leishmaniasis, cryptosporidium, and schistosomiasis, and there have been 20 scientific publications. With support from its funders, MMV is now assembling a "Pathogen Box" containing a wider range of hits from phenotypic screens.

Creating Scientist Entrepreneurs in the Developing World Through Public–Private Partnerships

Krishna Ella, Chairman and Managing Director of Bharat Biotech, discussed how public–private partnerships can create new entrepreneurs, new vaccines, IP, and publications in the developing world. Ella established Bharat Biotech in India in 1997 to focus on region-specific neglected diseases.[3] The business model from the start has been public–private and private–private partnerships. Public–private partnerships in India, he said, can help the local partners to learn new vaccine development; learn good clinical practice and protocols for clinical development; understand global expectations; and change the mindset of Indian institutes regarding public health problems. Private–private partnering can foster an understanding of good manufacturing practice and standards that help a company grow to the next level.

In India, approximately 120,000 children die from diarrheal disease due to rotavirus each year (Bhan et al., 2014). These are primarily poor children with no access to care, and there is little political attention to this public health problem. Ella explained that through a multinational public–private partnership with BMGF, the National Institutes of Heath (NIH), the U.S. Centers for Disease Control and Prevention (CDC), Stanford University, the Research Council of Norway, and others, Bharat Biotech developed Rotavac, India's first new vaccine, and conducted India's first efficacy trial (Bhan et al., 2014; Bhandari et al., 2014). The vaccine was launched by the prime minister in 2015, although Ella noted there is an ongoing legal challenge to the launch. Ella described a host of other partnerships that have resulted in vaccines for typhoid, Japanese encephalitis, and other threats, as well as ongoing research on vaccines for chikungunya, paratyphoid and non-typhoidal Salmonella, Chandipura virus, malaria, and other infectious diseases relevant to India.

Ella highlighted the range of challenges the small Indian company has faced, including legal challenges; purchase commitments that were withdrawn; inconsistent government policies and changing priorities; difficulty securing government loans or venture capital; price competition from cheaper products from China; lack of attention to timelines, resulting in delays; and getting the government to recognize emerging threats.

Public–private partnerships can inspire entrepreneurship, Ella concluded, and these partnerships in India help to build confidence in the system and in product development; increase credibility; generate personal satisfaction; foster new development ideas and manufacturing platforms;

[3] For more information about Bharat Biotech see http://www.bharatbiotech.com (accessed October 30, 2015).

provide funding; and create a network that spreads science, develops new vaccines, and builds new IP.

Other Successful Initiatives and Collaborations

Lynn Marks, Senior Vice President for Projects, Clinical Platforms, and Sciences at GlaxoSmithKline (GSK), highlighted several early examples of successful public–private partnerships for product development, including the TB Alliance, the Drugs for Neglected Diseases initiative (DNDi), and MMV (discussed above). More recently, Marks said, industry has been working more directly with government, including the Biomedical Advanced Research and Development Authority (BARDA) within the U.S. Department of Health and Human Services (HHS), the Defense Threat Reduction Agency within the U.S. Department of Defense (DoD), and other government funders, on challenges such as antimicrobial resistance. Rajeev Venkayya, President of the Global Vaccine Business Unit at Takeda Pharmaceuticals, elaborated that the 2001 anthrax attacks in the United States spurred a series of actions in the government, ultimately culminating in the creation of BARDA. Together, BARDA, NIH, CDC, the U.S. Food and Drug Administration (FDA), and other partners make up the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), which is focused on developing public–private partnerships to deliver medical countermeasures (MCMs) to address such threats. As a result BARDA is now funding 150 products in its MCM pipeline, Venkayya said.

Pharmaceutical companies are also developing new ways of working together to address global health challenges and drive efficient development of new products. Marks described TransCelerate Biopharma, Inc., a nonprofit initiative that demonstrates a new mindset across industry of working together to improve quality, decrease cost, and reduce redundancy in clinical trial efforts.[4] Marks also described a new "biopreparedness organization" (BPO) that will be housed in GSK's new vaccine research and development center in Maryland.[5] The BPO will have end-to-end capabilities to develop new vaccines (including biohazard laboratory facilities and pilot plants) that can be used in collaboration with other companies, funding partners, and stakeholders to focus on the next generation of vaccines for public health threats. Another example is the Tres Cantos Open Lab Foundation in Spain, an independent organization supported by GSK, where visiting researchers can have open access to GSK expertise, processes,

[4] For more information see http://www.transceleratebiopharmainc.com (accessed October 30, 2015).

[5] For more information see http://www.gsk.com/en-gb/media/press-releases/2015/gsk-to-establish-global-vaccines-randd-centre-in-the-us (accessed November 18, 2015).

and facilities including, for example, a high-throughput screening facility and Biosafety Level 3 laboratories.[6]

Based on his experience as Influenza Pandemic Task Force Leader for Roche from 2005 and 2010, Reddy said that important principles in Roche's pandemic response were establishing networks and partnerships to reduce or share risk; aligning around common principles; advanced planning; and clear, transparent, ongoing communication. Key elements of Roche's planning activities, he continued, were risk analysis and risk mitigation, forming partnerships to mitigate the risks, acknowledging the World Health Organization (WHO) as the global leader in the event of a pandemic, establishing an advisory board of ethicists, clearly defining and documenting the company's role during an outbreak, and collaborating with independent research laboratories around the world. To support government pandemic stockpiling of oseltamivir (Tamiflu), Roche increased its seasonal influenza manufacturing capacity 15-fold (from 27 million courses of treatment per year to 400 million per year) through partnerships with other manufacturers around the world. As part of its risk-sharing approach, Roche made payments to partner companies to maintain idle capacity during periods of underutilization. Reddy also stressed the need for a portfolio of products that can take into account the evolutionary biology of emerging infectious agents and drug resistance.

Venkayya mentioned the investments made by BMGF in more than 16 mission-focused product development partnerships. While a company generally leverages its own internal technologies, platforms, and capabilities in advancing a particular product candidate (occasionally licensing in additional capabilities), a product development partnership takes a portfolio approach to developing a tool to address a specific threat, readjusting the portfolio depending on the performance of the program (i.e., stopping programs that are not advancing and reinvesting in more promising options).

CREATING A BLEND OF INCENTIVES FOR ENGAGEMENT OF PARTNERS

Kevin Outterson, professor at Boston University, referred participants to a Chatham House report on a new global business model for antibiotics as an example of incentives for product development in an area of great

[6] For more information see http://www.openlabfoundation.org/about.html (accessed October 30, 2015).

need: the global spread of antibiotic-resistant organisms.[7,8] The new model is based on delinking the return on investment for research and development from sales or reimbursement revenues. The model considers funding and incentives for developers while prioritizing both global access and promoting appropriate use of antibiotics (i.e., preventing overmarketing or overuse that could lead to further resistance). Marks concurred with Outterson on the need to delink company investment in product development from the need to drive volume sales and earn revenue to recoup that investment. This is especially true for antibiotics, for which sales of a new product may be heavily restricted to conserve efficacy.

Panelists discussed the need for a combination of both push and pull incentives to motivate product developers.[9] Venkayya said that pull incentives are usually not sufficient when the market is very uncertain, such as in biodefense or when the threat of a pandemic is unclear (e.g., Middle East respiratory syndrome [MERS]). Marks and Venkayya mentioned priority review vouchers as one example of a pull incentive that could be effective, acknowledging that there are drawbacks (e.g., diverting regulatory agency attention away from more urgent matters to meet the priority review timeline).

Venkayya cautioned that the concept of awarding financial prizes to pharmaceutical companies is generally not publicly or politically palatable. However, Outterson urged participants not to broadly dismiss prizes. A partial delinked incentive approach is more like enhanced reimbursement, he said. For example, a novel drug for very narrow spectrum use might need to be reserved for use in only the most egregious circumstances. A company could be rewarded for implementing a stewardship plan with milestone payments over a 5- or 10-year period (in other words, rewarding the company for rationing the sale of the drug). Developing new antibiotics needs to be seen as something akin to insurance, Outterson said, ensuring the availability of therapies in case the organisms evolve. People are used to the concept of paying for insurance for events that might not occur (and that they generally hope do not occur). Yamada suggested that a portion of insurance premiums could be applied to creating incentives for research

[7] The Chatham House report, released on October 9, 2015, is available at https://www.chathamhouse.org/publication/towards-new-global-business-model-antibiotics-delinking-revenues-sales (accessed October 30, 2015).

[8] For further background on addressing the global threat of antibiotic resistance see the Special Supplement to volume 43, issue 2, of the *Journal of Law, Medicine & Ethics*, Summer 2015, pp. 1-78. http://www.aslme.org/media/downloadable/files/links/f/i/file_1_105.pdf (accessed October 30, 2015).

[9] A push incentive provides funding up front to spur research and development by removing barriers to entry (e.g., grants, tax credits), while a pull incentive provides rewards based on output or impact (e.g., prizes).

and development, allocating money from premiums for use to prevent a pandemic, as opposed to paying out if the pandemic occurs. He noted that the reinsurance company, Swiss Re, has built a very small risk of pandemic influenza into their premium.

Rex and Outterson emphasized that an incentive or reward would need to be substantial to motivate a company to act against its commercial interest. Paul Stoffels, Chief Scientific Officer at Johnson & Johnson, said that lump-sum prizes are not generally attractive to a large pharmaceutical company as they do not contribute to company growth. He suggested that regulatory mechanisms such as pediatric exclusivity have been very successful in bringing new pediatric drugs to market. Stoffels and Yamada suggested that a reward in the form of a transferable 6-month market exclusivity—a hybrid between the pediatric extension and a priority review voucher,[10] Yamada suggested—might be attractive to a company. Rex agreed that a one-time prize is not an adequate incentive for industry, given the realities of the drug development process; instead, he noted, spreading out a reward for innovation over 5 to 10 years (e.g., earning rewards for specific behaviors/milestones) is a better approach. Margaret Hamburg, Foreign Secretary of the National Academy of Medicine, agreed that prizes are not a sustainable economic driver of ongoing innovation; however, she said, prizes could have value in initiating a cycle of innovation and bringing new people and expertise to bear on a problem. Rudi Pauwels, CEO of Biocartis NV, added that the typical diagnostic company does not have the huge resources of a large pharmaceutical company. He agreed that an award or prize is a good way to initiate the nucleation of the innovation, but other types of incentives are needed to ensure that new diagnostics are ultimately delivered.

Slingsby highlighted the need for more push mechanisms that would provide more immediate incentive for companies (e.g., a tax credit), rather than waiting for prizes or rewards at the end. Venkayya said that some push approaches that have worked for product development partnerships include co-investment in research and development, and investment in capital expenditures or capital infrastructure. Outterson noted that there is ongoing discussion about a modified version of the Orphan Drug Act for antibiotics, including a refundable or fully transferable tax credit for qualified research and development expenditures. Much of the antibiotic development work is being done in small- and medium-sized enterprises

[10] While not presented at the workshop, for further background and criticisms of FDA's priority review voucher program, see Regulatory Explainer: Everything You Need to Know About FDA's Priority Review Vouchers at http://raps.org/Regulatory-Focus/News/2015/03/13/21722/Regulatory-Explainer-Everything-You-Need-to-Know-About-FDA%E2%80%99s-Priority-Review-Vouchers (accessed December 2, 2015).

with no taxable income for them to offset, so a fully refundable tax credit represents immediate cash for the company. Ella suggested that a small, privately held company has more flexibility in models for returning value to its investors (and therefore perhaps more flexibility to take risks and innovate for prizes and rewards), whereas a publicly listed company is beholden to the mandate of returning value to shareholders.

ELEMENTS OF SUCCESS

Venkayya and Mel Spigelman, President and CEO of the TB Alliance, both observed that much has been learned over the past 10 to 15 years of forming public–private partnerships to help address the market failures described by Chan. Controlling emerging pathogens cannot be done by any one sector alone, Spigelman said. Formulating a good partnership involves learning how to share sovereignty and decision making, and developing a level of trust between the partners. A successful partnership also relies on leadership on the part of the different partners. Spigelman noted that a partnership must address potential conflicts of interest, pointing to the GHIT Fund, discussed by Slingsby, as a model. He emphasized the importance of coming together to form partnerships and work out these issues far in advance of a crisis.

Venkayya said that product development partnerships can provide accountability, taking responsibility for the portfolio and ensuring that a countermeasure is delivered. Flexibility in the working relationships among participating organizations is also needed, and incentive structures should be developed with input from industry. A supportive ecosystem is also needed (e.g., an environment of adaptive regulation and innovative regulatory science to support these products as they go through development).

Joan Awunyo-Akaba, Executive Director of Future Generations International, Ghana, commented that local civil society organizations and local nongovernmental organizations (NGOs) could be valuable partners in this enterprise and can advocate to promote the work being done by the partnership. They also understand the social determinants of health that are often an overlooked part of the discussion. Dzau highlighted the importance of universities as partners, as they are intellectual drivers of new drugs or new technology and can also play many different roles (e.g., conducting trials). Spigelman agreed, and said that there are academically oriented institutions that now have the type of expertise that once was resident only in the pharmaceutical industry.

CHALLENGES

Venkayya stressed that, before programs can advance, the threat needs to be identified and prioritized. A comprehensive global threat assessment or prioritization has not been done. The U.S. government has developed a list of agents that it is most concerned about from a biodefense perspective, and initial investments were directed toward six categories of potential threat agents.[11] BMGF also clearly defined its organizational priorities early on. The U.S. Department of Homeland Security issues material threat determinations for any new threat that requires investment in countermeasures. Outterson added that the Chatham House report calls for a global threat assessment to identify and prioritize bacterial pathogens and guide the targeting of incentives. He noted that CDC conducted a U.S.-based threat assessment in 2013, and the European Centre for Disease Control and Prevention is updating its assessment for Europe. However, such prioritization has not occurred in the global health space, Venkayya said, and there is an urgent need to define what the threats are and assign accountability for developing the tools.

Peter Dull, Deputy Director for Vaccine Development at BMGF, emphasized the importance of having these prioritization discussions now, before the next outbreak, and to move relevant products for those pathogens forward in development to a point where they could be launched into clinical trials should the need arise.

Yamada, Spigelman, and Graeme Bilbe, Research and Development Director at DNDi, discussed that sustainability is a major issue. Spigelman noted a misalignment between the type of funding received and the type of work that these partnerships do. For example, a product development partnership might launch a phase III clinical trial (a multiyear commitment) without having secured guarantees of continued funding from year to year. Participants discussed possible approaches to funding the needed research and partnerships. For example, participants noted that organizations such as BMGF, WT, NIH, and select others tend to fund where others will not, including funding a significant amount of early stage, higher risk research. Yamada added that one of the unique aspects of the GHIT Fund is that BMGF is able to leverage its money, doubling it with the match from the Japanese government.

Yamada and Pauwels both emphasized the need to shift the nature of the discussion from considering these crises to be exclusively health crises to considering them to be issues of human and national security as a means of ensuring that they are prioritized and receive sustainable funding.

[11] For more information see https://www.niaid.nih.gov/topics/biodefenserelated/biodefense/pages/cata.aspx (accessed November 18, 2015).

Yamada noted that DoD recognizes emerging infections as a U.S. national security issue. Perhaps even small, resource-poor nations would invest in infrastructure and research and development if they thought their nation was at great risk, he said.

3

Discovery Research

Drawing on the Global Health 2035 report, Adel Mahmoud, Professor in Molecular Biology and Public Policy at Princeton University, said that achieving convergence in global health involves rapid scale-up of existing and new life-saving interventions, and building the health care structure to deliver them.[1] However, many of the drugs, vaccines, diagnostics, and other devices needed to address global health challenges do not yet exist. Participants discussed current scientific tools, technologies, and capacities that enable the rapid discovery, development, and evaluation of medical products and highlighted gaps and needs for advancing research. Highlights and main points are summarized in the box below.

Highlights and Main Points Made by Individual Speakers and Participants[a]

- Attention could address the translational gap between the discovery research, which takes place in academic, government, and industry laboratories, and the product development that for the most part takes place in the pharmaceutical industry. It will be beneficial to work across those silos to shape research and development plans from the beginning with the end in mind, and to guide early researchers on conducting

[1] For more information about the Global Health 2035 initiative see http://globalhealth2035.org (accessed October 30, 2015).

studies suitable for further product development. (Hamburg, Mahmoud, Pfleiderer)

- Platforms offer the potential to move quickly from identification of a pathogen to development and manufacturing of a product. It might be possible to preapprove platforms for more rapid regulatory approval of final products; however, it was acknowledged that platforms will not work in all cases. Platform technology would benefit greatly from information sharing and regulatory convergence among different actors. (Hamburg, Mundel, Yamada)
  - Promising vaccine platforms discussed included the seasonal influenza vaccine platform, nucleic acid–based vaccines (RNA-based vaccines, DNA plasmid vaccines, live viral-vectored vaccines), and vectored delivery of immunogenic antigen (e.g., adeno-associated virus [AAV] vectored). (Mundel, Yamada)
  - Examples of therapeutic platforms include high-throughput screening of compound libraries/repurposing existing compounds, convalescent plasma/fractionated plasma, high-yield production of neutralizing antibodies, and vectored-delivery antibody-coding sequence for sustained production of antibody in patients (e.g., AAV-encoding antibody). (Bilbe, Mundel)
- Research could also advance development of new devices, including diagnostics and personal protective equipment (PPE).
  - An understanding of the context of use is important in the development of diagnostics for use in emergency situations. Considerations include rapidity of results, validity of the test, point-of-care testing, training (sample collection use of test, maintenance of equipment), infrastructure (cold chain storage, electric power, transport of samples), and costs (device, equipment, disposal of consumables, transport of product, equipment, and technicians). (Goldstein, Mundel, Pauwels)
  - Syndromic diagnostic panels could aid in surveillance of emerging or evolving infections. (Mundel, Pauwels, Yamada)
  - PPE research includes both testing for efficacy of protection as well as performance of the product under the intended conditions of use, which may change depending on the pathogen, the user, and the location of use (e.g., heat and humidity). (Colton, Hall)

- Intellectual property (IP) is a research and development (R&D) tool to enable and incentivize health product innovation; however, there are numerous legal, regulatory, administrative, competitive, commercial, interpersonal, and other issues affecting the ability to share data and materials. Participants highlighted the potential for international coordination and formalization of agreements to facilitate data sharing and collaboration. A range of models for managing IP/data sharing were discussed, from full transparency (e.g., open access) to a host of licensing strategies. When discussing the costs of sharing IP, it is important to recognize that the alternative—to keep reproducing the same work—would cost even more (in both resources and time). (Adler, Marks, Mulder, So)

[a] This list is the rapporteurs' summary of the main points made by individual speakers and participants and does not reflect any consensus among workshop participants.

ADVANCING THE SCIENCE OF DISCOVERY

Platform Approaches to Vaccine and Therapeutic Research

Trevor Mundel, President of the Global Health Division of The Bill & Melinda Gates Foundation (BMGF), reviewed some of the platforms or approaches that could be used to address unanticipated pathogens for which there are no tools available, and for which traditional methods are unlikely to be successful. New vaccine platforms in development include nucleic acid–based vaccines (RNA-based vaccines, DNA plasmid vaccines) and live viral-vectored vaccines (the three main Ebola vaccine candidates are live viral-vectored vaccines). AAV vector technology is being studied not only as a vaccine approach to deliver immunogenic antigen, but also as a way to confer passive immunity through vector production of antibody. The potential for these platforms is the ability to switch in a nucleic acid "cassette" for the desired expression product. In a very short period of time, one could theoretically go from having the genetic sequence of a pathogen, to inserting a gene construct into an approved platform, to having a vaccine candidate(s) that can be taken into clinical trials. A key regulatory question, Mundel noted, is what set of evidence will be required for approval of a platform, so that preclinical studies do not need to be replicated?

Another platform is a convalescent plasma/fractionated plasma approach to therapy. This is based on the principle that patients who mount an immune response will produce effective neutralizing antibodies

against novel epitopes, and that plasma from those patients could potentially confer passive immunity to other patients. Mundel said that, during the Ebola outbreak, BMGF had bloodmobiles equipped with plasmapheresis and blood-cleansing capacities airlifted into West Africa to facilitate a convalescent plasma study (results are pending). New techniques are also being used to compare antibody responses to a given pathogen by survivors versus those who succumbed to fatal disease (including HIV, malaria, and Ebola). Mundel noted that there were challenges moving samples between countries and exporting samples out of West Africa for fractionation, and a meeting of the health ministers from the three countries was ultimately convened to secure permission for sample movement. New high-yield production systems have made the prospect of using neutralizing antibodies as therapeutics plausible. As noted above, there is also the potential to deploy vectored antibodies (e.g., AAV vectored) for sustained production of antibody in patients in an emergency circumstance. A key challenge for this platform is ensuring adequate process control to guarantee product quality, Mundel said.

As mentioned by Bilbe, one platform for rapid drug discovery is repurposing existing compounds. Companies have extensive compound libraries of well-characterized compounds, some of which have been through preclinical or clinical testing. Starting with a compound from one of these libraries can substantially reduce development timelines, often from years to months. One of the challenges from a regulatory point of view, Mundel noted, is scrutinizing and prioritizing the vast sea of compounds proposed for clinical testing, given the very limited capacity to conduct clinical trials.

Yamada raised the question of whether an AAV antibody platform could be preapproved, in similar fashion to the platform used for production of seasonal influenza vaccine. Could the gene coding for a protective antibody isolated from a survivor of an outbreak be inserted into the vector, and approved for passive immunization without the need for additional clinical trials? Hamburg responded that it might be possible to issue an emergency use authorization (EUA), depending on the foundation of data, the experience with the platform, and the understanding of the nature of the particular outbreak. The seasonal influenza vaccine experience does provide a model for the concept of having a flexible platform in which a new product can be rapidly approved based on an existing set of safety and efficacy data. However, it becomes more complicated, and there is less confidence, when the platform would be dealing with potential unknown factors including the nature of the disease and the level of risk people are willing to take in the context of a true public health emergency.

Michael Pfleiderer, Head of the Viral Vaccines Section at the Paul-Ehrlich-Institut, highlighted the need for scientific convergence on product development issues of global concerns. For example, what is the right pan-

demic influenza construct (e.g., booster versus primary vaccination, number of doses) and manufacturing approach (e.g., if the amount of antigen per dose needed can be reduced, such as through the use of adjuvant, more vaccine can be made and more people protected).

Mahmoud, Pfleiderer, and others highlighted the gap (often called "the valley of death") between the discovery research that takes place in academic, government, and industry laboratories and the product development that necessarily takes place in pharmaceutical companies. Hamburg noted that many opportunities are being missed because studies being done in academic or other early research settings are not being guided toward full product development. It is essential to work across the silos to shape the research and development plans from the beginning with the end in mind, so that the right studies are done as effectively and efficiently as possible, and products reach the people that need them, at the scale and timing needed. As an example of this gap, Mahmoud noted that Ebola virus is among the top 20 viruses considered by the U.S. government to be a potential biothreat, yet several Ebola vaccine candidates had been tested in animals 10 to 15 years ago and then sat in freezers with no further development until recently. To help span the development gap, Mahmoud and others have proposed a Global Vaccine Development Fund that would fund activities spanning from the discovery of a candidate to the end of phase II clinical testing (Plotkin et al., 2015). Funding would come from governments, foundations, and industry donors and would be awarded through a competitive process. Yamada added that, because much of the basic scientific advancement comes from academia, one of the challenges is how funding is distributed in academia.

Rex reminded participants of a prior Institute of Medicine (IOM) workshop that discussed selecting one or two pathogens from the threat list each year and running the exercise of bringing a product from discovery research through to a designated stopping point (phase I or phase II of clinical development) or to completion (acknowledging that further clinical trials might not be possible in the absence of cases). Many issues could be solved in advance of a crisis (e.g., methods, IP), and the result of the exercise would then be a product ready to be developed further, along with the developed expertise to do it, if the threat does emerge (IOM, 2015a).

Devices: Diagnostics and Personal Protective Equipment

Charles Goldstein, Chief Scientific Officer for Greater Asia at Becton Dickinson, emphasized the need to develop products that are appropriate for the intended market. Devices and diagnostics need to fit with the way health care is practiced in the targeted countries, and the availability of infrastructure and training for health workers.

Pauwels observed that many of the diagnostic solutions used in the Ebola response (e.g., the mobile laboratories) were slow to deploy, the logistics were costly and complex, and sustainability remains uncertain. Costs include not only the cost of the devices themselves, but, for example, the costs of disposal of consumables, transport and maintenance of equipment, and transport or training of people to do the work. Pauwels added that the physical transfer of samples must also be addressed. The practical field realities for deploying Ebola diagnostics included blood samples that were a "pink slurry" upon arrival, samples without names or addresses, or all samples labeled with the same name.

Pauwels emphasized the importance of bringing diagnostic testing capability closer in time and space to where the patients are (i.e., at the point of care). A typical situation in Sierra Leone, he said, was for exposed or symptomatic individuals to stay in holding or treatment centers for 2 to 3 days while awaiting results of the molecular diagnostic test. This meant that the 70 percent of people who ultimately tested negative for Ebola virus were sharing the same space with the 30 percent who were positive for Ebola. Building more laboratories across these regions is not necessarily the solution, Pauwels said. Data show that the accuracy and reproducibility of laboratory testing is highly variable, and the number of diagnostic errors is substantial. This is likely due to the complexity of the technologies, the instability of reagents, and other factors.

Pauwels described Idylla, a real-time polymerase chain reaction (PCR)-based molecular diagnostics system developed by Biocartis that is fully automated from clinical sample to result. It is a compact, cartridge-based, closed system (no dedicated PCR laboratory infrastructure is needed, and contamination is reduced); all reagents are on board (no cold chain needed); results are rapid; and there is less than 2 minutes of hands-on time by the operator. The system is fully integrated, scalable, and can test for up to 30 biomarkers in one sample simultaneously. Local people can be trained as Idylla users, and minimal infrastructure is needed (an autonomous, mobile diagnostic laboratory powered by batteries and an onboard generator are in development).

Pauwels added that Idylla can be used to create a real-time, sustainable diagnostic grid for surveillance. Idylla sentinels transmit test results to a central control room that monitors the data for trends. Pauwels said that feedback from local clinicians indicates that they need syndromic diagnostic panels (to test for, e.g., respiratory infections and central nervous system infections). There is also a need to assess viral loads and monitor evolving pathogenicity and emergence of drug resistance. Yamada suggested that a syndromic diagnostic panel including the top 10 priority diseases, for example, would be very informative and would help to identify emerging diseases. Mundel also noted the potential of diagnostic platforms as tools

for surveillance and added that machine learning tools are being deployed for automated monitoring of media reports in local languages to detect signals of emerging infections.

Craig Colton, Division Scientist at 3M Personal Safety Division, said that PPE (e.g., respirator, suits, gloves, and goggles) plays an important role in delivering health care during infectious disease outbreaks. PPE is regulated relative to both approval for marketing and conditions for use, as proper use is essential for protection of the worker. Colton pointed out that the way each infectious agent is transmitted (e.g., inhalation, touch, both, or other methods) affects how PPE will be used and drives the research and testing that need to be done for each product. Parameters include, for example, conditions of use, length of wearing time, or use in conjunction with other PPE. The product must not only be effective, but must be robust enough for the particular environment in which it will be used. For example, the Ebola outbreak posed new challenges for the development and use of respirators in that no skin was to be exposed, Colton said. This affects donning and doffing, including how double-gloving might impact the ability to manage the respirator strap. This drove research on new strap materials and new ways to grab hold of the strap. Another challenge was finding materials that would be better suited to the heat and humidity in the outbreak regions, and that might actually cool the workers. In some cases, there are surrogates for predicting performance (e.g., filter effectiveness in the face of various biological challenges). However, for other parameters (e.g., fluid resistance), the tests are not as developed. Colton added that some research and development of PPE (e.g., the effectiveness of a biocide as part of a product) could require working with infectious agents that the PPE industry does not generally have the facilities for.

Shanelle Hall, Director of the Supply Division at the United Nations Children's Fund (UNICEF), underscored that products cannot be developed in isolation from how they will be used, and PPE use by untrained health workers in a community care center will be very different than that used by highly qualified people in an emergency treatment unit. Development is an iterative process, informed by how products are actually being used.

Regulatory Science Capacity

Developing new platforms and technologies is only the first step, Mundel said. Effectively deploying interventions requires partnership with regulators, including developing their competence and capacity in regulatory science, as well as addressing the broader community and political constructs. Pfleiderer observed that the regulatory field has changed drastically in recent years, and now the process is more of a partnership with

product developers. Hamburg agreed and added that the U.S. Food and Drug Administration (FDA) experience shows that the time for the research and development can be reduced when the regulator is involved early, and in a continuing way, in the research and development plan.

Hamburg highlighted the need for a new emphasis on building regulatory science capacity. Academic, industry, and government science need to come together to ensure that the knowledge and tools are available to be able to assess a promising candidate product for safety and efficacy; achieve an acceptable risk–benefit ratio; and ensure that the product can be manufactured consistently, with quality, and scaled up. Hamburg highlighted several critical areas of science that are ripe for further development including identification, characterization, and validation of biomarkers; the use of surrogate end points; the development of innovative clinical trial designs; the use of information technologies for disease detection and surveillance or post-market pharmacovigilance; the use of modeling and simulation; and predictive toxicology.

INTELLECTUAL PROPERTY AND SHARING OF DATA AND REAGENTS

Researchers, public health institutions, and companies alike have concerns over the access to the building blocks of knowledge, key research tools, and technology platforms necessary for developing a diagnostic, drug, or vaccine, said Anthony So, Professor of the Practice of Public Policy and Global Health at Duke University. As an example, So described the case surrounding the "ownership" of the Middle East respiratory syndrome (MERS) coronavirus (see Box 3-1). At the core of the controversy is the Erasmus Medical Center Material Transfer Agreement (MTA). Although it was claimed that the Erasmus MTA was based on the Uniform Biological Materials Transfer Agreement (UBMTA),[2] the Erasmus MTA in fact gave Erasmus ownership rights over any inventions made by recipients that directly relate to the material, in perpetuity. Under the UBMTA, the agreement may be terminated if the material becomes generally available from third parties (e.g., a reagent catalog or public depository).Yamada, So, and others discussed that there is no definitive answer on the status of the ownership of a vaccine strain that has been derived from a patient. Some countries consider it to be a naturally occurring substance that would not be patentable; others assert that under the Convention on Biological Diversity countries have sovereign control over such samples.

[2] The UBMTA is intended to facilitate the transfer of biological materials between the institutions, while protecting the rights of the provider to commercialize the material, and allowing the recipient to publish research findings in a timely way.

BOX 3-1
Case Example: Who Owns the MERS Coronavirus?

In June 2012, Dr. Ali Zaki, a consulting physician, sent blood and sputum samples from a patient who died in a hospital in Jeddah, Saudi Arabia, to Erasmus Medical Center in the Netherlands after initial testing of those samples came back negative from the Saudi Ministry of Health. Researchers at Erasmus identified the cause as a new coronavirus, MERS. In October 2012, Zaki and the Erasmus researchers jointly published their findings. In November 2012, Erasmus filed a patent application for the gene sequence in the Netherlands, and began sharing virus samples with laboratories around the world, entering into MTAs with more than 40 institutions. Saudi officials maintained that Zaki had violated Saudi rules in sending the samples abroad, and this resulted in his dismissal. A copy of the Erasmus MTA only became public because of a public records request for the agreement with 1 of the 40 institutions. Officials then claimed that the Erasmus MTA included restrictions on sample sharing. Erasmus has countered that the MTA was modeled on the UBMTA and did not overly restrict access to virus samples. The Erasmus MTA, however, gave Erasmus ownership rights over any inventions made by recipients that directly relate to the material. Erasmus thus became the steward of diagnostics or treatments for a disease that is not endemic in the Netherlands. Erasmus contends that it continues to send the MERS coronavirus free of charge and without restrictions to all research institutions that work to benefit public health.

SOURCE: So presentation, August 19, 2015.

So highlighted some of the challenges to sharing data and reagents. There are transaction costs of assembling knowledge, and institutional arrangements need to include efforts to search, cross-license, and keep in check undue royalty stacking. Scientists in competition for grant support might slow the dissemination of research materials or findings in their quest to publish first. Producing information or materials in response to requests also takes time and effort away from research. Sharing is also affected by whether the data or material have known commercial value. A company might be concerned about liability risk associated with the pursuit of a secondary indication (e.g., drug repurposing studies might find new adverse drug reactions, or result in deaths when tested in a sicker population than the original intended targeted population).

Patents, licensing, MTAs, and other IP arrangements can powerfully shape the innovation ecosystem, So said. Patent holdouts can occur when the original company refuses or delays the licensing of IP to others. Patent thickets result from overlapping IP rights of multiple patent owners, all of which must be dealt with before moving forward. There can also be a

temporal lag between the pace of emergent disease outbreaks and the prosecution of patents (i.e., it takes longer to resolve the patent claims than for the outbreak to subside).

There are many variations of collecting IP for medical research and development. Patents and licensing range from exclusive licenses of proprietary information, to patent pools of nonproprietary information. MTAs range from negotiated access to private compound libraries to public repositories of compounds. Similarly, data sharing spans negotiated access to proprietary data, to open-access databases. Publication of data ranges from traditional paid subscriber access to open-access journals.

Pooling arrangements have often relied on centralized institutions as facilitators. For example, the Biomarkers Consortium[3] pools data on biomarkers that might be used in the regulatory process. Public- and private-sector contributors offer a limited, nonexclusive, royalty-free license to their IP to others in the pool. In the World Intellectual Property Organization (WIPO) Re:Search consortium,[4] contributors agree to grant recipients royalty-free licenses to both data and other IP (e.g., reagents) for research and development of products addressing specific neglected diseases in the least developed countries. Pooling arrangements can also involve a proprietary compound library that is made available for screening to a product development partnership by a research group (e.g., the Tres Cantos Open Lab Foundation established by GlaxoSmithKline [GSK]). Hits identified during the compound screening process remain confidential, and the compound owner has the right of first refusal for development of the compound. The converse, So said, is essentially crowd-sourcing promising compounds for company-defined disease targets. Eli Lilly's Open Innovation Drug Discovery Initiative,[5] for example, provides compound design tools in the cloud for outside investigators to use. In silico screening is done on the neutral network, protecting information from access inside or outside of the company. Outside investigators can then decide whether to submit their compound designs to Eli Lilly or not. To be effective, these pooling arrangements must have strategic fit within a larger innovation ecosystem, So said. He cited the Pandemic Influenza Preparedness Framework as one such innovation ecosystem that brings together multiple stakeholders who, in exchange for access to virus samples, commit to donating pandemic vaccine or drug or reserving production capacity to supply the World Health Organization (WHO) stockpiles for low- and middle-income countries. There are lessons from other sectors as well, So said. The International

[3] For more information see http://www.biomarkersconsortium.org (accessed October 30, 2015).

[4] For more information see http://www.wipo.int/research/en (accessed October 30, 2015).

[5] For more information see https://openinnovation.lilly.com/dd (accessed October 30, 2015).

Treaty on Plant Genetic Resources for Food and Agriculture is noteworthy for having codified a compensatory liability regime that allows researchers to freely take the materials for any research purpose, without the need for any permission to use, and requires payment of equitable compensation if the research leads to a commercial application and gain.

Shaping the innovation ecosystem is the responsibility of governments, So said, and demands a multilevel framework that creates an enabling environment for sharing of data and reagents, and enabling medical research and development to meet emerging needs.

Stoffels suggested that large companies secure patents to preserve the freedom to operate. A company can decide to give patented IP away, but if it does not patent, it ends up paying royalties to third parties to use that IP. So suggested that one approach could be to create a research semi-commons, whereby patent offices would waive the patent filing and maintenance fees for IP that is "parked" for the main purpose of preserving the freedom to operate. This IP would then be available more readily for research.

Reid Adler, founder of Practical Innovation Strategy, noted that the ecosystem for transfers of infectious materials and related data involves many different control points (e.g., national laws; international treaties; public health organizations; the rules and procedures of research institutions, funders, companies, publishers, biological materials depositories, and others; and interpersonal relationships). Numerous factors affect or impede the sharing of biological material and data, including

- regulations,
- expectations of affordable access to products developed through use of shared materials,
- time and administrative burden of dealing with legal provisions in agreements,
- cost and logistics of sharing materials,
- concerns about opportunity costs,
- competition among researchers/institutions,
- diversity of materials being shared,
- misperceptions or frustrations about IP, and
- expectations about access to training or technology (poorly characterized, processed, or labeled materials).

Adler mentioned several successful models and frameworks that address sharing, including the National Institutes of Health (NIH) grants policy, the UBMTA, the WHO Pandemic Influenza Preparedness Framework, and the BMGF AIDS research agreement. Examples of data-sharing efforts discussed by Marks and others included Data Sphere (which facilitates sharing of de-identified patient-level data from cancer clinical trials), GA4GH

(the Global Alliance for Global Health, facilitating responsible sharing of genomic data), and TransCelerate BioPharma (creating standards for clinical data transparency that preserve patient privacy). Dzau referred to a recent IOM report that made specific recommendations for the timing of the release of clinical trial data (IOM, 2015b).

Adler emphasized the need for frank and open communication, relationship building, and establishing trust, all of which are more difficult to do in the midst of an emergency. Trusted rules or agreements should be negotiated and agreed to in advance of when needed, he said. Ask researchers and institutions what they need to be able and willing to share data and materials, he suggested, and learn from experiences where sharing of materials was not optimal. Providing practical training to researchers and institutions about material sharing and related agreements (e.g., patents, MTAs, informed consent, and benefit sharing) could increase understanding about sharing and make the system work more smoothly.

Michelle Mulder, Manager of Technology Transfer, Grants, and HIV Program at the South African Medical Research Council (SAMRC)[6] said that SAMRC has a dual role in both funding and conducting health research, and supports IP protection for three main reasons: to ensure control over how it is used, to leverage partnerships, and to incentivize private investment. The approach to IP and data sharing seeks to balance the global access principles with profit motive. The primary objective is to get products to those who need them most, at affordable prices. SAMRC is bound by the South African Intellectual Property Rights Act of 2008, which is aimed at ensuring that benefits from publicly funded research accrue to South Africa. Mulder noted that the Act allows SAMRC to award free licensees to IP for research. Together with international partners, SAMRC has also developed a socially responsible licensing guide. SAMRC also promotes public and precompetitive access to data (generally after protection/publication). For example, the Regional Prospective Observational Research for Tuberculosis South Africa is a network of institutions and investigators who will collaborate on established clinical studies, using a standardized set of definitions, standardized protocols, and well-characterized populations. All collaborating institutions will be required to place certain data and specimens in a central repository for availability to all collaborating institutions within the network. The broader tuberculosis research community may apply for access under certain conditions. Similar data-sharing provisions are part of the Malaria Drug Discovery Program, the H3 Africa consortium (Human Heredity and Health in Africa), and the HIV Reagent and Data repositories.

Marks pointed out that when discussing the potential costs of transpar-

[6] Further information about SAMRC is available at http://www.mrc.ac.za (accessed October 30, 2015).

ency and data sharing, it is important to recognize that the alternative—if researchers have to keep reproducing the same work—will cost even more. He said that GSK is emphasizing a transparency model, placing both positive and negative data in the public domain, and the Tres Cantos Open Lab Foundation is just one model of how to manage IP and sharing of information and reagents. Marks observed that there are ever fewer players in the infectious disease space, and showing them examples of successful ways to manage transparency issues, data sharing, and IP could remove a barrier to entry. Yamada observed that companies have repeatedly shown they are willing to work together on an issue in times of crisis, but they are prohibited by antitrust laws from discussing pricing.[7] Pricing is a critical issue for the distribution of a vaccine, and the inability to discuss price leads to incomplete discussion and sharing of the science.

A question was asked about compulsory licensing in pandemic situations, noting that it applies only to patents and not to materials.[8] So responded that compulsory licensing is currently done at the national level, but there has been some discussion of the issues of collective action, such as an economic bloc acting as a group to implement a joint compulsory license. So suggested that a compulsory license is not very valuable if the market is for a single, small country, especially a developing country. Mulder said that South Africa has compulsory licensing and there have only been three applications thus far, and all have been denied. She noted that even though compulsory licensing applies only to patents, there are requirements that the materials needed to enable the patent must be deposited in a publicly available repository.

Sharing Negative Data

The importance of sharing negative data was emphasized. A participant observed that during the Ebola outbreak there were negative data that were not publicly available, and treatment decisions were informed only by the publicly available data. It was noted that industry is now releasing both positive and negative data, but negative data from academic and government laboratories are often not published or released. Marks noted that most journals are not interested in publishing negative results.

[7] Though not presented at the workshop, discussion and proposals about price, particularly that aim to ensure that a product is affordable, can be undertaken with relevant stakeholders, such as the case of the MenAfriVAC vaccine under the Meningitis Vaccine Project. For more information see http://www.meningvax.org/faq.php (accessed November 13, 2015).

[8] Briefly, a compulsory license is granted by a government to a generic drug-maker for the production of a generic version of a patented product without the patent owner's consent. Grounds for granting compulsory licenses are determined by the individual country.

LIABILITY

Participants also briefly discussed liability concerns, which can be a disincentive for engagement in research. So said that a review by WHO of international no-fault systems for vaccines found that 19 countries have vaccine compensation systems to address liability: 13 in Europe, and none in developing countries. Typically, national governments are involved, funding may be derived from a manufacturer's tax, the products that are covered vary, and eligibility and compensation decisions might depend on a standard of proof. In the United States, for example, systems include the National Vaccine Injury Compensation Program, and the countermeasures injury compensation provisions of the Public Readiness and Emergency Preparedness (PREP) Act. Venkayya added that, before passage of the PREP Act, potential liability was the primary impediment to companies engaging in pandemic influenza preparedness, and biodefense preparedness after the terrorist attacks. After the PREP Act was implemented, this liability was no longer a barrier to engagement. This legislation, he said, was critical to creating an environment in which companies were willing to make investments to address unknown threats, or known threats with an unknown time frame for emergence. Venkayya called for globalization of this concept, before the next crisis, and he suggested that an independent entity propose legislative language for consideration by countries.

4

Development

Development encompasses the process of bringing a candidate identified in the discovery research phase to market and generally spans preclinical testing, clinical assessment, and regulatory approval. Much of the discussion of development at the workshop focused on the design and conduct of clinical trials during a public health crisis. Participants also discussed the importance of engaging affected communities as stakeholders and partners in the development process (regulatory issues are discussed in the following section). Highlights and main points are summarized in the box below.

Highlights and Main Points Made by Individual Speakers and Participants[a]

- The importance of distinguishing between trials of vaccines and those of therapeutics when discussing trial design was emphasized, as the immunogenic mechanisms of vaccines are different from the therapeutic mechanisms of action of drugs. However, scientific rigor is a key component in both. (Binka, Kalil, Rex)
- Regulatory entities need to see interpretable data. From an ethics perspective, no study should be undertaken unless the results will be interpretable. (Borio, Califf, Kalil)
- The core issue for robust clinical trial design is appropriate controls or comparators.

  - For trials of therapeutic products, a randomized controlled trial is most rigorous. The appropriate control is usually the standard medical care for the condition (although, for emerging diseases, the only option might be supportive care). (Borio, Kalil, Kilmarx, Levine)
  - For vaccine trials, there could be more flexibility for novel clinical trial designs (e.g., the Ebola ring vaccination trial with the 21-day vaccination delay control group). (Borio, Levine)
  - Historical controls are unreliable and do not represent what is currently happening in the field. Studies comparing two investigational products can be misleading. (Borio, Kalil, Kilmarx)
  - Adaptive clinical trial design and analysis could be helpful, including the use of traditional (frequentist) and Bayesian statistical methods. Adaptive randomized trial design can allow for multiple interventions (perhaps from multiple manufacturers) to be evaluated against one shared control group, resulting in greater efficiency and fewer participants receiving the standard of care control intervention. (Borio, Kalil, Kilmarx)
- Participants acknowledged that during the Ebola outbreak many decisions regarding optimal trial designs were made quickly and under challenging circumstances. Participants also discussed the need for more sustained communication among governments, researchers, nongovernmental organizations (NGOs), and communities to better align and be more prepared for future outbreaks. (Binka, Califf, Lee)
- Participants acknowledged the challenges of clinical trials in the face of extremely limited infrastructure and inadequate capacity and discussed the need to consider studies in the context of the reality on the ground. (Kilmarx, Levine)
- It is important that clinical studies be acceptable to the affected populations. Engaging the community, including all community leaders, is key for success. Educate the public about the disease, the dynamics of epidemics and prevention, and clinical trials. Fight fear with facts, in local languages with meaningful messages. The most effective communication is two-directional, with feedback from the community informing policy, practice, and service delivery. (Awunyo-Akaba, Bell, Binka, Borio, Califf, Hall, Kilmarx, Sow, Yamada)

- Infrastructure and capacity building across the areas of physical infrastructure, human resources, laboratory capacity and quality assurance, data management capacity, systems of ethical review, and training (including ethical reviewers, NGO leadership, and others) are important. (Awunyo-Akaba, Bell, Binka, Kilmarx)

[a] This list is the rapporteurs' summary of the main points made by individual speakers and participants and does not reflect any consensus among workshop participants.

ETHICAL PRINCIPLES AND METHODOLOGICAL FRAMEWORK FOR CLINICAL TRIAL DESIGNS

Design and Conduct of Clinical Trials During a Public Health Crisis

During the 2014-2015 Ebola outbreak, the global scientific community organized and made progress on identifying and accelerating progress of promising vaccines and therapeutic interventions, since none had yet been approved (Adebamowo et al., 2014). Many of these interventions had never been tested in humans and so, over the course of the response, a global debate ensued over how to best assess the clinical safety and effectiveness of novel interventions during the public health crisis (Adebamowo et al., 2014; Cox et al., 2014). Some in the scientific and medical communities believed that the situation on the ground made the prospect of conducting randomized controlled trials (RCTs) untenable from a practical perspective, and that alternative study designs that could be implemented more rapidly needed to be pursued (Adebamowo et al., 2014). Others contended that randomization with controls is fundamental to collecting reliable data on the safety and efficacy of novel products and must be preserved (Cox et al., 2014). The presentations and discussions at the workshop articulated these different perspectives. Discussion focused on the methodological design considerations for both vaccine and therapeutic clinical trials and the practical challenges encountered by those conducting trials in West Africa during that time.

METHODOLOGICAL DESIGN CONSIDERATIONS

In his presentation, Andre Kalil, Director of the Transplant ID Program at the University of Nebraska Medical Center, noted that the most optimal and ethical study design for evaluating experimental drugs with low availability, in diseases affecting low-resource areas, is the one that offers the highest probability of detecting true success or true failure with the

experimental drug. The study design with the most robust methodology and the highest probability of detecting the effect of an experimental drug and distinguishing true signal from noise (e.g., patient selection bias, confounding, and chance) is the RCT, he continued. He remarked that no other study design offers a higher benefit–risk ratio with the most treatment equipoise to all patients, better utilizes the limited availability of experimental drugs, evaluates the efficacy of experimental drugs in a timely fashion for the benefit of those impacted today, or accrues as valid and reliable results for the benefit of all patients now and in the future.

Kalil listed and refuted some of the arguments made against randomized controlled trials in the context of the Ebola outbreak. A key argument made was that patients and health care professionals in Africa would not accept randomization because Ebola mortality is so high. Kalil countered that RCTs for acute illnesses with very high mortality are done every day all over the world to evaluate new therapies (e.g., septic shock hospital-acquired infections, encephalitis, and necrotizing fasciitis). Another argument made was that patients and health care professionals in Africa would not consent to having a random chance to receive either the investigational drug or the control. In reality, Kalil said, randomized trials for acute and chronic illness have been performed with an appropriate consent process in tens of thousands of patients in Africa, for a multitude of diseases (e.g., severe sepsis, tuberculosis, malaria, HIV, and meningitis). It has also been argued that observational trials can be done faster than randomized trials. In fact, Kalil said, RCTs can be done quickly, especially with adaptive, Bayesian, and sequential group analysis designs. Several experimental therapies can be tested in a timely fashion, and new participants can be added to more promising intervention arms as data are collected, with a potential overall result that fewer patients are unnecessarily exposed to an ineffective or harmful drug, while more patients are exposed to effective or beneficial drugs during the trial. It is also not the case, Kalil said, that randomized trials are more expensive. For a new experimental drug, he noted, randomized designs are actually less costly and require fewer resources than other designs because the information gathered will bring at once (instead of from multiple observational studies) a more definitive (less biased) result regarding the drug's efficacy. Moreover, the addition of an adaptive Bayesian design makes randomized trials even more cost effective. Another argument is that randomized studies are unnecessary if a drug has demonstrated very high survival success in small animals and nonhuman primate models. Kalil cautioned that medical history is full of experience with prospective drugs that showed impressive benefits in animals models but failed in randomized human studies (e.g., a variety of monoclonal and polyclonal antibody therapies).

Kalil also stressed the dangers of using a historical control rather

than concurrent controls, stating that historical controls do not necessarily reflect what is happening in the field. Factors such as disease severity and supportive care change from facility to facility in the same area, from country to country, and over time. Kalil then described an ongoing multicenter, randomized safety and efficacy study of Ebola treatment sponsored by a National Institutes of Health (NIH) trial (NCT02363322).[1] The study is being done at a variety of sites around the United States and in Guinea, Liberia, and Sierra Leone, and employs an adaptive study design.

Kalil raised concerns that, through small uncontrolled single-arm studies being done in Africa, patients are being exposed to lower-quality study designs with low probability to produce interpretable valid replicable results. Kalil proposed that, unless an infectious disease outbreak is associated with 100 percent mortality, no single-arm trials should be initiated in a country due to the following reasons: high likelihood to produce uninterpretable and uninformative results, high likelihood to produce biased and not-replicable results, and results too uncertain to be applied during the outbreak, so they would not benefit current patients or change the course of the outbreak and would further deplete the availability of experimental drugs for RCTs. From a business perspective, a drug could be found falsely ineffective or unsafe, or falsely effective or safe, for reasons unrelated to the drug.

Peter Kilmarx, Deputy Director of the Fogarty International Center at NIH, elaborated on the challenges of clinical trials in the face of extremely limited infrastructure and inadequate capacity (e.g., limited physical infrastructure and human resources; lack of training; lack of laboratory capacity, systems, and quality assurance; lack of data management capacity and data; and lack of systems of ethical review). A controlled clinical assessment should generally be done for any novel treatment or pathogen, Kilmarx said, acknowledging that there are some exceptions (e.g., seasonal influenza vaccine, and possible compassionate use of promising interventions when there are too few cases to conduct a clinical trial). The most appropriate clinical trial design, from the NIH standpoint, is the randomized placebo-controlled double-blinded trial. Kilmarx concurred with Kalil that this generates the most robust data in terms of safety and efficacy of the product, as well as duration of protection for vaccines. He also agreed that declining incidence makes it inappropriate to use historical controls for a vaccine or prevention study. Kilmarx said the use of peramivir under an emergency use authorization (EUA) during the 2009 H1N1 pandemic underscores the importance of the randomized controlled clinical trial. Although there were attempts to capture data during use of the product, the data derived from this uncontrolled use were not reliable or interpretable (Borio et al., 2015).

[1] See https://clinicaltrials.gov/ct2/show/NCT02363322 (accessed October 30, 2015).

Subsequent clinical trials showed no benefit or harm from the treatment (despite suggestion during the use under EUA that there was increased mortality).

Kilmarx briefly reviewed the NIH adaptive randomized trial design, which allows for multiple interventions to be evaluated against one shared control group, resulting in greater efficiency and fewer participants receiving the standard-of-care control intervention. Interim analysis and early stopping points allow for the discontinuation of trial arms where there is demonstrated toxicity or lack of efficacy (Borio et al., 2015). This model was the basis for the Partnership for Research on Ebola Virus in Liberia 2 study.[2]

Nancy Lee, Senior Policy Advisor at Wellcome Trust (WT), countered that in the case of the recent Ebola outbreak in West Africa, circumstances on the ground, including lack of trust by the people, lack of government cooperation, and serious time and resource constraints, led to the determination that RCTs were not feasible and alternative designs needed to be considered. She stated that WT's priorities were to achieve (1) rapid results, (2) ethically appropriate implementation, and (3) interpretable data. Considering those priorities, she said, they believed that they needed to look into an alternative to the RCT and decided to first conduct single-arm studies, to collect as much information as possible on the novel therapeutics. Dull noted that The Bill & Melinda Gates Foundation (BMGF) considered single-arm or observational studies to be a step in part of a larger study group that led to RCTs as well. Dull contended that observational studies could be useful in that context and especially for identifying highly efficacious or kill products.

Myron Levine, Associate Dean for Global Health, Vaccinology, and Infectious Diseases at the University of Maryland School of Medicine, offered another perspective on ways of conducting clinical trials in a crisis, calling for more flexibility in trial design. With regard to the need for randomized studies of treatments, Levine agreed with Kalil but added that one must consider studies in the context of the reality on the ground. Levine's opinion diverged somewhat with regard to vaccine trials, for which he said much wider possibilities are needed. Historically, he said, there has been licensure of vaccines that have proven to be critical public health tools without classical randomized controlled trials (e.g., the *Haemophilus influenzae* Type b [Hib] conjugate vaccine, part of the vaccine preparations that the United Nations Children's Fund [UNICEF] gives out to developing countries, was licensed on the basis of serological noninferiority to two

[2] For more information on the study see http://www.niaid.nih.gov/news/newsreleases/2015/Pages/ZMapp.aspx (accessed October 30, 2015).

other polysaccharide conjugate vaccines which had been evaluated in classic randomized controlled double-blind studies).

Levine described the very rapid development of two existing Ebola vaccine candidates, the chimpanzee adenovirus-3 vectored vaccine (ChAd3) and the vesicular stomatitis virus–vectored Ebola vaccine. Ethical Review Committees, regulatory agencies, funders, and most political authorities partnered in the highly accelerated timeline for phase I trials, final dosage levels were rapidly selected, less stringent cold chain conditions were worked out, and large-scale phase III trials were planned or initiated based on phase I/II results. Levine posed the questions of whether these studies could have been done even faster, and asked whether this experience could be repeated. The Guinea ring vaccination trial, Levine explained, was a novel randomized trial design where all participants received vaccine. Following identification and confirmation of a case of Ebola by the public health service, contacts received immediate vaccination or vaccine after a 21-day delay. That 21-day delay, he said, afforded biostatisticians the ability to compare the difference if one started counting cases 10 days after the ring vaccination began. Levine suggested that licensure of one or more Ebola vaccines based on nonhuman primate protection results and human safety and immunogenicity data from accelerated phase I and II trials could have allowed field effectiveness to be studied through less complex post-licensure designs (Levine et al., 2015).

Participants shared many opinions on the merits and limitations of the clinical trials conducted during the Ebola outbreak. It was suggested, for example, that the ring vaccination strategy in Guinea was fortuitous as it provided short-lived but high-level protection for those at high risk. A trial designed to randomly allocate vaccine to the general population would likely have had a much lower demonstration of efficacy, and perhaps not even reached its end points. Freire noted that the Foundation for the NIH, with funding from BMGF, has hired McKinsey to do a comprehensive study of the clinical landscape during the Ebola crisis. It is expected that the results will be housed on the World Health Organization (WHO) website and would be publicly available for study.

Participants discussed at length the benefits and limitations of the different approaches to clinical trials in a crisis situation. Rex emphasized the need to distinguish between trials of vaccines and those of therapeutics when discussing trial design, but, in either case, scientific rigor is essential, he said. Borio reiterated that the core issue for clinical trial design is appropriate controls, and there are many ways to establish an appropriate control for vaccine studies. For therapeutic trials of emerging infectious diseases, options are limited, despite our best creative efforts, Borio said, and historical controls are simply unreliable, she reiterated. The best approach for therapeutics would be to use Bayesian designs and adaptive clinical trials.

Participants discussed the elements of adaptive clinical trial designs, including the use of traditional (frequentist) and Bayesian statistical methods in adaptive trial design and analysis.[3] Califf summarized that one size does not fit all. He observed that many of the decisions made relate to how affected populations perceive what is being done to them, and how governments react. The concept of randomization is not well understood, and more education of the public and researchers about the value and implication of randomization is needed.

Dull relayed that, in the chaotic setting of the Ebola pandemic, it was extremely challenging to work with development partners that had never run clinical trials before, and to conduct clinical trials of a product that had not yet entered into phase I testing. He noted that BMGF has worked to develop platform-based clinical trials that investigators could "plug and play" different products into, and has engaged in discussions with the U.S. Food and Drug Administration (FDA) about having study protocols in place so that a trial can be launched much more quickly in the event of an outbreak.

Bilbe suggested that one approach to meeting extremely short time frames for product delivery in a crisis is to repurpose drugs from other settings. He noted that the Drugs for Neglected Diseases initiative (DNDi) grew out of a recognition by Médecins Sans Frontières (MSF, Doctors Without Borders) of the lack of needed medicines in the developing world. In a pandemic setting, when a disease is emerging and may be yet unknown, one approach is to study the course of disease while the patient is being treated. Bilbe observed, however, that MSF was so overloaded with the avalanche of patients during the Ebola outbreak that data simply could not be collected as part of the treatment process. This is a major drawback in terms of learning about the usefulness of drugs being administered in that setting, he said. Spigelman added that MSF treats more multidrug-resistant tuberculosis patients than any other single entity, and yet there has been no prospective data coming out of that resource.

[3] FDA guidance states that "an adaptive design clinical study is defined as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study. Analyses of the accumulating study data are performed at prospectively planned timepoints within the study, can be performed in a fully blinded manner or in an unblinded manner, and can occur with or without formal statistical hypothesis testing." See *Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics* at http://www.fda.gov/downloads/drugs/guidancecomplian-%20ceregulatoryinformation/guidances/ucm201790.pdf (accessed October 30, 2015).

ETHICAL REVIEW

Fred Binka, Vice Chancellor at the University of Health Allied Sciences in Ghana, said that ethics is a major pillar of clinical research, and, simply, if the trial design is not good, it is not ethical. National ethics policies in Africa are often driven by requirements from external funders. With the exceptions of Malawi, Senegal, South Africa, and Tanzania, most countries in Africa have not enacted laws to regulate research ethics. Modalities for ethical reviews are varied (e.g., whether fees are charged, and if there is funding from central government). There were major efforts to try to improve ethical reviews of clinical research in Africa, and several African associations were developed (e.g., the Pan-African Bioethics Initiative), but Binka noted that efforts have waned in the absence of resources. Currently, there are 170 research ethics committees in various stages of maturity, but most countries do not have a national ethics committee. Committees are generally within institutions and, while membership is adequate, the committees are not well supported or well trained. There are large volumes of protocols for review, and attrition rates for the volunteer committee members are high. Funding for ethics committees is variable, with most now charging fees because support from their governments is not adequate.

Binka noted that the African Vaccine Regulatory Forum (AVAREF) is pursuing regulatory reform. This group, established in 2007, is a platform for information sharing by product developers on vaccine candidates, target countries, and timelines for clinical trials. It fosters communication and collaboration among the national regulatory authorities and ethics committees in most countries and provides expertise to regulators in support of the review process. Twenty-two countries are now members of AVAREF, and Binka called for development at the African Union level and the creation of an African Regulatory Agency. Support from stakeholders is needed to develop research ethics capacity in Africa through AVAREF, and for training in specialized areas (e.g., novel designs, genetic studies, and tissue storage for long-term use), he said. The goal, he concluded, should be the formation of national ethics committees with appropriate funding to protect participants in research.

Stoffels said that, in addition to designing the best study within the range of possibilities, it is also essential to give confidence to African communities that they will have first access to the product being tested once it is approved (i.e., that they are not simply being used as a test population).

REGULATORY PERSPECTIVE

Rob Califf, Deputy Commissioner for Medical Products and Tobacco at FDA, echoed the comments of other speakers that making clinical deci-

sions without robust evidence is bad social, cultural, and health policy. Califf agreed that the classical randomized clinical trial is the method of choice where possible, but he pointed out that many trials being done in some fields now have a single arm (e.g., oncology trials). Hans-Georg Eichler, Senior Medical Officer at the European Medicines Agency (EMA), agreed that there are new oncology and orphan drug products authorized in the United States and European Union (EU) that have not been tested in an RCT. He called for flexibility in using the entire spectrum of evaluation methodologies available, and not restricting development to RCTs only. However, some participants, including Kalil and Borio, cautioned that oncology trials and acute infectious disease trials are different in that most of the oncology single-arm trials are for cancers with 100 percent mortality, and the trial participants have generally already exhausted all other chemotherapy options. Moreover, the disease processes for cancer and for acute infectious diseases are very different.

Borio said that FDA needs to see interpretable data coming out of clinical studies, and generally speaking, that means randomized trials where the test product is evaluated against an appropriate control. These types of trials can take many shapes and forms. Trials of vaccines could be, for example, a classic RCT (as was done in Liberia) or a trial comparing outcomes in those that receive immediate versus delayed vaccination (as was done in Sierra Leone). Trials to test vaccines may have an added flexibility, she said, in that a clinical end point is desirable, but not always required. Vaccines could also be evaluated based on immunogenicity studies (demonstrating production of protective antibodies). FDA is committed to embracing scientifically sound innovation, Borio said, noting the example of using Bayesian analytical techniques to guide trial design.

For trials of therapeutic products to lead to interpretable data, the product must be compared to an appropriate control, which is usually the standard medical care for the condition (often a preexisting therapy), she said. Borio noted that for emerging infectious diseases for which there is no specific therapy, supportive treatment might be the standard-of-care comparator (e.g., intravenous fluids for electrolyte replacement and hemodynamic support). She stressed that studies comparing two investigational products can be misleading. For example, comparing what might be a relatively safe but ineffective product to a toxic product could give the illusion that the safe but ineffective product was actually helpful, which could lead to the adoption of the ineffective therapy and impede development of a truly effective product.

For a truly successful outcome, Borio concluded, clinical studies need to be feasible, ethical, scientifically valid, and acceptable to the affected populations. Borio reminded participants that clinical trial outcome is only

part of the licensing application; trials must be appropriately executed with integrity, and a quality product must be manufactured consistently.

Freire noted that, while academia has a critical role in basic research, to truly be a partner at the clinical trial level, there needs to be education on what it takes to conduct a trial that will generate the type of information needed for regulatory agency review.

PRACTICAL CONSIDERATIONS AND COMMUNITY ENGAGEMENT

Samba Sow, Director General of the Center for Vaccine Development–Mali (CVD–Mali),[4] discussed practical considerations and community engagement in the context of the Ebola clinical trials conducted in Mali. Sow emphasized the importance of leadership, and of having field centers from which surveillance, monitoring, basic research, and clinical trials can be managed.

Sow highlighted some of the many practical challenges of conducting Ebola clinical trials in Mali. He relayed that the Ministry of Health required that the protocol be presented to all of the institutional review boards (IRBs) in the country, which amounted to three valid IRBs, only one of which, he said, was well trained. It was a very difficult process, in large part due to a lack of understanding of clinical trials and the concept of randomization. There are also complicated issues surrounding trial insurance and malpractice insurance. In Mali, after securing IRB approval and obtaining insurance, it is necessary to get an import permit, and then a formal authorization from the Ministry of Health. Only then can investigators begin to provide information to community leaders, local associations, traditional healers, and community members.

Sow summarized some of the other challenges as the speed of the recent Ebola crisis; the influx of partners, many of whom were focused on their own interests rather than those of the country; the lack of border control between countries; political instability; the safety and security of health workers; funeral practices (where cultural ceremonies include washing of the body, touching the deceased); a low literacy rate; religious beliefs (e.g., concerns that vaccines may contain material of pork origin such as gelatin); cultural beliefs, sensitivities, and myths (e.g., that vaccines cause sterility in women or infants); and the power and influence of traditional healers and

[4] CVD–Mali was created in 2001 under an agreement between the University of Maryland Center for Vaccine Development and the Ministry of Health of Mali, and is administratively part of the Ministry of Health. The mission of CVD–Mali is to prevent, control, and treat endemic and epidemic infectious diseases in Mali and to train Malian specialists in vaccine-preventable infections, disease surveillance, and field research.

local doctors (many of whom were not knowledgeable about Ebola and its modes of transmission, and died in their efforts to treat patients). Sow noted that it is very difficult to talk about a double-blind RCT to people who have only known traditional medicine all of their lives.

Sow shared a harrowing account of his personal experience of Ebola's arrival in Mali, when the Minister of Health asked him to see three men coming from Guinea with suspected cases of Ebola. His only protective equipment was a pair of gloves; one afflicted man fled the health center into the community and was not retrieved by police until 24 hours later; and the health center was surrounded by dozens of people who threatened the lives of Sow and the patients. They were relocated to a "safer" location, in an old meningitis epidemic quarantine facility infested with snakes. The government sent more than 100 heavily armed soldiers to surround his place of work where he tried to set up a treatment center, and also Sow's home, where he ultimately decided to take the patients.

Any effort involving public health, including research, must start and end with the community, Sow said. One must understand the situation in the field, and Western textbook science and academic center trial designs do not apply necessarily to West Africa. In engaging members of the community it is important to recognize community values, beliefs, attitudes, and behaviors about vaccines or other treatments, clinical trials, and around research in general. Community knowledge and understanding of the disease is key, Sow said, noting that there was resistance to a proposed vaccine trial because there was no Ebola in Mali at the time. It was challenging to explain that the vaccine trial was important for prevention, not treatment. Education involves organizing meetings with local leaders and the community (before, during, and after), with assistance from the military or other security leaders. Involving all community leaders is important (including the traditional, religious, administrative, political, and sociocultural leaders). Researchers also need to understand the role of traditional healers and engage them. It is important to use simple, local, understandable language, to convey how the trial could directly and indirectly benefit participants and communities, to address issues of vulnerable groups, to discuss the results and impact of previous studies, and to highlight the experience of the investigators. Sow added that it is best to use experienced local investigators if possible. After getting community permission to proceed, individual consent or assent must be obtained from participants. Sow added that in Mali, the national language office translates the consent form into the local language, both in writing and to audiotape.

Awunyo-Akaba spoke from the civil society perspective. The global health risk framework is for the people, she said, country led but community owned. Building on the picture of Mali created by Sow, Awunyo-Akaba said Ghana has 10 regions, 225 districts, and 44,000 communities. The

communities are expected to take care of everything, from providing their own electricity poles and water, to building their own health compounds, and much more. There are no industries in those communities and most residents are subsistence farmers. The people of Ghana have myriad qualities, traditions, dynamics, values, and norms that cannot be violated. The traditional leaders in the villages are the source of authority and decision making, but they cannot make good decisions for their people without information. To be successful, a global risk framework must engage the community and community systems, including religious leaders, traditional leaders, and peer groups. She urged product developers also to keep the challenges for frontline workers on the ground in mind (e.g., terrain, temperature, and limited infrastructure). Cold chain storage, for example, is a significant challenge for a health worker that must travel an hour each way by public transportation to pick up a vaccine as well as wait an hour in the sun for the bus to come.

Civil society groups and local NGOs are willing to go to the communities because, Awunyo-Akaba said, they live with the people, speak their language, understand the nuances, and, in some cases, have earned their trust. However, local NGOs that have been able to reach communities are struggling without adequate funding or resources. NGOs and communities also need information. It is not enough to tell people not to touch each other, as some television advertising campaigns did. Tell them what is being done, she said, and tell them the truth. Awunyo-Akaba called for clear mechanisms for scientists to work with civil society and local NGOs, to build the capacity of NGO leadership, and to support NGOs in engaging the community and spreading information. She added that children are agents of change, and even in Ghana, they all know the popular characters from Western television and movies. She suggested that primers be created for children that teach the dynamics of epidemics and prevention in their own language, so that they grow up with this knowledge, and enhance it.

Binka described the reactions to a proposed Ebola vaccine trial in Ghana. The Ghana Academy of Arts and Sciences (GAAS) set up a committee to consider concerns about the trial, including a stated concern about a lack of clarity about who decides which vaccines should be tested in Ghana, the likelihood of "escape" of the virus into the community, and the likelihood that the vaccine would cause disease in humans. GAAS was also concerned that Ebola patients would need to be imported into Ghana for a phase II trial, as Ghana had no recorded cases of Ebola (though this was not the case as the trial was proposed to be conducted in healthy volunteers). These concerns, Binka said, "raised absolute panic." A health NGO mounted a campaign, there were public demonstrations, and members of Parliament made statements, asking for the trials to be stopped. The Minister of Health was then summoned to Parliament to explain why these

trials were being done in the country. Ultimately, a statement was published announcing the suspension of the clinical trials, and the minister requested national public education on the trial. For 2 months, Binka traveled to four regions in Ghana, organizing local forums to educate the public on the phase I Ebola vaccine trial. Binka also met with the Parliamentary Subcommittee on Health, the Parliamentary Privileges Committee, GAAS, and many others. At the same time, there were numerous articles in the press, many quite sensational, discussing the proposed trial as well as the reactions of politicians and the public. A leading scientist who made a negative comment on the radio about Parliament stopping the clinical study was put on trial and ordered to publicly apologize.

It all comes down to communication, Binka said. Ultimately, the Paramount Chief in the region where the trial was to be done stated in an interview that he never had any concerns about the vaccine trial, because the researchers had met with all the traditional leaders in the municipality, and they felt well informed and were satisfied, long before the political "hullabaloo."[5] One positive outcome of the experience was that it created a forum for discussion and forged a bond between the Food and Drug Authority and investigators. Moving forward, Binka said, community engagement should start from day one. Actively engage and educate stakeholders, community groups, and journalists, and fight fear with facts. He added that moderation of public engagement events by WHO helps to provide assurance and legitimacy.

Beth Bell, Director of the National Center for Emerging and Zoonotic Infectious Diseases at the U.S. Centers for Disease Control and Prevention (CDC), echoed the comments by Sow and Awunyo-Akaba on the importance of civil society and social mobilization. Often, the most severely affected are also the most vulnerable. She said that it is essential to understand the local context of the outbreak and mobilize local partners in the community to help respond. Bell reminded participants that research conducted in the context of an outbreak must be done in coordination with public health, so that the research supports the outbreak response and does not interfere with public health efforts to control the outbreak. In addition, research capacity is connected to basic public health capacity, which is built on surveillance, early detection, and fundamental laboratory capacities, as well as training and response. The world now sees what happens when there is no infrastructure and no capacity, Bell said. Califf agreed that health care research capacity building is critical and that the same infrastructure is necessary for research on noncommunicable diseases that also affect populations in low-resource countries. We are going to have to be able to do trials that are relevant to the population there, he said.

[5] See http://starrfmonline.com/1.5277489 (accessed October 30, 2015).

Communication

Participants discussed further the issues of communication raised by Sow, Awunyo-Akaba, Binka, and Bell. The community response in the face of a need for public health interventions and clinical trials is an important component of success in interrupting transmission; however, health communication to facilitate a positive response is not always done well. It is important to listen carefully to what the community is saying, Bell said, and things that may seem small to nonlocal providers or researchers could be significant to the community. For example, by listening to the local population, CDC learned that the term "Ebola vaccine" led people to think that the vaccine would give them Ebola, and that saying "Ebola prevention vaccine" was more clearly understood and accepted.

Yamada suggested that many clinical trial participants who have given informed consent may not have really given educated consent. They have been informed of the risks and benefits but do not necessarily understand what the trial is about, or about clinical trials in general and that their purpose is to test new medicines that might not work as expected, and might cause harm. Yamada suggested a marketing approach to providing education, using words and messages that are meaningful to the target audience. Binka said that it is very difficult to explain in the consent process that these are investigational drugs and that the study is to prove whether they work or not. People commonly ask, if it does not work, why are you here to give it to people? Sow said that the concept of clinical studies is new in these parts of the world. He added that there are more than 150 languages in Mali, and not one of them has a good translation for "randomization," so getting the message across can be very difficult. A participant said that, for some trials, a comprehension exam was given to participants as part of the consent process, to demonstrate their knowledge about, for example, the use of placebo, or their risk of infection. In Guinea, where there are 39 local languages, communication can also be very challenging. A participant noted that Sierra Leone has done several national knowledge, attitudes, and practices surveys to help inform a robust set of communication activities.

Awunyo-Akaba suggested developing clear fact sheets about preventable diseases, translated into local languages. Preventable diseases have been somewhat forgotten; for example, few frontline health workers have seen a case of diphtheria. Mothers know that their children have received all of their immunizations, but they do not actually know what the child was immunized against. Even the average NGO worker who works to create demand for immunization cannot explain the symptoms of these diseases and the basic actions to take if one of these diseases is suspected. Fact sheets would help to guide those who educate and interact with the

community (including the children, who are often called on to read and interpret for their illiterate parents).

Hall observed that communication and social mobilization in crisis situations such as the Ebola outbreak are often one-directional, with no feedback from the community. This is a huge problem, she said, because in many cases the community simply cannot take the action described in the information given (e.g., there may be no safe, trusted place to take people for isolation, and no burial teams to collect loved ones). The concept of one-way communication without matching service delivery is not likely to be successful, she said.

5

Convergence of Regulatory Expectations, Review, and Approval

Participants discussed the need for regulatory convergence and enhanced global regulatory capacity to be able to deploy new products quickly across multiple countries, each with their own regulatory systems and regulations. (Highlights and main points are summarized in the box below.)

Highlights and Main Points Made by Individual Speakers and Participants[a]

- Harmonization of regulatory processes and regulatory science standards among global regulatory authorities is key to being able to more effectively and rapidly assess complex products and define acceptable levels of risk in global public health emergency situations. (Eichler, Hamburg)
- Regulatory coordination is a core component to meaningful action in a public health emergency, given the often limited clinical trial capacity (population to study, and clinical sites) and limited window of time for study. (Eichler, Hamburg)
- Participants discussed actions to take now, ahead of the next crisis, to enhance regulatory convergence, including preapproval of clinical trial designs and protocols, development and approval of prototype or plug-and-play platforms and capabilities, building clinical trial infrastructure, and negotiating agreements for data sharing among authorities. (Eichler, Hamburg, Pfleiderer)

- Pharmacovigilance was highlighted as an important part of an early access framework, for all products used in an emergency. (Chua)
- Standards and regulations for personal protective equipment (PPE) are evolving and vary across countries, leading to confusion about differences that can affect selection and use. (Colton)

[a] This list is the rapporteurs' summary of the main points made by individual speakers and participants and does not reflect any consensus among workshop participants.

COORDINATION, HARMONIZATION, AND CONVERGENCE

Infectious diseases do not adhere to national boundaries, and countries are obligated to work together in a more coordinated and streamlined way in regulating products to treat these diseases, Hamburg said. The Ebola crisis was marked by pressure to ramp up product development and provide access as soon as possible, and by frustration that products were not already available, given that Ebola had long been established as both an infectious disease concern and a potential threat to national security. Heated debates centered around the level of evidence required, the criteria for scientific study, the approach to clinical trial designs, and the nature of ongoing oversight needed for product development in the thick of the crisis.

Hamburg emphasized the need for streamlining processes, including decreasing bureaucratic and logistical complexities, better sharing of data, aligning across jurisdictions regulatory expectations of companies and the scientific community in terms of the burden of proof for product review and approval, moving toward common data and evidence standards, and advancing regulatory science (i.e., identifying gaps and developing the knowledge and regulatory tools necessary for more streamlined oversight). Working together, Hamburg said, global regulatory authorities will be better able to meet expectations in terms of scientific review, more effectively share information about advances in science and emerging technologies, and develop more flexible approaches to assessing complex products and defining acceptable levels of risk in public health emergency situations. Regulatory coordination is vital in a public health emergency to ensure meaningful action, especially given the often limited population to study or time sensitivity. Working together more effectively also helps to ensure quality and safety, Hamburg noted, citing the prevalence of fraudulent products and inappropriate use of products in public health emergencies. During the Ebola outbreak, for example, the U.S. Food and Drug Admin-

istration (FDA) helped to prevent governments from purchasing products that had no proven value. She also suggested that authorities also need to work together to support manufacturing capacity. Hamburg highlighted areas where concrete advances could be made now, ahead of the next crisis:

- pre-positioning clinical trial protocols and templates;
- building clinical trial infrastructure, including training and resources;
- developing prototype or plug-and-play platforms and capabilities that can be quickly built on;
- negotiating agreements for information sharing; and
- creating mechanisms to fast-track development and approval of important new diagnostics.

Hamburg highlighted the International Coalition of Medicines Regulatory Authorities (ICMRA) as an activity geared toward enhancing global regulatory convergence and capacity.[1] This is an executive-level coalition (comprising heads of medicine regulatory authorities) committed to providing umbrella leadership to ensure sustained critical activities and to developing a global framework for increased convergence and more coordinated action and accountability of the global regulatory community (acknowledging that each authority will always be accountable to its sovereign national laws, and there will always be differences in approaches and capabilities). Hamburg added that there are major activities under way to strengthen regulatory capacity in developing economies. Countries with immature regulatory systems are starting to produce important medical products, or components of medical products, that could potentially put all of us at risk if there is not appropriate regulatory oversight and coordination, she said.

Convergence on Regulatory Content and Process

Eichler said that, even though regulators have the same overall goals, there are many different actors and often a divergence of outcomes. There are costs and risk associated with nonconvergence among regulators and other decision makers. Different evidence standards, for example, lead to opportunity costs (e.g., developing a product for a global market might require one study for regulator A and a different study for regulator B, etc., which ties up capital that could be used for other innovations). Multiple assessments of priority or probability of success can lead to uncoordinated competition for clinical trial participants and trial sites, resulting in delays in bringing products to market. Differing regulatory procedures also affect

[1] For more information on ICMRA see http://apps.who.int/medicinedocs/documents/s21800en/s21800en.pdf (accessed October 30, 2015).

timelines and opportunity costs. Different outcomes (e.g., market authorization in one country or region, but denial in another; product licensed, but not funded or reimbursed) can lead to delayed or unequal patient access to products, as well as political tensions.

Regulators can to help minimize these costs through regulatory convergence on both content and process. Convergence on content includes, for example, alignment on how to balance speed, feasibility of studies, and affordability of product with quality, validity, and robustness of information. In order to have content convergence there is a need for agreement on the kind of evidence needed. Other content areas include agreement on outlines of study protocols; development of bridging authorizations; flexible regulatory tools to give legal certainty to manufacturers to deploy products in countries of need; and building clinical trial infrastructure in country. Convergence on process involves aligning how interactions with product sponsors are handled from beginning to end, and across authorities. Eichler suggested that timelines could be shortened by undertaking some processes in parallel rather than serially (such as product assessment by the European Medicines Agency [EMA], the World Health Organization [WHO] prequalification, and local authorization from the country where the product will be used).

It was discussed whether FDA and EMA could agree on an evidence threshold under which products would be ready for human use under an emergency use authorization (EUA), and whether such guidance could be codified to perhaps give industry more confidence to invest in bringing these medical countermeasures (MCMs) along in development. Hamburg responded that FDA and EMA have regular collaborative meetings, called clusters, across a number of product and disease areas. These clusters look at shared issues in the product review process (e.g., use of biomarkers, clinical trial design), so there is no reason why it could not be discussed. Eichler agreed and added that the legal framework provides for a great deal of flexibility. Revision of the overarching framework is not needed, he said; rather, there is a need for agreement on how to apply it, and how to be more predictable in its application.

A Dynamic Regulatory Environment

Pfleiderer also remarked that convergence of regulatory principles is essential. For nonemergency vaccines and medicines, there is a well-structured pathway from development to testing to licensure to use. In a pandemic situation, however, steps might need to be done in parallel, but the product must still be well tested and well defined. Risk assessment is dynamic, and the benefit–risk ratio of a product is situation dependent. The worse an epidemic situation is, the fewer data are needed in order to con-

clude a positive benefit–risk ratio, he said. For a milder emergency scenario, more data are needed in order to come to the same conclusion. Risk–benefit analysis takes into account whether products are for therapy or prophylaxis, efficacy data, safety data, and the opinion of stakeholders' representation. The regulatory tools applied in an emergency situation are flexible (e.g., to address situations where there is no time for data generation).

The European Union (EU) pathway for product approval is similar to that of the United States, but the language and legal provisions are different, Pfleiderer noted. EMA tools to approve products that are urgently needed include early approval pathways, and early access options for select populations. A scientific and regulatory framework that would allow licensure of candidate Ebola vaccines, for example, could base approval on animal studies (e.g., the U.S. Animal Rule), immunologic markers predicting efficacy, a combination of data sets (e.g., a comparative analysis of animal challenge data and human data), or efficacy data. A dynamic regulatory environment allows for use of incomplete data sets early in the outbreak, calling for full data sets as the disease burden wanes. From scientific, regulatory, and economic perspectives, Pfleiderer added, it is not possible to start from scratch every time another crisis occurs. Platform approaches, and associated regulatory guidance, need to be further considered and developed for application in other urgent product manufacturing scenarios.

Regulatory Capacity Building in Developing Countries

Mike Ward, Coordinator, Prequalification Team Essential Medicines and Health Products at WHO, emphasized the importance of capacity building for the national regulatory authorities in affected countries, and where epidemics or pandemics would be predicted to take place. These regulatory authorities are confronted with incomplete data sets, rolling submissions, complex clinical trial protocols, and changing strategies in the face of a changing epidemic profile. Many of these regulatory authorities have immature regulatory systems and, in many cases, have little or no experience with clinical trial assessment in a routine situation, much less a crisis situation. Ward relayed that some of the agencies ask for the assistance of WHO because they do not know how to confront scientific issues arising when a plethora of products or compounds are submitted to them (e.g., whether to authorize compassionate use, limited clinical trial, or other options), let alone from a sheer workload perspective. Scientifically and ethically, he said, these countries want to do the right thing.

Leveraging the Capacity of Other Regulatory Authorities

Raymond Chua, Group Director at the Health Sciences Authority, Singapore, explained how Singapore uses a very streamlined process that leverages other countries' regulatory approvals. The Health Sciences Authority facilitates routine national stockpiling of medicines and vaccines for emergency situations according to usual registration processes, and within usual targeted timelines. Expedited review to facilitate access to critical unregistered medicines and vaccines during emergency situations can be completed within several days, and conversion of a registered prepandemic vaccine to a pandemic vaccine (via a strain change) can be completed in 1 day. Chua explained that the Health Sciences Authority uses a confidence-based approach for evaluation of new drugs and vaccines to be registered in Singapore. If there has been no prior approval of a product by any regulatory authorities, a full dossier review will be done, taking as much as 270 working days. If the product has been approved by any regulatory agency, an abridged dossier containing full quality data and abridged clinical data is reviewed, taking about 180 working days. If the product has been approved by two reference agencies,[2] evaluation of a verification dossier containing the reference agency assessment report is completed in about 60 working days. A similar approach is used for diagnostic kits that are regulated as medical devices. Chua suggested that this could be a model for a global harmonization framework to bring products to patients quickly in an emergency situation. If a product is approved for use by a leading regulatory authority in collaboration with WHO experts, then other authorities could use that approval to allow early access in their own countries without going through a long regulatory process. Chua emphasized post-market surveillance as an important part of an early access framework, and stressed the importance of collecting safety signals or adverse events at a global level.

Yamada expanded on the possibility of an international organization of the major regulatory agencies agreeing on certain parameters and then, in an emergency, one would review a product and all others would accept that review. He acknowledged that there are some critical issues on clinical trial design for which there is not currently interagency agreement (e.g., use of adjuvant, and trial arms/comparators). Eichler responded that no country wants to give up its sovereignty, and that it took the EU almost 40 years to implement the current system of one centralized review that is accepted by all member states. He was hopeful that it could be done, but said that it will take time. Chua said that Singapore has been working with different regulatory authorities on ways to pool resources and share

[2] Reference regulatory agencies include Australia Therapeutic Goods Administration, EMA, FDA, Health Canada, or UK Medicines and Healthcare Products Regulatory Agency.

work. For example, a consortium between Australia, Canada, Singapore, and Switzerland works together on parallel review. One submission goes to the four regulatory authorities, a working group considers the application, and approval is issued by the four authorities simultaneously. Hamburg said that this is something that needs to be first undertaken in day-to-day interactions, working together, learning to share information, and developing trust.

Ward noted that there is interest in regions of Africa on joint reviews of products. There have also been two instances thus far of parallel processes, where the WHO prequalification process was done in parallel with joint reviews by the East Africa community regulators.[3] Ward said that AVAREF played a key role during the Ebola crisis in helping to accelerate the scientific assessment of Ebola vaccine trials by facilitating a partnership approach to assessment.

Evolving PPE Standards and Regulations

Since the severe acute respiratory syndrome (SARS) outbreak, many countries have put standards and regulations for PPE in place, especially for respirators, and they are all different, Colton said. In some cases, people who have jurisdiction or influence over selection of PPE do not understand the differences between the standards, which affects their selection and use. For example, during the SARS outbreak, a recommendation was made for a product that met the U.S. standard, which led to the world demanding that particular product, resulting in outstripped supply. It took some education by WHO about the differences between the EU and U.S. standards to establish that other products could be similarly effective. He added that there is an International Standards Organization effort under way to standardize or harmonize the performance of the requirements for respirators.

[3] Though not presented at the workshop, other key initiatives in joint regulatory procedures include Article 58 of Regulation (EC) No. 726/2004 among WHO, EMA, and national regulatory authorities. For more information on Article 58, see http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000157.jsp (accessed November 13, 2015).

6

Manufacturing, Stockpiling, and Distribution

Research and development is not completed until whatever has been developed can be successfully manufactured and deployed, Yamada said. Manufacturing of products for emergency responses can be complex because the products are often for problems that have not yet occurred. There are decisions to be made regarding how much to produce, and at what cost. The cost of manufacturing vaccines is quite high, and is very much dependent on volume (i.e., the more doses made, the lower the cost per dose). Decisions such as whether to use adjuvant or not in global pandemic influenza vaccines can significantly affect manufacturing capacity. Issues on the ground can affect supply chain or deployment, Yamada said. Another critical issue is who receives an intervention first in an emergency situation, especially when it takes time to produce. Yamada noted that, in the case of pandemic influenza, those who got the vaccines first were those who could pay for them, not necessarily those who needed them most. When vaccine manufacturing becomes nationalized, as happened with pandemic influenza vaccine, the output from each country's manufacturing facility serves that nation first, before any doses are exported. This creates difficult moral and ethical dilemmas, should the global need be greater than the national need. Participants discussed needs and gaps in current manufacturing practices as they apply to the production of medical products for use in public health emergencies, and approaches for delivery and deployment of products that are manufactured outside of the affected region. (Highlights and main points are summarized in the box below.)

Highlights and Main Points Made by Individual Speakers and Participants[a]

- Research on manufacturing processes could fill significant and urgent gaps in knowledge about how to supply needed products. For drugs, a switch from batch to continuous manufacturing approaches could benefit both routine and emergency production. For multipurpose solutions such as platform technologies, it is possible that process development, validation of the scaled-up commercial process, and regulatory approval of the platform could be completed in advance of a crisis, potentially facilitating rapid "plug-and-play" manufacturing. (Hamburg, Venkayya, Yamada)
- Participants discussed the logistical and financial challenges of maintaining spare or idle manufacturing capacity for emergency use. One approach is to establish a network of manufacturers (e.g., through partnerships with companies, contract manufacturing organizations, and publicly funded infrastructure) that could rapidly scale up production of products. (Ella, Marks, Venkayya, Yamada)
- Stockpiling is not restricted to final, filled product; product can be stockpiled at an intermediate manufacturing step for finishing when needed (e.g., bulk vaccine stocks), potentially saving space and extending expiration. (Ella, Hall)
- Those at greatest risk, and with most need, are often those with the least access to care and interventions (financially and geographically). Equitable access frameworks that are defined before the next crisis could accompany and inform medical product development. Nationalizing stockpiles can create unnecessary scarcity of products for those most in need. (Hall, Ripin, Venkayya, Yamada)
- Better demand forecasting could create much-needed improvements. Participants discussed the difference between need (number of cases) and demand (what the health system actually has the capacity to deliver), and the potential of scenario-based planning. (Hall, Venkayya, Yamada)
- The local community is not only a beneficiary but also a partner in the delivery of care. Deployment of products can include community care workers, lay providers, and untrained health workers. (Ripin)

- A broad base of support could reinforce the supply chain spectrum, from international air freight service to local trucking services. Also discussed was the critical role of the international military in deployment of facilities, services, and capabilities in a crisis, and local armed forces in supporting logistical and operational functions. (Hall, Pauwels, Yamada)

[a] This list is the rapporteurs' summary of the main points made by individual speakers and participants and does not reflect any consensus among workshop participants.

POLICY PERSPECTIVE

Some of the most significant global manufacturing capacity building and stockpiling efforts in the past several decades began with the preparations for pandemic influenza in the early 2000s, following the emergence of H5N1 influenza as a potential pandemic threat. Venkayya said that political leadership of countries around the globe recognized the potential for a health catastrophe to set off a cascade of events affecting every element of society. He referred participants to the U.S. National Strategy for Pandemic Influenza and the associated Implementation Plan.[1] The strategy lays out the key principles around preparedness, response, communication, and other planning for a pandemic, including engagement of all segments of society. The implementation plan, which Venkayya noted is still being followed, outlines over 300 actions for the departments and agencies across the U.S. government that would have a role in a pandemic response and includes guidance for state and local authorities, and for individuals and their families. At that time, he said, the concern was that existing vaccine production capabilities would not be able to keep up to meet the demands of a second wave of infection, as was seen in the 1918 pandemic.

Manufacturing and stockpiling targets for 2006 outlined in the U.S. strategy and plan included domestic vaccine production capability to supply enough doses for the entire American population within 6 months of the declaration of a pandemic, stockpiling prepandemic vaccine to immunize 20 million people, and antiviral drugs to treat 75 million people, with a domestic stockpile of 6 million doses for containment of an outbreak. A $7 billion budget was put forward, half of which was dedicated to enhancing vaccine capacity and developing new vaccine technologies (De Gregorio and Rappuoli, 2014).

[1] See http://www.flu.gov/planning-preparedness/federal/index.html for these and related documents (accessed October 30, 2015).

The pandemic influenza model is not necessarily what is needed for emerging infectious diseases, Venkayya said, but it is a good starting point. For pandemic influenza preparedness, the changes in the ecology of the viruses in both the human and animal reservoirs are well understood, and there is massive global vaccine production capacity for seasonal influenza that could theoretically be repurposed toward pandemic vaccine production. This is not the case, however, for emerging infectious diseases. The challenge is how to deal with the "unknown unknowns."

Venkayya referred participants to the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) strategy and implementation plan,[2] which details what the U.S. government is doing to develop and stockpile agents to address both known threats for which it is unknown if, when, or where they will become a pandemic (e.g., Middle East respiratory syndrome [MERS]) and completely unknown threats. Experience with pandemic influenza and other outbreaks brought to light some of the challenges of manufacturing and stockpiling for a potential emergency situation (see Box 6-1).

Prioritization (who is treated first in an emergency when the supply of commodities is limited) is one of the toughest issues to resolve, Venkayya said. As an example of scenario-based planning and prioritization, Vankayya said that in 2007, the U.S. government published guidance for who would receive pandemic influenza vaccine first.[3] This was a very hard, but necessary, set of discussions, Venkayya said. He continued that in an actual pandemic these decisions will be revisited, but they serve as a good starting point.

Priorities for Preparedness

Venkayya emphasized the need for a framework for global ongoing emerging infectious disease risk assessment, and collective agreement on medical countermeasures (MCMs) prioritization, target product profiles, and supply requirements. He reiterated support for designation of accountable parties and development of multipurpose solutions such as platform technologies. Venkayya also called for development of global, platform-specific concepts of operations for scaling up manufacturing using a network of manufacturers, contract manufacturing organizations, and publicly funded infrastructure. Predetermining the legal, regulatory, and policy

[2] See http://www.phe.gov/Preparedness/mcm/phemce/Pages/strategy.aspx (accessed October 30, 2015).

[3] See http://www.flu.gov/images/reports/pi_vaccine_allocation_guidance.pdf (accessed October 30, 2015).

BOX 6-1
Manufacturing and Stockpile Considerations

Product Development and Stockpile Priorities

- known unknowns versus unknown unknowns
- prioritization of threats once identified
- a "one bug–one drug" approach is not feasible; broad-spectrum or platform approaches are needed
- impractical to stockpile MCMs for large proportions of world population
- challenge of engaging industry given uncertainty of threat and market

Manufacturing and Logistics

- different products require different manufacturing platforms
- infrastructure, experience, and time to bring new capacity online for biologics (i.e., vaccines)
- uncertainty of demand
- shelf life of stockpiled products necessitates ongoing investment (e.g., maintaining/funding a warm manufacturing base to produce large quantities of pandemic vaccine)

Policy/Access

- regulatory and legal frameworks
- ensuring equitable access to MCMs
- prioritization of populations to receive limited-availability MCMs
- policy maker/public appetite for investing in "insurance policies" for potential unknown health threats

SOURCE: Venkayya presentation, August 20, 2015.

framework that will support swift evaluation, licensure, and deployment of novel medical products is also essential, he said.

Ella suggested that small-scale contract manufacturing be set up for 10 candidates that are predicted to be likely to cause a pandemic. Planning, quality control standards, and stability studies can all be done ahead of time so that manufacturing can be started when needed. The manufacturing capabilities are there, he said, and the lines can be readily switched from one product to another. The prioritization of 10 potential candidates for which the global community can prepare is still needed.

Equitable Access

Outbreaks have the greatest impact on the most vulnerable populations, which are the least likely to have access to critical health infrastructure and interventions. Addressing inequity is most difficult in a crisis, when policy makers and political leadership are incentivized to act strictly in their own national interest, and it is extraordinarily difficult for a political leader in any country to give away potentially lifesaving tools to other countries. The time to plan and put the necessary access framework in place is now, Venkayya stressed, right after an emergency and before the next one. He added that a global access framework should be a required part of a multilateral product development strategy.

Venkayya said that for influenza vaccine, the World Health Organization (WHO) has established a framework to ensure that industry commits a certain proportion of its capacity to developing countries. WHO asks influenza vaccine manufacturers to make cash donations on the basis of their annual sales of seasonal influenza vaccine, to donate vaccine, to commit to providing a certain amount of vaccine at an affordable price, or other options. This will not meet the full need in developing countries, but it is an interesting first step, he said, adding that the approach needs to be expanded to other threats. Venkayya noted that fulfillment of obligations must occur in real time (e.g., a 10 percent commitment means that 10 percent of every month's production goes to the stockpile; a manufacturer should not hold off and give the last 10 percent of production, many months later, to the stockpile).

Hall said that governments nationalize supply from time to time, even when there is no outbreak. This is less of an issue when there is a diverse supplier base. She suggested that WHO should have the responsibility to decide where available vaccines should be deployed based on epidemiology, and it should be made public if countries nonetheless decide to nationalize their supply. Yamada also raised the issue of whether companies should be required to commit product to supply clinical trials.

MANUFACTURING CAPACITY

Yamada pointed out that dedicated pandemic manufacturing capacity would be sitting idle most of the time. Ella agreed and said that large companies can sustain this, but it will be very difficult for small and medium-sized companies to sustain idle production capacity. Marks explained that, as part of a multipart deal between GlaxoSmithKline (GSK) and Novartis, half of the space in one of the GSK facilities is being dedicated to creating vaccines for emergent uses. This is an end-to-end unit with capabilities from vaccine design through manufacturing. The details are still in develop-

ment, but this dedicated facility is embedded in a research and development organization, and is not an isolated piece by itself, affording the ability to respond when needed. Venkayya said that the Biomedical Advanced Research and Development Authority (BARDA) has established partnerships with three companies that have vaccines and biologics manufacturing and fill finish capabilities so that, once a vaccine is developed, BARDA can quickly contract with those companies to scale up the manufacturing of that product. These sites are in use for other products that the companies are making, but they are available to BARDA should the need arise. Stoffels said that production technology solutions can enable greater output in smaller spaces, allowing for production capacity that can stay idle because it will be only, for example, a $50 million plant instead of a $500 million plant. Yamada pointed out the need for government funding to subsidize such capacity. Mahmoud raised the concern that every vaccine is different, and it is not as simple as making vaccine X one day and vaccine Y another. He suggested that the focus should instead be on expanding the global capacity to make vaccines. Levine pointed out that there are other limiting factors and highlighted the importance of developing new technologies. The reliance on egg-grown influenza vaccine, for example, is affected by the current outbreak of avian influenza, which has led to mass mortality in chickens.

Hamburg said that more sophisticated, more efficient, and higher-quality manufacturing processes are needed for drugs than the current batch-processing approach. Continuous-manufacturing approaches would benefit routine production and would be highly beneficial in situations where rapid scale-up is needed in response to emergencies. New technologies to advance manufacturing of therapeutics is greatly needed, especially with biologics becoming more prominent. Yamada lamented that research on manufacturing technologies is not funded by the National Institutes of Health, and industry does very little research in this area. He and Hamburg agreed that this is an area of national need.

David Ripin, Executive Vice President of Access and Malaria and Chief Scientific Officer of the Clinton Health Access Initiative (CHAI), discussed on-demand manufacturing as an alternative to stockpiling. He also noted the potential of the continuous-manufacturing approach suggested by Hamburg, but said that facilities designed for continuous production of a given product tend to be less suitable for other general use. He observed that, for small-molecule drugs, there is a massive capacity globally to make active ingredients and tablets in multifunctional facilities. He pointed out that the world is moving toward just-in-time supply, and the capacity to switch over a manufacturing line to respond to an emerging need relies on the availability of buffer stocks and other supplies. A just-in-time manufacturing approach could also create vulnerabilities if switching a line to

manufacture the new product leads to a stock shortage of other key products that might also be needed. Ripin said there is a financing cost to suppliers carrying a larger stock of the products they sell, and suggested that programs should be paying that cost as a mechanism for reserving some of the available multifunctional capacity.

Pauwels emphasized the complexity of building manufacturing lines for diagnostics. He added that most diagnostic companies are developing products for the developed world and do not take issues such as availability of cold chain into account.

STOCKPILING LOGISTICS

Hall said that the United Nations Children's Fund (UNICEF) has developed capacity in supply and logistics to meet the needs of its own programs in 190 countries, as well as to support requests for assistance from governments for their own national procurement programs. UNICEF stockpiles around $220 million worth of supplies in 202 locations across 63 countries, and around one-third to one-half of the stockpile is for emergency response to meet UNICEF's commitments to support governments in UNICEF's programmatic areas. These commitments guide what is put into inventory at the country level, while a planning process with the UN country team, nongovernmental organizations, and the government defines who will stockpile what, Hall explained. The UNICEF Global Supply Warehouse in Copenhagen is the world's largest humanitarian warehouse. Hall noted that UNICEF does not stockpile any vaccines, instead working with companies to stockpile on UNICEF's behalf. This is due to both regulatory issues and the irregularity of demand. UNICEF does inventory medicines, and is good distribution practice (GDP) certified and inspected by the Danish Medicines Authority.

Hall observed that the humanitarian system excels at preparation and rapid response, identifying target populations and investing in inventory for identified risks. She noted that the humanitarian and public health sectors are very segmented in their planning, and she suggested there could be more sharing from a stockpiling and deployment perspective. Whether it is UNICEF, a company, or a government, anyone carrying inventory must weigh the risks and decide on the "right" amount to store, she said. Hall concurred with Venkayya that there needs to be ownership of the process, and a plan behind it that accounts for the risk being taken. She suggested considering not only final, filled product for stockpiling, but also making agreements for stockpiling different stages of product completion. Ella agreed and suggested that storing bulk vaccine takes less space and extends shelf life. For most manufacturers, bulk manufacturing is the easier step and the limitation is fill capacity. Vaccine could be stored in bulk in country,

and filled as needed by a contract fill-and-finish organization. He noted that there are some issues of legal liability that will need to be addressed.

Ripin said that the ability to effectively and affordably maintain a stockpile relies on developing products that are stable and storable. He added that U.S. Department of Defense (DoD), working with U.S. Food and Drug Administration (FDA) and others, recognized that the shelf-life of some stable products in the Strategic National Stockpile (SNS) could be extended continuously, deferring the need to procure replacement product. FDA comprehensively tests and analyzes drugs and other medical material in the SNS. Products that pass testing are granted extended expiration dates, but they must undergo ongoing testing to monitor continued shelf life. Products that fail testing at any time are destroyed.

SUPPLY CHAIN AND DISTRIBUTION

Supply chain encompasses everything it takes to get the product to the point of treatment, said Ripin. Recognizing the challenges faced in other areas will help inform product design, which Ripin said also includes studies of how the products can be most effectively deployed.

Lessons from Other Responses

A key lesson from the Haiti earthquake response, Ripin said, is to work with locally present groups. The philosophy of CHAI is to augment the capacity of the groups already present in a location. In Haiti, one of the strongest emergency relief partners in place was Partners In Health, which asked CHAI to manage supply for them, and that was the unmet need that CHAI worked to fill. Ripin suggested that community engagement is critical. It is not just a matter of educating the community, he said, but the community can also be a partner in delivering care. The delivery and deployment of products will include community care workers, lay providers, and untrained health workers. The Ebola response again demonstrated the importance of working with groups that are locally present.

Ripin also said to put local government in a leadership role, and to give the local leaders the tools and support they need to deliver care. There is a large infrastructure of health care delivery capacity in developing countries, but, Ripin said, we will have to accept that it might not look exactly the way that we want it to, and some of the care is not going to be delivered in the same way that we would necessarily choose to deliver it. Especially critical for international partners, Ripin said, is to be flexible and humble, and do whatever is needed, even if it is not necessarily the most attractive part of the response.

Ripin reiterated the point that there is a higher probability that a pan-

demic will emerge in locations that have more fragile health systems. As such, it is important to plan for products that can be delivered within that context. It is also important to remember that when a new infectious disease emerges and takes center stage, existing disease challenges still persist in the background and can have unrecognized costs. For example, malaria did not subside during the Ebola response. Ripin suggested that many cases of malaria likely went untreated during that time as people were fearful of going to clinics.

Supplying the Basics

Much of the discussion of stockpiling and rapid delivery has focused on vaccine and therapeutic products, but Ripin stressed the need to also ensure that basic supplies are in place. Regardless of the known or unknown threat, the global health community ought to have sufficient stocks of surgical gloves, basic masks, and basic protective garb, Ripin said. Even basic medical products such as intravenous fluids were a challenge to procure during the Ebola outbreak, he said. Earlier in the workshop, participants discussed the local stigmatization of patients and care providers during the Ebola crisis, but Ripin said that global stigmatization had a significant impact as well. As mentioned by Chan, closing borders and restricting travel was counterproductive and affected the supply chain of critical products, both interventions and basic supplies. Ripin noted that, despite the incredibly high mortality from Ebola at the beginning of the epidemic, only 2 of the last 14 cases of Ebola in Liberia died (one before getting to a health center and the other shortly after). The 12 that survived did so without any of the potential new investigational medical products (e.g., ZMAPP), and Ripin attributed their survival to a better care experience and access to basic medical supplies and diagnostics.

Delivering Supplies in a Crisis

UNICEF's support to national Ebola programs helped to provide supplies for primary health care facilities, treatment and holding centers, and community care centers, as well as supply kits for households and schools. The composition of what UNICEF provided to each service delivery point varied by country. Hall pointed out the iterative nature of the supply needs, requiring supply chains to adapt and repurpose products as the program evolved.

In delivering supplies in Sierra Leone, Hall said, the definition of the need was the most challenging part of the supply chain because programs and facilities did not know what was needed. This included deciding which personal protective equipment (PPE) components were suitable for which

service delivery locations (e.g., Ebola treatment units versus community care centers, which Hall noted often became places of triage and early isolation due to bed shortages in the treatment units). Procurement was one of the easier parts of the supply chain, Hall said. Once they were able to forecast the PPE need, UNICEF increased its PPE suppliers from 2 to 17. Because UNICEF has established relationships, delivery and clearance was not an issue even when trade was restricted. Hall said that UNICEF led an air bridge, booking at least one charter flight per week into each of Guinea, Liberia, and Sierra Leone. The logistics of moving the supplies to all the service delivery locations was enormous, Hall said. UNICEF continually assessed consumption levels and aggregated the data to develop country-specific demand scenarios.[4] She noted that Sierra Leone was well positioned for distribution efforts down to the district level as a result of a previous government health care and health supply chain initiative; however, this was not the case in Liberia and Guinea. Hall added that it is not just about delivering a supply. Health workers and burial teams need to be trained in use of the supplies, such as PPE. Awunyo-Akaba also stressed the need to consider the country-level issues for supply chain, such as the difficulty of terrain.

Yamada highlighted the many other players that have a critical role in a supply chain and that could have a significant impact on the rapidity and the cost of addressing a global emergency. These include, for example, international air freight service, trucking service, fuel suppliers, and others. Hall noted that for many of UNICEF's humanitarian responses they have received donated air cargo. In the case of Ebola, they prebooked 10 charter flights over a 3-week period in order to negotiate the price down. Pauwels, Yamada, and others also discussed the critical role of the international military in deployment of facilities, services, and capabilities in a crisis. Armed forces in the impacted countries were also important in supporting logistical and operational functions.

FORECASTING DEMAND

Hall emphasized the need to consider demand scenarios when discussing stockpiles and supply. Yamada said that predicting demand is difficult because it depends on pathogen-related factors such as the nature of the illness, the rate of spread, and the case fatality rate. But perhaps there could be predictive models of how intervention with MCMs would be done for different pathogens. Ripin pointed out the need to distinguish need from demand (i.e., what the health system actually has the capacity to deliver, regardless of the number of cases). To some extent, the maximum capacity

[4] See http://www.unicef.org/supply/index_75984.html (accessed October 30, 2015).

of health systems to deliver care is predictable and might represent more of the true demand (as opposed to the need, which is dependent on the rate at which an epidemic is expanding).

Venkayya said that the SNS uses a scenario-based planning approach. The detailed analysis of numbers of cases, geographic distribution, severity of illness, and the comprehensive set of resources that would be necessary to take care of individuals in a chemical, biological, radiological, or nuclear event was very helpful because it exposed gaps in the upstream supply chain (e.g., for ventilator tubing, antibiotics, and normal saline). Venkayya stressed the value of bringing together a core group of partners to do comprehensive scenario-based planning for multicountry true pandemic events. He noted that the Ebola outbreak was geographically limited, and there was relatively free flow of commodities. However, a multicountry MERS outbreak might result in some sporadic border closures, and there would be a significant demand for PPE and the raw materials necessary to make PPE, and there are innumerable places where the supply chain could come up short and the response would suffer.

Bell added that not fully understanding demand can be a barrier when countries are stepping up to make donations of products and supplies. There should be some way of identifying the need so that donations can be deployed in an efficient manner.

7

Critical Considerations for Facilitating Medical Product Research and Development

One way to be prepared for potential, but as yet unknown, pandemic events is to create platforms that could be deployed in responding to a broad array of scenarios. Drawing from the workshop discussions, Yamada applied a standard pharmaceutical company value-chain model to the discussion of key issues in facilitating more rapid, efficient, and successful medical product research and development for pandemic preparedness. He summarized the key takeaway messages from the discussions in the form of a strategic analysis map, collating ideas for the development of platforms that would drive stakeholder investment (i.e., incentives); product discovery (basic research); development (including clinical research); regulatory expectations, review, and approval; and manufacturing, stockpiling, and distribution (see Table 7-1). Insights from panelists Kilmarx; Stoffels; Glenda Gray, President and CEO of the South Africa Medical Research Council; and Robin Robinson, Director of the Biomedical Advanced Research and Development Authority (BARDA), and comments from participants during an open discussion helped to complete the strategic analysis map and highlight priorities.

DEFINING THE PRIORITIES FOR RESEARCH AND DEVELOPMENT

Yamada reiterated the concerns of many participants that there must be a process for prioritizing the diseases to be addressed first. The product discovery and development process is a long process, and it will be a disincentive to participate if the priority list changes every few years. Rex sug-

TABLE 7-1 Critical Considerations for Facilitating Medical Product Research and Development

	PLATFORMS	
Diseases/Priorities	Incentives	Discovery

• Categories
  o Diagnostics
  o Antibacterials
  o Respiratory viruses
  o Nonrespiratory viruses
• Prioritization methods
  o Look at CDC, BARDA, individual company lists and processes
• Advance priority platforms for tool (diagnostic, vaccine, drug, PPE) development
	• Self-driven approach is not continuously dependable
	• Early research investment by foundations and government (e.g., BMGF, Wellcome, NIH, MRC) provide "blue sky" funding
	• Development:
	  o Public–private partnerships (e.g., GHIT)
	  o Product development partnerships (e.g., TB Alliance, MMV)
	  o Prizes
	  o Insurance model
	• Health as part of the National Security Agenda; economic/ finance and security cabinets need to be on board
	• Multiyear commitments for funding
	• Delink money from utilization and effort from success
		• Drugs: academic research identifies potential targets, need to bridge the gap to development
		• Drug platforms: screen compound libraries/ repurpose existing compounds
		• Promising vaccine platforms
		  o Seasonal influenza cassette model
		  o RNA, DNA platforms
		  o AAV vectored
		  o Passive immunity
		• Diagnostics: rapid, point-of-care, low-cost (total cost), accurate
		• PPE: effective against agent and in anticipated conditions of use

CROSSCUTTING ISSUES

- Trust: regular communication among stakeholders in advance of crisis
- Community Engagement: to gain trust and support for development (clinical trials), distribution, and compliance; sociological and anthropological research can help identify approaches to engaging communities
- Ethical and Legal Framework: agreed upon IP/data sharing and liability standards
- Leadership: strategies will differ in routine versus emergency operations. In an emergency, the designated global leadership group should establish priorities for products to develop, test, manufacture, and distribute, to ensure efficient use of limited time/resources
- Communication: accurate information about the emerging disease threat, diagnosis, prevention and control, and available treatments including ongoing clinical trials and how they work. Communication is key across all the crosscutting themes as well as throughout the R&D chain
- Barriers: eliminate unnecessary process/policy barriers, foster sustainability across the research and development spectrum

Development	Regulations	Manufacturing	Distribution
• Differentiate between vaccine and drug trials • Results need to be interpretable • Vaccines: more flexibility for novel designs (e.g., 21-day delay control group) • Drugs: randomized controlled trial if possible, • How much data before going into a pivotal study? Be sensible and adaptable • Designated "traffic cop" that decides priority of trials • Clinical trial infrastructure/ capacity building needed	• Harmonization of processes and regulatory science standards • Preapproved clinical trial protocols, designs, platforms • Coordination and catalogue of activities required to ensure best use of limited clinical trial resources • Division/sharing of labor among global authorities; facilitated reviews during times of emergency • PPE: highly regulated with each country having own different standards • Clinical trial data transparency	• Research on more rapid and efficient manufacturing, especially for vaccines • Spare manufacturing capacity; system to make products for stockpiles • Spare pilot manufacturing for investigational clinical trial product (e.g., GSK BPO model) • Should not nationalize manufacturing capacity in times of crisis	• In-country expertise: community, NGOs • Role of military • Help from other industries: financial/ capability (e.g., freight/ transport, last-mile expertise) • Demand forecasting • Ethical construct for allocation of product

NOTES: This chart was presented by the workshop co-chairs at the workshop to highlight many of the main points of the workshop discussions and should not be construed as reflecting any group consensus. BARDA = U.S. Biomedical Advanced Research and Development Authority; BMGF = The Bill & Melinda Gates Foundation; BPO = biopreparedness organization; CDC = U.S. Centers for Disease Control and Prevention; GHIT = Global Health Innovative Technology Fund; GSK = GlaxoSmithKline; IP = intellectual property; MMV = Medicines for Malaria Venture; MRC = Medical Research Council; NGO = nongovernmental organization; NIH = U.S. National Institutes of Health; PPE = personal protective equipment; R&D = research and development; TB = tuberculosis.
SOURCE: Yamada and Freire summation of the workshop with input from participants during the final open discussion, August 21, 2015.

gested considering research priorities in four main categories: diagnostics, antibacterials, respiratory viruses, and nonrespiratory viruses. In splitting viral research into two categories, he explained that respiratory viruses have the potential for exponential spread that can cause public anxiety and paralyze the economy. Outterson highlighted the need for an inclusive global threat assessment that moves beyond the traditional silos (i.e., not just U.S.-focused, bacteria-focused, virus-focused, etc.). Freire noted that BARDA[1] has developed a list of priority diseases, and Bell suggested not only looking to the BARDA list as a starting point, but also looking at how the BARDA list was generated and considering whether a similar process for global diseases would be useful. Levine emphasized the need for constant surveillance for emerging pathogens to guide ongoing research and development. Kilmarx and Stoffels discussed the stratification of development priorities. For some products it might be critical to have a licensed product that is available and ready to launch. For others, the collection of preclinical data might be sufficient until the product is needed, at which point it would be ready for clinical trials. In the middle tier might be products for which phase I clinical trial data, and perhaps dose ranging studies, are desirable.

INCENTIVES

Pharmaceutical companies are motivated to participate, and are participating in many different ways, Yamada said. However, relying on self-driven research and development alone is not continuously dependable. One research incentive approach discussed was investments made by foundations and government in early, nontargeted research (sometimes referred to as "blue sky" funding). Public–private partnerships and product development partnerships were discussed as approaches to foster discovery and development, and the Japanese Global Health Innovative Technology Fund (GHIT) was reviewed as a model of how the public, private, and philanthropic sectors can come together to invest in products and technologies that advance health. Creatively structured prizes for product developers were discussed as a way to delink research and development costs from prices and revenues (similar to what has been done to foster the development of products to treat orphan diseases). The potential role of funding from insurance companies was also of interest, given that they factor risk into premiums. Marks observed that much of the discussion of incentives at

[1] BARDA supports the development and procurement of drugs, vaccines, and other products that are considered priorities for U.S. national health security, including chemical, biological, radiological, and nuclear (CBRN) accidents, incidents and attacks, pandemic influenza, and emerging infectious diseases. See https://www.medicalcountermeasures.gov/barda.aspx (accessed November 13, 2015).

the workshop had related to companies that are already involved in product development for emerging threats, but incentives are also needed to encourage entry by those companies that are not yet engaged (i.e., to reduce the barriers to participation).

Critical elements of government participation, Yamada noted, are the recognition that a global health crisis is a national security concern, and the support of the security and economic or finance cabinet leaders for the inclusion of health in the national security agenda. Gray added that science drives good distribution practice (Jaffe et al., 2013), and until the countries on the African continent understand this and invest in research and development, they will not become wealthy. Yamada also noted that any government investments to spur development must be multiyear commitments.

DISCOVERY

Investment in discovery is needed across the spectrum of drugs, vaccines, diagnostics, and PPE. Yamada stressed that funding for academic research is critical. Research in academia expands the understanding of mechanisms of illness and pathophysiology of infection and identifies potential vaccine and therapeutic targets. Marks pointed out the need to align academic grant awards and government contracts with national and global health risk priorities. Many workshop participants discussed vaccine platforms that could potentially be U.S. Food and Drug Administration (FDA) preapproved for use. Promising vaccine platforms discussed included the seasonal influenza vaccine platform, nucleic acid–based vaccines (RNA-based vaccines, DNA plasmid vaccines, and live viral-vectored vaccines), and vectored delivery of immunogenic antigen (e.g., adeno-associated viruses [AAV] vectored). Examples of therapeutic platforms discussed included a novel mechanism to confer passive immunity using an AAV vector, and high-throughput screening of compound libraries and repurposing of existing compounds. Research is also needed for new devices, including diagnostics and personal protective equipment. Yamada and Pauwels noted that diagnostics for use in global health crises should be inexpensive, rapid, accurate, and available at the point of care. Kilmarx noted, however, that some of the current rapid diagnostics used at the point of care are not particularly sensitive, which is of concern for a screening test, especially in the case of false-negative results. Research on PPE is driven by both the way each infectious agent is transmitted, and the anticipated conditions of use.

DEVELOPMENT

Several participants, including Yamada and Levine, emphasized the importance of differentiating between clinical trial design for therapeutics

versus vaccines. For approval of a therapeutic product, many workshop participants stated that a randomized controlled clinical trial is preferred. There must be interpretable evidence of efficacy and safety relative to a comparator (e.g., existing standard of care, placebo), and that comparator should not be a historical control, Yamada observed. Cultural and practical hurdles to performing a randomized controlled trial were also cited, however, throughout the workshop discussions. For vaccines, there is more flexibility for creative or novel clinical trial designs. Among the examples discussed were the Ebola ring vaccine trial in close contacts of Ebola patients, in which one group of participants was vaccinated immediately after exposure to an infected person, while those in a second group were vaccinated 21 days after exposure.

Yamada noted that the amount of data needed before a pivotal trial can be initiated, and the extent to which data requirements could be adaptable to the urgency of the situation, are topics that need to be addressed. Yamada and Awunyo-Akaba also mentioned the need for immediate investment in clinical trial infrastructure and capacity building, before the next emergency. Also, given the many different products being developed, and the limited capacity to do the clinical trials, especially when a limited number of impacted patients or trial participants are available, there needs to be a designated person or entity who has authority to determine the priority of the proposed clinical trials.

REGULATIONS

The workshop discussions highlighted the ongoing advantages that harmonization of regulatory processes and regulatory science offer. The concept of preapproved clinical trial designs and protocols was raised and discussed by Yamada and Hamburg, as well as the possibility of preapproval of vaccine platforms.

An important, and potentially contentious, issue is the concept of division of or sharing of regulatory labor and resources for product review during an emergency. Specifically, would approval by one country be sufficient to allow use of the product in other countries? Kilmarx emphasized that overall coordination and cataloging of activities is needed to ensure meaningful action in the face of often limited clinical trial capacity.

MANUFACTURING

Much of the discussion of manufacturing focused on the need to advance manufacturing technology. Yamada called for research on more rapid and efficient manufacturing processes, especially for vaccines. Another issue that was raised was the need for spare capacity and global capacity building,

both for the manufacturing and stockpiling of products, as well as spare pilot plant capacity for process development of investigational products. Models discussed included pharmaceutical manufacturers making portions of their capacity available, or creating a dedicated collaborative pilot manufacturing facility. Importantly, Yamada said, it is not just manufacturer capacity, but manufacturer knowhow and capability that need to be readily available. Yamada also emphasized concerns about countries nationalizing manufacturing capacity in times of crisis.

DISTRIBUTION

Distribution is a very complex process, Yamada said. Help is needed from people in country who know how to distribute in the area. In times of crisis, a broad base of support is needed, and additional assistance can come from the military, community, nongovernmental organizations, and other industries with last-mile delivery capabilities and expertise (Yamada suggested Amazon, Coca Cola, and FedEx as examples). Participants emphasized the critical role of accurate demand forecasting for successful distribution. The need for affordable pricing, particularly in regions such as Africa where prices of medical products are often set higher than in other countries, in part due to lower demand for products, was highlighted by Gray. There was also a call for attention to the ethical allocation of products. There is often misalignment between those who can pay and those at the greatest risk or with the greatest need. A global consensus for an ethical distribution construct is needed to ensure that the right drug is delivered to the right place at the right time, Yamada said.

8

Crosscutting Themes and Closing Remarks

Yamada highlighted six main themes[1] that emerged across the workshop discussions of the platform areas described in Chapter 7 (summarized in Table 7-1).

- **Trust among stakeholders** was discussed as an essential element of success in responding to a crisis. Building trusted relationships across sectors (public, private, and philanthropic), among organizations within sectors, and with governments and institutions in the developing world needs to start before a crisis strikes. In working to foster trust among stakeholders, it is important to remember that trust takes time to build and effort to maintain, and stakeholders can have diverse interests and goals when coming to the table.
- **Community engagement** is a key element of preparedness. The product, the remediation, and the patient all come together in the communities, Yamada said. Engaging a community requires an understanding of the sociology, politics, standard practices, and history of that community. Clinical trials for the development of vaccines and therapeutics need the support of all local community leaders (traditional, religious, administrative, political, and sociocultural leaders) to foster participation and enhance compliance. Once products are approved and available, they are only of use if they can reach the local community and are accepted by the

[1] These themes were presented at the workshop by Yamada and should not be construed as reflecting any group consensus.

patients, community leaders, and the larger community. The local community is also a partner in the deployment of interventions and the delivery of care.

- **Ethical and legal considerations** include issues such as patents, intellectual property, and data sharing; liability; and the general or blanket agreements and ethics assurances needed to conduct clinical trials. So that these issues do not act as barriers to a rapid collaborative response, Yamada said that the international community needs to come together around a legal framework and ethical principles that can be agreed upon (perhaps through treaties) during interepidemic periods and quickly implemented during emergencies.
- **Leadership** is essential in all areas of research and development. Leadership strategies will differ in routine versus emergency operations. It was discussed that in a public health emergency there is a need for a strong organizational system and a designated person or entity that will determine the priority of products to be tested in the face of limited clinical trial resources. This leadership structure should be established before the next crisis. Successful product development partnerships rely on leadership and accountability. It is also important to empower local leadership with the tools and support they need to deliver care to their people.
- **Communication** needs to take place at every step of the process. Local leadership and the public need to receive accurate information about the emerging disease threat, diagnosis, prevention and control, and available treatments including ongoing clinical trials and how they work (e.g., purpose, risks, benefits, and comparison groups), Kilmarx said. Awunyo-Akaba stressed the importance of also getting feedback from the community.
- **Barriers** to effective and efficient research and development of medical products for emerging infectious diseases were discussed across all steps in the process. The ability to continually learn and overcome barriers as they present will be critical for any plan to succeed. Rex highlighted the issue of sustainability as concern across the research and development spectrum. There is a common misconception, he said, that research and development is a tap that can be turned on and off: when something is needed, the tap is turned on and the results/products come out.

CLOSING REMARKS

Ceci Mundaca-Shah of the National Academies of Sciences, Engineering, and Medicine and Senior Program Officer for the Global Health Risk

Framework Commission, thanked participants on behalf of the Commission. She reiterated the dual purpose of the workshop, both as a product of the Institute of Medicine and as one of the pillars of evidence for the Commission in preparing its independent report and recommendations that will be presented at the World Health Assembly Executive Board Meeting in January 2016. Yamada thanked the participants and noted that the work of the Commission would also be informed by several consultation meetings with other government, academic, nongovernmental organization, and private-sector stakeholders.

A

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B

Workshop Statement of Task

GLOBAL HEALTH RISK FRAMEWORK: A WORKSHOP ON RESEARCH AND DEVELOPMENT OF MEDICAL PRODUCTS

An ad hoc committee will plan and conduct a 3-day public workshop that will provide a forum for relevant stakeholders to describe and provide input on the core needs and strategies to facilitate development of medical products to prevent, diagnose, treat, and protect from emerging threats such as global infectious diseases. The committee will define the specific workshop topics to be addressed, develop the agenda, select and invite speakers, and moderate workshop discussions.

The overarching objectives for the workshop include

- Gathering diverse perspectives of informed stakeholders to foster constructive discussion and facilitate the formation of collaborative solutions;
- Characterizing needs and gaps in current approaches to addressing global infectious disease outbreaks and other public health threats, and describing barriers to addressing those needs;
- Highlighting opportunities and potential approaches to improve the global system for addressing emerging threats;
- Documenting key successes and lessons learned from past global infectious disease outbreaks and other public health emergencies and how they may inform preparation and response to future outbreaks and emergencies; and

- Considering indicators and metrics that may be used to guide and assess the resilience of the global health infrastructure to future outbreaks and emergencies.

Speakers and workshop participants will be invited to describe and examine systems and approaches to discover and develop medical products to address emerging threats. The focus of the workshop will be on global systems and policy needs to foster communication, partnerships, and other strategies to advance medical product development. Workshop discussions will describe and examine the current state of approaches and infrastructure for research and development, barriers to the effective and efficient development of medical products, and potential strategies to address impediments to the research or development processes. The scope of medical products under consideration at the workshop will include therapeutics, vaccines, diagnostics and other medical devices, and personal protective equipment. Key areas for consideration may include

- **Product development:** describe current product development platforms; explore science and research needs, including needs for development of appropriate and effective regulatory science and evaluation tools;
- **Clinical development:** discuss clinical trials approaches, including clinical trial methods and ethics considerations around enrollment and access to developing products in an emergency;
- **Optimization for development:** explore incentives and infrastructure for product development, and conditions and needs for effective public–private partnerships and global/intergovernmental partnerships;
- **Regulatory review standards and systems:** address regulatory considerations, including approaches to global regulatory harmonization and regulatory systems capacity;
- **Manufacturing:** describe issues pertaining to supply chain management and product quality and integrity, and deployment of medical products;
- **Legal issues:** highlight key legal considerations including developer/manufacturer liability, distribution/sharing of biological samples, other patent/data exclusivity considerations, and sharing of clinical and clinical trial data; and
- **Indicators:** explore indicators to facilitate and measure success and advances in the face of new and emerging threats.

A summary will be prepared by a designated rapporteur based on the information gathered and discussions held during the workshop.

C

Workshop Agenda

August 19-21, 2015
Cheung Kung Hai Conference Centre, G/F,
William MW Mong Block, 21 Sassoon Road
Lecture Theatre 4
Hong Kong

The U.S. Institute of Medicine (IOM) of the National Academies of Sciences, Engineering, and Medicine will serve as the secretariat for an independent global commission that will conduct a study to recommend an effective global architecture for recognizing and mitigating the threat of epidemic infectious diseases. The Commission will receive input from four IOM workshops on governance for global health, financing response to pandemic threats, resilient health systems, and research and development of medical products, which will be coordinated.

This workshop will inform the Commission prior to the final release of its report by providing a forum for relevant stakeholders to describe and provide input on the core needs and strategies to facilitate development of medical products to prevent, diagnose, treat, and protect from emerging global infectious diseases. Speakers and workshop participants will be invited to describe and examine systems and approaches to discover and develop medical products to address emerging threats. The focus of the workshop will be on global systems and policy needs to foster communication, partnerships, and other strategies to advance medical product development.

The workshop will feature invited presentations and discussions that will describe and examine

- the current state of approaches and infrastructure,
- barriers to effective and efficient research and development, and
- potential strategies to address impediments to the research or development processes.

The workshop will focus on strategies to facilitate the development of medical products, including therapeutics, vaccines, diagnostics, and personal protective equipment. Key areas for consideration include product development, clinical development, optimization for development, regulatory review standards and systems, manufacturing, legal issues, and indicators relevant to medical product research and development.

The workshop is co-hosted by The University of Hong Kong and will be held on August 19-21, 2015. Participants will be invited from around the world to engage in dialogue and identify potential avenues for collaboration.

DAY 1

8:40a.m. **Meeting begins**

Welcome—Gabriel Leung, Dean, Li Ka Shing Faculty of Medicine, The University of Hong Kong
Welcome—Victor Dzau, President, National Academy of Medicine
Opening Keynote Lecture—Margaret Chan, World Health Organization (WHO)

SESSION 1: INCENTIVES AND DEVELOPMENT MODELS

Objectives:

- Review existing incentives, business models, and partnership approaches that support the research and development of medical products for emerging infectious diseases.
- Identify shortcomings in existing regulatory and financial incentives, and highlight promising ideas for improvements that can help advance the development of medical products for emerging infectious diseases.
- Discuss challenges to building and sustaining more effective business models and public–private partnerships; explore promising approaches and identify key attributes of a well-working collaborative approach.

Moderator: **Tachi Yamada,** Frazier Life Sciences

9:30a.m. ***Segment A:*** **Existing and Promising Incentives**

Keynote lectures: *20 min*

BT Slingsby, Global Health Innovative Technologies (GHIT) Fund

Panel discussion: *60 min*

Lynn Marks, GlaxoSmithKline

Rajeev Venkayya, Takeda Pharmaceuticals

Kevin Outterson, Boston University

10:50a.m. **Break**

11:00a.m. ***Segment B:*** **Sustainable and Effective Business Models and Public–Private Partnerships**

Keynote lectures: *40 min*

David Reddy, Medicines for Malaria Venture (MMV)

Krishna Ella, Bharat Biotech International Limited

Panel discussion: *50 min*

Mel Spigelman, TB Alliance

Graeme Bilbe, Drugs for Neglected Diseases initiative

Peter Dull, The Bill & Melinda Gates Foundation

12:30p.m. **Lunch**

SESSION 2: SCIENCE AND REGULATORY CONVERGENCE AND CAPACITY

Objectives:

- Review and characterize the needs and gaps in current scientific tools, technologies, and capacities to develop and evaluate products.
- Highlight promising common platforms to enable nimble and rapid development and evaluation of products.
- Discuss whether and how discordant regulatory specifications hinder efficient development and evaluation of medical products, and possible approaches for convergence.
- Characterize the critical needs of country regulatory authorities in times of public health emergency and discuss potential strategies regulators and international organizations can take to help address these needs.
- Discuss potential strategies for encouraging the sharing of knowledge, clinical, and clinical trial data to speed clinical assessment of investigational products for emerging infectious disease.

Moderator: **Maria Freire,** Foundation for the National Institutes of Health (NIH)

1:30p.m. *Segment A:* **State of the Science**

Keynote lectures: 40 min

Michael Pfleiderer, Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines

Trevor Mundel, The Bill & Melinda Gates Foundation

Panel discussion: 50 min

Margaret Hamburg, National Academy of Medicine (NAM)

Rudi Pauwels, BioCartis NV

Charles Goldstein, Becton Dickinson (BD)

Adel Mahmoud, Princeton University

Craig E. Colton, 3M Personal Safety Division

3:00p.m. ***Segment B:*** **Sharing of Data and Reagents, Intellectual Property, and Liability**

Keynote lecture: *20 min*

Anthony So, Duke University

Panel Discussion: *60 min*

Michelle Mulder, South African Medical Research Council

Lynn Marks, GlaxoSmithKline

Reid Adler, Practical Innovation Strategy

4:20p.m. **Break**

4:30p.m. ***Segment C:*** **Global Regulatory Convergence and Capacity**

Keynote lectures: *40 min*

Margaret Hamburg, NAM

Hans-Georg Eichler, European Medicines Agency (EMA)

Panel Discussion: *50 min*

Raymond Chua, Singapore Health Sciences Authority (HSA)

Mike Ward, WHO

6:00p.m. **Adjourn Day 1**

DAY 2

SESSION 3: CLINICAL ASSESSMENT

Objectives:

- Examine barriers to the clinical assessment of the safety and efficacy of investigational medical products in communities experiencing a public health emergency from an emerging infectious disease.
- Discuss a framework for determining when investigational products should be subjected to controlled clinical assessment and when they should be used more broadly under other mechanisms.
- Describe responsible and adaptive clinical trial designs that could be developed for use in times of public health emergencies and discuss ethical considerations associated with the possible options.
- Consider ethical and methodological standards that may be used to determine optimal trial designs for assessing the readiness of investigational medical products prior to broader deployment during public health emergency.
- Highlight strategies for engaging communities during times of public health emergency to determine how and when to undertake controlled clinical assessment and, where trials are used, to facilitate rapid and fair enrollment in trials for investigational products.

Moderator: **Maria Freire,** Foundation for the NIH

9:00a.m. *Segment A:* **Ethical Principles and Methodological Framework for Clinical Trial Designs**

Keynote Lectures: 40 min

Andre Kalil, University of Nebraska Medical Center

Fred Binka, University of Health and Allied Sciences, Ghana

Panel Discussion: 80 min

Luciana Borio, U.S. Food and Drug Administration (FDA) (via video conference)

Paul Stoffels, Johnson & Johnson

Mike Levine, University of Maryland School of Medicine

Peter Kilmarx, Fogarty International Center, NIH

Rob Califf, U.S. FDA (via video conference)

11:00a.m. **Break**

11:10a.m. ***Segment B:*** **Practical Considerations and Community Engagement**

Keynote Lecture: *20 min*

Samba Sow, Center for Vaccine Development, Mali

Panel Discussion: *60 min*

Joan Awunyo-Akaba, Future Generations International (FUGI), Ghana

Beth Bell, U.S. Centers for Disease Control and Prevention

Fred Binka, University of Health and Allied Sciences, Ghana

12:30p.m. **Lunch**

SESSION 4: MANUFACTURING, STOCKPILING, AND DEPLOYMENT

Objectives:

- Characterize the needs and gaps in current manufacturing, stockpiling, and supply chain mechanisms for medical product development and deployment during public health emergencies.
- Highlight promising approaches for delivery and deployment of products that are manufactured outside of an affected region during public health emergencies.

- Discuss the ethical considerations of different manufacturing approaches and deployment capabilities.

Moderator: **Tachi Yamada,** Frazier Life Sciences

1:30p.m. *Segment A:* **Manufacturing and Stockpiling**

Keynote Lecture: *20 min*

Rajeev Venkayya, Takeda Pharmaceuticals

Discussion Panel: *60 min*

Krishna Ella, Bharat Biotech International Limited

Shanelle Hall, United Nations Children's Fund (UNICEF)

2:50p.m. **Break**

3:00p.m. *Segment B:* **Supply Chain Mechanisms and Deployment**

Keynote Lecture: *20 min*

David Ripin, Clinton Health Access Initiative (CHAI)

Discussion Panel: *60 min*

Shanelle Hall, UNICEF

Rajeev Venkayya, Takeda Pharmaceuticals

4:00p.m. **Adjourn Session 4**

DAY 3 (HALF DAY)

SESSION 5: TOP PRIORITIES FOR FACILITATING MEDICAL PRODUCT RESEARCH AND DEVELOPMENT

Objectives:

- Examine the ethical and practical considerations for setting priorities to facilitate medical product research, development, and availability.

- Discuss potential strategies for developing a structure and process to select priorities for medical product research, development, and availability.
- Discuss potential strategies for encouraging collaboration and information sharing among private companies to speed research and development for top priorities.
- Explore how to align regulatory considerations, development milestones, and financing models for designated top priorities.

Moderators: **Maria Freire,** Foundation for the NIH, and **Tachi Yamada,** Frazier Life Sciences

9:00a.m. ***Summary Lecture:*** *20 min*

Tachi Yamada, Frazier Life Sciences

Panel Discussion: *120 min*

Robin Robinson, Biomedical Advanced Research and Development Authority, U.S. Department of Health and Human Services (via video conference)

Peter Kilmarx, Fogarty International Center, NIH

Paul Stoffels, Johnson & Johnson

Glenda Gray, South African Medical Research Council

11:20a.m. **Adjourn Session 5**

11:20a.m. **Closing Remarks—Ceci Mundaca-Shah,** National Academies of Sciences, Engineering, and Medicine

11:30a.m. **Adjourn Public Workshop**

D

Workshop Speaker Biographies

Reid Adler, JD, has been involved with intellectual property and technology transactions in the life sciences field for more than 30 years. His legal career includes experience as a senior partner of two international law firms, Morrison & Foerster and Morgan Lewis, and as general counsel of the J. Craig Venter Institute for genomics research. He continues to advise clients on life science matters in his current law practice. Most recently, he founded Practical Innovation Strategy, consulting on innovation management and translational research for nonprofit organizations and on intellectual property (IP) strategy for a major multinational pharmaceutical company. He also publishes the "Practically Strategic" blog. Mr. Adler was the founding director of the National Institutes of Health (NIH) Office of Technology Transfer, and played a key role in developing policies and model agreements, research integrity guidelines and the Uniform Biological Material Transfer Agreement. He holds a law degree from the George Washington University. After law school, he clerked for Judge Giles Rich at the U.S. Court of Appeals for the Federal Circuit and after that was a fellow at the Max Planck Institute for Foreign and International Patent, Copyright and Competition Law in Germany. Mr. Adler has testified before Congress on technology transfer, has published numerous articles, and has taught courses in innovation management, strategic planning, technology transfer, and legal aspects of biotechnology for Johns Hopkins University and DePaul University Law School. He has also chaired the boards of several community nonprofit organizations involved with education and the fine arts.

Joan Awunyo-Akaba, PhD, MCommH, is Executive Director, Future Generations International (FUGI) and a member of the Ghana Coalition of Nongovernmental Organizations (NGOs) in Health. She has a PhD in medical sociology, University of Ghana Legon (2007). She is a Community Health Development Consultant, and the Founder and Executive Director of FUGI, a Ghana-based NGO. A registered nurse, she has penetrated the development sector by her dedication and sensitization of child rights and maternal and child health, including childhood immunization advocacy, behavior change communication, youth development and empowerment, school sanitation and hygiene, and promotion of income generation activities for women. She is involved in civil society organizational activities, has served as National Vice Chairperson of the Ghana Coalition of NGOs in Health (2010-2012), and has also served as a board member and former Vice Chair of ActionAid International Ghana, a nonprofit NGO that targets poor and marginalized people to eradicate poverty (2005-2010). She recently served as the civil society organizations representative on the Board of Gavi, the Vaccine Alliance, Geneva, Switzerland (2012-2015).

Beth P. Bell, MD, MPH, is the director of the National Center for Emerging and Zoonotic Infectious Diseases (NCEZID). She provides leadership for the prevention and control of a broad spectrum of infectious diseases, including rare but deadly diseases like Ebola and anthrax, and more common conditions like foodborne diseases and health care–associated and antibiotic-resistant infections. In addition, Dr. Bell provides oversight for a diverse portfolio of science-based programs that promote water safety, global health and the health of migrating populations, and the identification and control of diseases transmitted by animals and insects. She is responsible for providing leadership and direction for NCEZID's world-class laboratories, which are developing new tests, vaccines, and, since the 2014 launch of advanced molecular detection, next-generation sequencing to enable faster diagnosis and more effective prevention and control of infectious diseases. Since Dr. Bell assumed the position in 2010, she has led NCEZID's response to several major infectious disease threats, including the largest Ebola epidemic in history affecting multiple countries in West Africa, chikungunya spreading throughout the Americas, a multistate outbreak of fungal meningitis that exposed thousands of patients who had received contaminated steroid injections, the second-largest outbreak of West Nile virus disease in the United States, the worst cholera outbreak in recent history that caused more than 8,000 deaths in Haiti, and dozens of outbreaks of foodborne disease that occur each year.

Graeme Bilbe, PhD, is the Research & Development Director, Drugs for Neglected Diseases initiative (DNDi). Dr. Bilbe has the overall responsi-

bility for advancing the discovery and development of new treatments for neglected diseases and building DNDi's project portfolio. Prior to joining DNDi in 2012, Dr. Bilbe was Global Head of Neuroscience Discovery at Novartis, tasked with discovery and early development to proof-of-concept testing of novel treatments for brain diseases. During his scientific leadership of Novartis Neuroscience Discovery, he and scientific teams participated in development and registration of new therapies for Alzheimer's and Parkinson's disease and multiple sclerosis. Under Dr. Bilbe's leadership, the Neuroscience Discovery group built and developed a portfolio of novel therapies up to clinical efficacy testing for Parkinson's disease, fragile X mental retardation, cognitive disorders, gastroesophageal reflux disease, epilepsy, and chronic pain states. Dr. Bilbe held executive leadership positions within both the Novartis Institutes for Biomedical Research as well as the Novartis Franchise Board for Neuroscience and was a visiting professor at the University of Liverpool. He currently is a member of Scientific Advisory Boards for Biotech Companies, Public Institutions and the Special Program for Research and Training in Tropical Diseases (TDR). Dr. Bilbe completed post-doctoral fellowships at the Zentrum for Molecular Biology in Heidelberg and Imperial College, University of London. He received his PhD in biochemistry from the University of London, Imperial College, and his BSc in zoology and biochemistry from the University of Nottingham.

Fred Binka, PhD, MBChB, MPH, is Vice-Chancellor, University of Health Allied Sciences, Ho, Ghana and Professor of Clinical Epidemiology. He holds an MBChB (Ghana, medical degree), MPH (Jerusalem), and PhD in epidemiology (Basel). Before joining the University of Health and Allied Sciences, he had held the position of Dean, School of Public Health, University of Ghana, and worked with the Ghana Ministry of Health for more than 20 years in several capacities, including Director of the Navrongo Health Research Centre. He was a member of the initial team that developed the Roll Back Malaria Initiative at the World Health Organization (WHO) in Geneva. He established the Indepth Network, an international health research NGO. His research interests are in malaria (epidemiology, control), intervention studies (drugs and vaccines of tropical diseases), and Ebola vaccines. Dr. Binka is a recent recipient of the Ronald Ross Medal (2010) from the London School of Hygiene & Tropical Medicine, and was the first recipient of the Rudolf Geigy Medal (2000) by the Swiss Tropical Institute. Dr. Binka is a strong advocate for research capacity strengthening in Africa, through support from African governments and their partners.

Robert M. Califf, MD, MACC, is Deputy Commissioner for Medical Products and Tobacco for the U.S. Food and Drug Administration (FDA).

Appointed in February 2015, Dr. Califf provides executive leadership to the Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, and Center for Tobacco Products. He also oversees the Office of Special Medical Programs and provides direction for crosscutting clinical, scientific, and regulatory initiatives, including personalized medicine, orphan drugs, pediatric science, and the advisory committee system. He attended Duke University both as an undergraduate and for medical school, completing his residency at the University of California, San Francisco, before returning to Duke for a cardiology fellowship. Dr. Califf served as the Donald F. Fortin, M.D., Professor of Cardiology at Duke and, most recently, Vice Chancellor for Clinical and Translational Research. An international leader in cardiovascular medicine, health outcomes, health care quality, and medical economics, he is recognized by the Institute for Scientific Information as 1 of the top 10 most cited medical authors, with more than 1,200 peer-reviewed publications. Dr. Califf co-chaired the Clinical Trials Transformation Initiative, a public–private partnership co-founded by Duke and FDA to identify and promote practices that will increase the quality and efficiency of clinical trials. He also served as co–principal investigator (PI) of Duke's Clinical and Translational Science Award, funded by the National Center for Advancing Translational Sciences; PI for the coordinating center of the NIH Health Care Systems Research Collaboratory, a Common Fund program that develops, tests, and disseminates innovative methodologies for pragmatic clinical research; and co-PI for the Baseline Study, a collaboration among Duke University, Stanford University, and Google that seeks new understandings of states of health and disease in humans.

Margaret Chan, OBE MD, DSc, MScPH, FFPHM, JP, from the People's Republic of China, obtained her medical degree from the University of Western Ontario in Canada. She joined the Hong Kong Department of Health in 1978, where her career in public health began. In 1994, Dr. Chan was appointed Director of Health of Hong Kong. In her 9-year tenure as director, she launched new services to prevent the spread of disease and promote better health. She also introduced new initiatives to improve communicable disease surveillance and response, enhance training for public health professionals, and establish better local and international collaboration. She effectively managed outbreaks of avian influenza and of severe acute respiratory syndrome. In 2003, Dr. Chan joined WHO as Director of the Department for Protection of the Human Environment. In June 2005, she was appointed Director, Communicable Diseases Surveillance and Response, as well as Representative of the Director-General for Pandemic Influenza. In September 2005, she was named Assistant Director-General for Communicable Diseases. Dr. Chan was elected to the post of Director-

General on November 9, 2006. The Assembly appointed Dr. Chan for a second 5-year term at its 65th session in May 2012. Dr. Chan's new term began on July 1, 2012, and continues until June 30, 2017.

Craig E. Colton, CIH, MA, is a certified industrial hygienist in the Regulatory Affairs and Technical Service group of the 3M Personal Safety Division with experience specializing in respiratory protection. Currently a Division Scientist, he has conducted workplace protection factor studies on 3M respirators, monitored and responded to regulatory affairs issues related to respiratory protection, and provided technical assistance to respirator users. Previous to working for 3M, he was an instructor at the Occupational Safety and Health Administration (OSHA) Training Institute, where he was course chair for the respiratory protection course covering OSHA, the National Institute for Occupational Safety and Health, the National Research Council, the American National Standards Institute (ANSI), the Compressed Gas Association, the Canadian Standards Association, and the National Fire Protection Agency standards, as well as the complete range of respiratory protective devices. While at OSHA he was a member of the four-person team that first implemented quantitative fit testing for OSHA personnel. Mr. Colton has also taught continuing education courses for several universities and associations. He is a past chair of the American Industrial Hygiene Association Respiratory Protection Committee and Americas' Section of the International Society for Respiratory Protection (ISRP) (1998-2000). Presently he is serving as the vice chair of the Americas' Section of ISRP. He has authored several articles and book chapters on respiratory protection. He is currently a member of the ANSI Z88 Committee on respiratory protection and a member of the Z88.2 subcommittee. Mr. Colton was a member of the last ANSI Z88.10 (2010) subcommittee on fit testing. He is also a member of the International Standards Organization (ISO) committee developing respiratory protection standards (TC94 SC15). This work included serving as convener for the working group that produced ISO 16972 on respiratory terminology.

Peter Dull, MD, MS, is Deputy Director for Integrated Clinical Vaccine Development within the Global Health Division at The Bill & Melinda Gates Foundation. In this role he provides technical and strategic guidance to the foundation's program strategy teams and external partners. During the Ebola response, he was seconded to WHO to support in facilitating clinical trial coordination in West Africa. He joined the foundation after 10 years at Novartis Vaccines and Diagnostics, where he was the Clinical Franchise Head for Meningitis and Sepsis Vaccines. At Novartis, he led the clinical development and global licensure for infants, adolescents, and adults of a quadrivalent meningococcal glycoconjugate vaccine (Menveo®; Men-

ACWY-CRM) as well as a protein-based serogroup B vaccine (Bexsero®; 4CMenB). In addition, he led the clinical development for the Group B strep glycoconjugate vaccine, which is targeted to pregnant women to prevent neonatal disease. Prior to joining Novartis, he was an Epidemic Intelligence Service officer in the Meningitis and Special Pathogens Branch at the U.S. Centers for Disease Control and Prevention (CDC), where he was responsible for conducting ongoing surveillance and investigating outbreaks of pathogens such as meningococcus and *Bacillus anthracis*. Dr. Dull holds a BS in physics and an MS in neuroscience. He attended medical school at the University of Wisconsin–Madison and completed his internal medicine training at Oregon Health & Science University in Portland, Oregon. After his service as an Epidemic Intelligence Officer, he completed subspecialty training in infectious diseases at Emory University.

Victor J. Dzau, MD, is the President of the National Academy of Medicine (NAM), formerly the Institute of Medicine (IOM). In addition, he serves as Chair of the IOM Division Committee of the National Academies of Sciences, Engineering, and Medicine. Dr. Dzau is Chancellor Emeritus and James B. Duke Professor of Medicine at Duke University and the past President and CEO of the Duke University Health System. Previously, Dr. Dzau was the Hersey Professor of Theory and Practice of Medicine and Chairman of Medicine at Harvard Medical School's Brigham and Women's Hospital, as well as Chairman of the Department of Medicine at Stanford University. Dr. Dzau has made a significant impact on medicine through his seminal research in cardiovascular medicine and genetics and his leadership in health care innovation. His important work on the renin angiotensin system (RAS) paved the way for the contemporary understanding of RAS in cardiovascular disease and the development of RAS inhibitors as widely used, lifesaving drugs. In his role as a leader in health care, Dr. Dzau has led efforts in innovation to improve health, including the development of the Duke Translational Medicine Institute, the Duke Global Health Institute, the Duke–National University of Singapore Graduate Medical School, and the Duke Institute for Health Innovation. As one of the world's preeminent health leaders, Dr. Dzau advises governments, corporations, and universities worldwide. He has served as a member of the Advisory Committee to the Director of the NIH and as Chair of the NIH Cardiovascular Disease Advisory Committee. Currently he is a member of the Board of the Singapore Health System and Hamad Medical Corporation, Qatar. He was on the Board of Health Governors of the World Economic Forum and chaired its Global Agenda Council on Personalized and Precision Medicine. Among his many honors and recognitions are the Gustav Nylin Medal from the Swedish Royal College of Medicine, the Distinguished Scientist Award from the American Heart Association, Ellis Island Medal of Honor, and the

Henry Freisen International Prize. In 2014, he received the Public Service Medal from the President of Singapore. He is a member of the NAM, the American Academy of Arts and Sciences, and the European Academy of Sciences and Arts. He has received eight honorary doctorates.

Hans-Georg Eichler, MD, MSc, is the Senior Medical Officer at the European Medicines Agency 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. Prior to joining the European Medicines Agency, 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. In 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 MIT's NEWDIGS initiative. Dr. Eichler graduated with an MD from Vienna University Medical School and a master of science degree 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.

Krishna M. Ella, PhD, MS, is the Chairman and Managing Director of Bharat Biotech International Ltd. He received his PhD from the University of Wisconsin–Madison. Bharat Biotech has invested more than $138 million toward facilities and projects, and sold more than three billion doses in 65 countries. Under the Social Innovation concept, Dr. Ella developed the ROTAVAC vaccine in collaboration with the government of India's Department of Biotechnology, The Bill & Melinda Gates Foundation, PATH, CDC-Atlanta, and NIH-USA, and the first novel vaccine was launched by the Honorable Prime Minister of India. Bharat Biotech entered into a partnership with the University of Maryland to work on nontyphoid Salmonella vaccines for Africa with a grant of $4 million from Wellcome Trust. Bharat Biotech obtained more than 65 global patents with 8 new molecules. Dr. Ella has been awarded more than 100 national and international awards, which include Bio Spectrum Person of the Year in 2013, University of Wisconsin Distinguished Alumni Award (2011), Business Leader of the Year 2011, and Best Technology and Innovation Award from the Prime Minister of India in 2008. He has served on numerous committees, including as

member of the Scientific Advisory Committee to the Government of India (SAC-C); member of the Governing Body of the Council of Scientific & Industrial Research; Chairperson of the Board of Governors of the National Institute of Technology, Warangal; and Co-Chairman of Indo-USA High Technology Cooperation Group for 5 years on behalf of the government of India; he also facilitated the knowledge initiative bill signed by the United States.

Maria Freire, PhD, is the President and Executive Director and Member of the Board of Directors of the Foundation for the National Institutes of Health (FNIH). Prior to this appointment, Dr. Freire was the President of the Albert and Mary Lasker Foundation, from 2008 to 2012, where she established novel programmatic initiatives that expanded the brand and reach of the foundation. From 2001 to 2008, she served as President and Chief Executive Officer of the Global Alliance for TB Drug Development (TB Alliance), a not-for-profit organization that develops drugs to fight tuberculosis (TB), and directed the Office of Technology Transfer at NIH from 1995 to 2001. Dr. Freire obtained her BS degree at the Universidad Peruana Cayetano Heredia in Lima, Peru, received her PhD in biophysics from the University of Virginia, and completed post-graduate work in immunology and virology at the University of Virginia and the University of Tennessee, respectively. She is active on national and international boards and committees, including the Board of the Global Alliance for Vaccines and Immunization (GAVI) Alliance and Alexandria Real Estate Equities, Inc. She is Chair of the Science Board of FDA, which advises the Commissioner. Dr. Freire was selected as 1 of 10 Commissioners of WHO's Commission on Intellectual Property Rights, Innovation and Public Health, and is a member of the Executive Committee of the United Nations' Sustainable Development Solutions Network. She is the recipient of numerous awards, including the U.S. Department of Health and Human Services (HHS) Secretary's Award for Distinguished Service, The Arthur S. Flemming Award, and The Bayh-Dole Award. Dr. Freire is a member of the NAM and of the Council on Foreign Relations.

Charles Goldstein, PhD, MA, MSE, is Chief Scientific Officer, Greater Asia, Becton Dickinson (BD) Technologies, a position he assumed in October 2013. Dr. Goldstein is responsible for the strategy and global performance of BD's regional research and development (R&D) operations in Asia. The strategic goal of the role Dr. Goldstein fills is to enhance the company's growth in emerging countries via market-appropriate solutions. In 1997 Dr. Goldstein was appointed BD's Vice President, Research, responsible for BD Technologies. Some of BD's accomplishments include commercialized microneedle-based drug delivery devices, nanotechnology-based point-of-

care diagnostics, and novel products for stem cell growth. From 1988 to 1998 Dr. Goldstein was Vice President of R&D for BD's Hypodermic and Injection Systems business. During this period the major product development work was done for BD's highly successful health care worker needle stick prevention safety products. Prior to joining BD, Dr. Goldstein led the product development efforts for Millipore Corp in Bedford, Massachusetts. Dr. Goldstein has received numerous high-level awards at BD recognizing his leadership and innovation contributions. Dr. Goldstein served on the Board of North Carolina Biotechnology Industry Organization (BIO), the local affiliate of national BIO. Dr. Goldstein was Chairman of the Board of Ibiliti, a nonprofit focused on supporting and growing the Med Tech industry in North Carolina. Dr. Goldstein served as Chairman of the Board of the Singapore Bio Venture Center, an incubator that was a joint venture between BD and Johns Hopkins Medical. Dr. Goldstein served on the Board of Synecor. He is a member of numerous professional organizations and engages in outside charitable and philanthropic efforts on behalf of the Juvenile Diabetes Research Foundation (JDRF) and Princeton University. He served 6 years as a board member of the Eastern North Carolina chapter of the JDRF. Dr. Goldstein serves on advisory committees for the Chemical and Biological Engineering Department at Princeton, the Whiting School of Engineering at Johns Hopkins, and the Chemical and the Biomolecular Engineering Departments at Johns Hopkins. He recently received an award from Johns Hopkins University for distinguished alumni service. He received several awards from JDRF for service to that organization as well. Dr. Goldstein has a PhD and an MA from Princeton University, an MSE degree from Johns Hopkins University, and a BChE degree from the City College of New York.

Glenda Gray, MBBCH, FCPAED (SA), is the President of the Medical Research Council in South Africa, a non-Executive Director at the Perinatal HIV Research Unit, in Soweto, South Africa, and a Professor of Pediatrics in the Faculty of Health Sciences at the University of Witwatersrand. Dr. Gray's prior research has focused on studies of prevention of mother-to-child transmission, pediatric treatment trials, large-scale HIV clinical trials (including HIV vaccine trials), tuberculosis, influenza, and human papillomavirus (HPV) vaccine studies in infants, children, adolescents, and adults. Dr. Gray has been the recipient of multiple grants from NIH, including an R21 and a U01. In 2009, she received the N'Galy Mann Lectureship award at the Conference on Retroviruses and Opportunistic Infections. She has been the Soweto Clinical Trials Unit PI since 2010. In addition, Dr. Gray is the HIV Vaccine Trials Network co-PI, and Director of International/Africa Programs. She has been involved in HIV research in South Africa for more than a decade. She is currently leading the clinical development of South

Africa's first two HIV vaccines. Dr. Gray has expertise in HIV prevention in adolescents, and is the co-chair for a pivotal study investigating the efficacy of coitally dependent tenofovir gel, called FACTS 001. This multicentered study involves nine clinical trial sites and is a purely South African–run consortium, giving Dr. Gray the necessary experience and expertise in leading multicentered studies. She is on the WHO/Joint United Nations Programme on HIV/AIDS (UNAIDS) Vaccine Advisory Board, and on the data and safety monitoring board for two vaccine studies in Africa. Dr. Gray chairs the standing committee on health for the Academy of Science, and represents the academy in the South African National Research Committee. As a recently inducted member of the NAM, she serves on the Global Health Committee and the Vaccine Committee.

Shanelle Hall is the Director of the United Nations Children's Fund's (UNICEF's) Supply Division and oversees UNICEF's global logistics and procurement function. In this capacity she is responsible for the effective, efficient, and ethical provision of essential and emergency supplies to children in need, through direct UNICEF programs and cooperation with governments and partners. UNICEF's global annual expenditures in these areas approach $3.382 billion. Prior, she was the Chief, Immunization, where she is credited with introducing the concept of "vaccine security" as a means of ensuring a sustainable, uninterrupted supply of affordable, quality vaccines to the world's poorest countries. Ms. Hall has traveled extensively in Africa and Asia in addition to working out of Europe. Prior to joining UNICEF, Ms. Hall worked for 9 years in the private sector where she was involved in energy sector infrastructure development in various countries.

Margaret A. Hamburg, MD, is the former Commissioner of FDA, having stepped down from that role in April 2015 after almost 6 years of service. As the top official at FDA, Dr. Hamburg emphasized the critical role of innovation in meeting the nation's rapidly growing public health needs and set the agency's course for fulfilling two central public health tasks. She launched a nationwide public–private effort to strengthen regulatory science as a means for advancing the development and evaluation of innovative, breakthrough medical products, and led FDA's transformation into a global regulatory agency capable of ensuring the safety and quality of imported food, drugs, and medical devices. Before taking on the post of FDA Commissioner, Dr. Hamburg was founding Vice President for Biological Programs at the Nuclear Threat Initiative, a foundation dedicated to reducing the threat to public safety from nuclear, chemical, and biological weapons. Prior to that she served as Assistant Secretary for Planning and Evaluation in HHS. Dr. Hamburg's other public health responsibilities also included Assistant Director of the National Institute of Allergy and Infec-

tious Diseases, as well as Commissioner of the New York City Department of Health. Dr. Hamburg earned her BA from Harvard College and her MD from Harvard Medical School and completed her residency at Weill Cornell Medical Center and currently is a member of the NAM where she now serves as Foreign Secretary.

Andre Kalil, MD, MPH, FACP, FIDSA, FCCM, is currently a Professor of Medicine at the University of Nebraska Medical Center, Omaha, Nebraska. He is a faculty member of the division of Infectious Diseases, Department of Internal Medicine, Department of Pathology and Microbiology, and Department of Anesthesiology and Critical Care. Dr. Kalil received his training in infectious diseases at the Massachusetts General Hospital–Harvard University (Boston, Massachusetts), Critical Care Medicine at NIH (Bethesda, Maryland), and Internal Medicine at the Jackson Memorial Hospital, University of Miami (Miami, Florida). Dr. Kalil's primary research is focused on viral and bacterial infections in critically ill and immunosuppressed patients, as well as on clinical research methodology. He is a referee for 30 scientific journals and has more than 140 peer-reviewed publications in scholarly journals such as the *New England Journal of Medicine*, *JAMA*, *Annals of Internal Medicine*, *Lancet*, and the *British Medical Journal*.

Peter H. Kilmarx, MD, FACP, FIDSA, is the Deputy Director of the John E. Fogarty International Center (FIC) of NIH, a preeminent center for global health research and capacity building. The FIC achieves its mission through supporting and facilitating global health research conducted by U.S. and international investigators, building partnerships between health research institutions in the United States and abroad. After graduating from Dartmouth College in 1983, Dr. Kilmarx served in the Peace Corps in Zaire (Democratic Republic of Congo [DRC]) as a fisheries volunteer. Dr. Kilmarx earned his MD degree in the Dartmouth–Brown combined program in medicine, graduating in 1990. He completed his internship and residency in internal medicine and initiated a fellowship in infectious diseases at Johns Hopkins. In 1994, Dr. Kilmarx joined the Epidemic Intelligence Service at CDC in Atlanta. He directed CDC's northern Thailand HIV and sexually transmitted disease prevention research field station from 1996 to 2002 and CDC's Botswana office from 2002 to 2005, implementing the President's Emergency Plan for AIDS Relief and conducting HIV and TB prevention research. He served in the CDC Division of HIV/AIDS Prevention as the Chief of the Epidemiology Branch from 2006 to 2010 and as the Senior Advisor to the Director for Health Reform from 2010 to 2011. Dr. Kilmarx directed CDC's Zimbabwe office from 2011 to 2015. He is a Captain in the U.S. Public Health Service and is board certified in internal medicine and infectious diseases. Dr. Kilmarx led household surveillance in the Ebola

outbreak in Kikwit, DRC, in 1995, and initiated the CDC response to the Ebola outbreak in Kasai Occidental, DRC, in 2007. He served as the CDC Ebola response team leader in Sierra Leone in September and October 2014 and principal deputy team leader in Guinea in January and February 2015. He is the recipient of numerous awards and the author or co-author of more than 100 scientific research articles and book chapters.

Myron M. (Mike) Levine, MD, DTPH, is the Bessie & Simon Grollman Distinguished Professor at the University of Maryland School of Medicine, Associate Dean for Global Health, Vaccinology and Infectious Diseases, and the Founder and Former Director of the Center for Vaccine Development (1974-2014). He has extensive experience in design and evaluation of vaccines to prevent bacterial enteric infections, particularly Salmonella and Shigella. Dr. Levine is a vocal advocate for mucosal immunization, i.e., the administration of vaccines by oral and intranasal routes. He has made substantial contributions in basic vaccinology, bacterial pathogenesis, clinical research, field epidemiology, and public health. He sits on editorial boards of several journals, consults for many organizations (e.g., WHO, NIH, NAM, U.S. Department of Defense) and serves on Scientific Advisory Boards of multiple vaccine companies. He has authored 581 scientific articles, 115 book chapters, and is Senior Editor of *New Generation Vaccines*. A few of his achievement awards include the Albert B. Sabin Gold Medal Award for lifetime achievement in vaccine development and implementation; the American Society for Microbiology's 2012 Maurice Hilleman/Merck Award for contributions to pathogenesis, vaccine discovery and development, and control of vaccine preventable diseases; the Donald Mackay Medal of the American Society of Tropical Medicine and Hygiene; and the American College of Physicians Award for Outstanding Work in Science as Related to Medicine. He is a member of the NAM.

Adel A. F. Mahmoud, MD, PhD, is a professor at Princeton University. He recently retired as President of Merck Vaccines. Prior to that, he served at Case Western Reserve University and University Hospitals of Cleveland as Chairman of Medicine and Physician-in-Chief. Dr. Mahmoud's academic pursuits focused on investigations of host resistance to infections. At Merck, Dr. Mahmoud led the effort to develop four new vaccines, including a combination of measles, mumps, rubella, and Varicella; rotavirus; shingles, and human papillomavirus. He is a member of the NAM. He received the Bailey K. Ashford Award of the American Society of Tropical Medicine and Hygiene, and the Squibb Award of the Infectious Diseases Society of America. He is a past president of the International Society for Infectious Diseases.

Lynn Marks, MD, is Senior Vice President, Projects, Clinical Platforms & Sciences, GlaxoSmithKline (GSK). He currently has operational accountability for clinical trials over a broad range of disease and therapeutic areas on a global scale ranging across the phase I to IV development landscape. Additionally, he has responsibility for business support functions such as performance metrics, clinical systems support, clinical trial contracting, outsourcing strategy and implementation and good clinical practice, as well as core training across R&D. Further, his remit includes key capabilities such as project planning and management, study and data management, clinical trial monitoring, programming, and statistics (nonclinical and clinical). Areas of analytical science and modeling are included through the Global Health Outcomes, Genetics, Computational Biology, pharmacokinetic/pharmacodynamic modeling and Epidemiology teams. He is the Corporate Secretary and chaired the initial Operations Committee for Transcelerate Biopharma, which is a not-for-profit collaborative effort across approximately 20 pharmaceutical companies. He joined the company in 1993 working in the Infectious Diseases Clinical organization with increasing levels of accountability. He then was appointed head of the Infectious Diseases Therapy area. Over the next 10 years, he had the opportunity to grow and learn from varying organizational changes with resultant shifts in accountability as head of the Infectious Diseases Development group. Dr. Marks is board certified in internal medicine and infectious diseases. Before joining GSK, he was on faculty at the University of South Alabama Medical Center with joint appointments in infectious diseases, microbiology, and pharmacology. In addition to teaching and patient care responsibilities, he led an NIH grant-funded research effort focused on the molecular genetics of bacterial pathogenicity.

Michelle Mulder, PhD, has a dual role with the Strategic Health Innovation Partnerships unit of the South African Medical Research Council (SAMRC), where she manages the Technology Transfer Office and the HIV Programme. She also oversees the Grants Management Division of the SAMRC. Her responsibilities include IP management and commercialization, coordinating and managing funding for HIV product development, and oversight of the external grant mechanisms of the organization. Dr. Mulder has a doctorate in medical microbiology from the University of Cape Town and has post-doctoral experience in a startup biotechnology company emanating from the University of Cambridge (UK). She spent 10 years consulting on technology innovation through her company Idea to Industry cc (I2I), including 5 years driving business development for two plant-based medicine companies. She has also been involved for the past 10 years in the strategic management and commercialization of the MRC's IP and in extensive capacity building in these areas in Southern and East

Africa. Dr. Mulder has served as a member of the Executive Committee of the Southern African Research & Innovation Management Association (SARIMA) since 2005, including 3 years as Vice President: Innovation and Technology Transfer, and 2 years as President. She served previously as Chair of the Board of Acorn Technologies, a life sciences incubator, a director of the Licensing Executive's Society South Africa, the South Africa Liaison for the Life Sciences Committee of LESI, and a member of the Higher Education South Africa Strategy Group for Innovation and Technology Transfer. She recently received the South African Department of Science and Technology/SARIMA award for Excellence in the Leadership of Innovation Management.

Ceci Mundaca-Shah, MD, DrPH, is a senior program officer with the National Academies of Sciences, Engineering, and Medicine Board on Global Health. She is currently directing the Multi-Stakeholder Initiative for *Creating a Global Health Risk Framework for the Future*. Prior to directing this study, she was the study director for the Academies Board on the Health of Select Populations report *Beyond Myalgic Encelphalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness*. She also served as a postdoctoral fellow with the Academies Board on Global Health on the *Outcome and Impact Evaluation of Global HIV/AIDS Programs Implemented Under the Lantos-Hyde Act of 2008*. Prior to joining the Academies, Dr. Mundaca-Shah was employed as head of the Surveillance Center of the Emerging Infections Program in the U.S. Naval Medical Research Unit 6 in Lima, Peru. In that role, she led the successful implementation of a technology-based disease surveillance system (Alerta) at sites across the nation and the initial phase of a project sponsored by the U.S. Southern Command to expand Alerta to five other countries in South America. Alerta is a partnership involving the Peruvian Navy and the U.S. Navy. Dr. Mundaca-Shah also led the collaborative syndromic surveillance pilot implementation in the Peruvian Ministry of Health. She was part of the Early Warning Outbreak Recognition System Working Group and participated in several studies, including a field visit to evaluate the performance of the system in Lao People's Democratic Republic. She obtained her MD from San Marcos University, Lima, Peru, and her MPH and DrPH degrees from the Uniformed Services University of the Health Sciences, Bethesda, Maryland. Her dissertation work focused on developing a framework to guide the implementation of disease surveillance systems in developing countries. Dr. Mundaca-Shah completed a certificate in emerging infectious disease epidemiology at the University of Iowa.

Trevor Mundel, PhD, MSc, MBBCh, is president of the Global Health Division, The Bill & Melinda Gates Foundation. Dr. Mundel leads the foun-

dation's efforts in research and development of vaccines, drugs, and diagnostics to address major global health challenges in the developing world. He oversees the foundation's strategies in HIV, TB, malaria, pneumonia, diarrheal disease, enteric and diarrheal diseases, and neglected infectious diseases. Under Dr. Mundel's leadership, the Global Health Division also works on platform technologies to accelerate development of global health solutions. All of this work occurs in collaboration with an international network of grantees and partners. Prior to joining the foundation in 2011, he was global head of development with Novartis, and previously was involved in clinical research at Pfizer and Parke-Davis. A native of South Africa, Dr. Mundel earned his bachelor's and medical degrees from the University of the Witwatersrand in Johannesburg. Dr. Mundel also studied mathematics, logic, and philosophy as a Rhodes Scholar at the University of Oxford, and he earned a PhD in mathematics at the University of Chicago.

Kevin Outterson, JD, LLM, is a Professor and N. Neal Pike Scholar in Health and Disability Law, Boston University. Mr. Outterson teaches health law and corporate law at Boston University, where he co-directs the Health Law Program. His research work focuses on the organization and finance of the health sector. Areas of specialization include global pharmaceutical markets, particularly antibiotics and other antimicrobials that can degrade in usefulness over time through resistance. He leads an interdisciplinary project on the legal ecology of antimicrobial resistance. He is an Associate Fellow at the Royal Institute of International Affairs (Chatham House) and a founding member of the Antimicrobial Resistance Working Group at CDC. He was a senior consultant on the Eastern Research Group study on antibiotic markets for FDA/HHS. Starting in October 2014, he joined DRIVE-AB, a 3-year, €9 million project on antibiotic business models sponsored by the European Union's Innovative Medicines Initiative. Mr. Outterson also serves on the Advisory Panel for the Longitude Prize for an inexpensive rapid point-of-care antibiotic diagnostic. He serves as the Editor-in-Chief of the *Journal of Law, Medicine & Ethics*; faculty co-advisor to the *American Journal of Law & Medicine*; past chair of the Section on Law, Medicine & Health Care of the Association of American Law Schools; and a member of the Board of the American Society of Law, Medicine & Ethics. Mr. Outterson is an occasional author for the *New England Journal of Medicine* on health law topics.

Rudi Pauwels, PhD, co-founded Biocartis SA and Biocartis Group NV in 2007 and serves as its Chief Executive Officer. He is a scientist-entrepreneur. Following a 3-year sabbatical at the Swiss Federal Institute of Technology-École Polytechnique Fédérale de Lausanne (Lausanne, Switzerland) where he became more familiar with the advances in micro- and nanotechnologies,

he took the initiative to create Biocartis to address new needs in the field of diagnostics. He was a Venture Partner of Advent Venture Partners. He co-founded Tibotec-Virco Virology BVBA in 2001 and served as its Managing Director. He was Laboratory Head at the Rega Institute. Dr. Pauwels is a pharmacist who started as a researcher at the Rega Institute for Medical Research in Leuven, Belgium, an academic research center that is internationally known for its pioneering work in the field of antiviral chemotherapy. For more than two decades Dr. Pauwels mainly focused on the search and development of anti-HIV drugs, a number of which have been approved and introduced on the market, and the development of diagnostic tools to allow personalized HIV treatment. His research as well as his entrepreneurial career is driven by medical needs and the passion to advance and significantly impact medicine. In 1994, he co-founded Janssen Infectious Diseases-Diagnostics BVBA. As Chief Executive Officer and Chief Scientific Officer, he recruited and guided a passionate team of co-workers and collaborators who made Tibotec one of the most productive companies in the field of anti-HIV drug discovery. In 1995, he co-founded Virco. In 1999, he co-founded Galapagos Genomics, a joint venture between Tibotec and Crucell. Dr. Pauwels serves as Executive Chairman of Biocartis Group NV. He served as Chairman of Galapagos Genomics from 1999 to 2002. He serves as a Member of the Scientific Advisory Board at Interuniversity Micro-Electronics Center. He has been an Independent Director of MDxHealth SA since 2013. He served as an Independent and Non-Executive Director of Galapagos NV from January 2007 to April 27, 2010. Dr. Pauwels is a co-author of more than 150 publications in peer-reviewed journals. He received several awards for his scientific and entrepreneurial initiatives and serves on the boards of several companies and research institutes. His credentials are in the discovery of several new antivirals such as d4T and TIBO. He played a key role in the scientific development of phenotypic resistance testing. Besides his scientific background, he has a strong track record in automation and informatics. He is (co-)author of more than 150 publications in peer-reviewed journals. He has received several awards for his scientific and entrepreneurial initiatives. Dr. Pauwels completed his PhD in pharmaceutical sciences and virology (1990) at the Rega Institute for Medical Research (University of Leuven) in Belgium.

Michael Pfleiderer, PhD, is a biologist holding a PhD in molecular virology. After his university career, he worked on various aspects related to the production of recombinant medicinal products, including vaccines in the molecular biology laboratories of IMMUNO AG, Vienna, Austria (now BAXTER). Since 1998 he has worked at the Paul-Ehrlich-Institut (PEI), German Federal Institute for Vaccines and Biomedicines. In his current position he is the Head of the Human Viral Vaccines Section and respon-

sible for all issues related to vaccine licensing and regulation, as well as for batch testing and release. On a national level, Dr. Pfleiderer is a member of a number of advisory boards, in particular with regard to issues related to pandemic influenza vaccines and pandemic preparedness planning. On the European level, Dr. Pfleiderer is a member nominated by Germany for the Biologics Working Party (BWP) of the Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA) in London, as well as for the BWP Influenza ad hoc Working Group which he is chairing. For the CHMP Vaccine Working Party (VWP), Dr. Pfleiderer is acting as Chairman. In this position he also is a member of the CHMP Coordination Group. For EMA, Dr. Pfleiderer was chairing the Pandemic Task Force (ETF) coordinating regulatory and scientific issues related to the latest influenza pandemic. Under the new mandate, Dr. Pfleiderer is acting as the vice chair of the ETF. Dr. Pfleiderer has significantly contributed to EMA and WHO guidance on scientific and regulatory issues related to vaccines. For WHO Dr. Pfleiderer frequently acts as a temporary advisor. He is a member of various SAGE subgroups. The European Centre for Disease Prevention and Control nominated Dr. Pfleiderer as an expert for the Scientific Expert Panel on Vaccines and Immunisation. The Viral Vaccine Section that Dr. Pfleiderer heads at PEI has a leading function for many of the Marketing Authorization Applications for vaccines submitted so far to EMA, either as a rapporteur, co-rapporteur or peer reviewer. Moreover, many pieces of scientific advice submitted to EMA for vaccines have been assessed by the Viral Vaccine Section. Finally, this section acts on behalf of Germany as the Reference Member State (RMS) for the European Union for a broad range of vaccines, in particular seasonal influenza vaccines.

David Reddy, PhD, has been CEO of Medicines for Malaria Venture (MMV) since January 2011. Under his leadership, this not-for-profit research foundation has brought forward five new antimalarial drugs, and broadened its malaria-drug pipeline to include nine novel drugs in clinical development. In addition, MMV has received board and donor endorsement of a 5-year strategy focused on developing new medicines to address the unmet needs of vulnerable populations most affected by malaria. Prior to joining MMV, Dr. Reddy was a Vice President in the Global Product Strategy unit at F. Hoffman-La Roche Ltd., Basel, Switzerland, where he served as Pandemic Taskforce Leader. Prior to that he was the Global Franchise Leader for HIV/AIDS at Roche, where he oversaw the successful development and introduction of enfuvirtide, the first HIV fusion inhibitor. He was also responsible for developing Roche's HIV drug access policies and initiatives. His resume includes more than 20 years of "Pharma" experience, including successful leadership of drug development teams, licensing and alliance management, product and disease area management, market analytics, and

business planning. His roles also included interfacing with governments, NGOs, and patient advocacy groups around access to medicines for priority diseases. Dr. Reddy holds a PhD in cellular and molecular biology from the University of Auckland, New Zealand. His PhD thesis involved cloning the serotypic antigen for rotavirus and development of a recombinant rotavirus vaccine. He completed a post-doctoral fellowship at the Freidrich Miescher Institute in Basel, where he cloned and expressed developmentally regulated brain-derived microtubule-associated proteins.

David Ripin, PhD, is the Executive Vice President of Access and Malaria, and the Chief Science Officer at the Clinton Health Access Initiative (CHAI). In these roles, he oversees CHAI's work on increasing access to medicines and diagnostics for HIV, malaria, TB, and other disease areas through the use of sustainable market interventions. CHAI's Access program has successfully implemented agreements with pharmaceutical companies and diagnostic manufacturers to lower the price of key drugs and diagnostics by up to 80 percent, among other achievements. He also oversees the strategy and work of CHAI's Malaria program. Dr. Ripin joined CHAI in 2007. Prior to assuming his current role, he led CHAI's Pharmaceutical Sciences Team, which conducts research and development work. These efforts focus on reducing the cost of key drugs through recommending formulation, manufacturing process, and sourcing improvements, as well as conducting the transfer of these processes to manufacturing partners. Dr. Ripin is actively involved in setting international priorities for HIV drug optimization work, including organizing the Conference on Antiretroviral Drug Optimization in 2009. Before joining CHAI, he worked at Pfizer Inc. for 10 years as part of the research and development group, focusing on the commercialization and manufacturing of drug candidates.

Robin Robinson, PhD, was appointed in April 2008 as the first director of the newly, created federal agency, Biomedical Advanced Research and Development Authority (BARDA), and Deputy Assistant Secretary in the Office of the Assistant Secretary for Preparedness and Response within HHS by the Pandemic and All-Hazards Preparedness Act of 2006. BARDA develops and provides medical countermeasures to man-made and natural threats, including chemical, biological, radiological, and nuclear threats, pandemic influenza, and emerging infectious diseases. BARDA meets this mission by supporting product innovation, advanced development, acquisition and stockpiling, and building manufacturing infrastructure. Dr. Robinson led the nation's effort to develop and manufacture the largest amount of vaccine in U.S. history in response to the 2009 H1N1 pandemic. Dr. Robinson previously served from 2004 to 2008 as the Director for the Influenza & Emerging Disease Program within BARDA and its predecessor agency

at HHS. Dr. Robinson was recruited by HHS from the vaccine industry in May 2004 to establish a Manhattan-like program with scientific and technical experts to implement the strategic plans and policies for medical countermeasures outlined in the National Strategy for Pandemic Influenza (November 2005). These tactical measures included development, acquisition and establishment of national medical countermeasure stockpiles, and expansion of domestic manufacturing surge capacities for influenza vaccines, antiviral drugs, rapid diagnostics, and nonpharmaceutical countermeasures including respiratory devices. For his leadership in this role, Dr. Robinson was the recipient of the Department of Defense's Clay Dalrymple Award in 2008 and a finalist for the Service to America Medal in 2009. Dr. Robinson received a bachelor's degree in biology from Millsaps College in 1976, a doctoral degree from the University of Mississippi Medical School in medical microbiology under the mentoring of Dr. Dennis O'Callaghan in 1981 with a dissertation on herpesvirus oncogenesis, and completed in 1983 an NIH postdoctoral fellowship with the State University of New York at Stony Brook in molecular oncology under the mentoring of Dr. Arnold Levine on p53 tumor suppressor gene and tumor virus activation of cellular genes. While on faculty in the Department of Microbiology and Immunology at the University of Texas Southwestern Medical School from 1983 to 1990, his laboratory investigated the molecular pathogenesis of herpesviruses and HIV gene expression. Later at the NIH National Cancer Institute (1990-1992), he studied the regulation of negative repressor factors on HIV replication. Subsequently for 12 years in the pharmaceutical industry as Director of Vaccines at Novavax, Inc., he developed patented platform vaccine technologies including virus-like particles and subunit protein vaccines for human pathogens including malaria, human papilloma, hepatitis, and influenza and for prostate, melanoma, and cervical cancers. Dr. Robinson also serves on WHO international expert teams on pandemic influenza vaccines. Additionally, he continues to serve as an editorial board member and reviewer for several professional scientific and technical journals on virology, vaccines, public health, and biotechnology.

BT Slingsby, MD, PhD, MPH, is CEO and Executive Director of the Global Health Innovative Technology (GHIT) Fund. Previously, he was the global head for access strategies at Eisai Co., Ltd., where he developed new business models for R&D and overlooked market access in the developing world. Dr. Slingsby has helped launch numerous startups in Japan and the United States, and currently advises at the Graduate School of Medicine at the University of Tokyo and Kyoto University. He sits on the Forum on Public–Private Partnerships for Global Health and Safety at the National Academies of Sciences, Engineering, and Medicine in the United States, and has published more than 50 peer-reviewed articles on

medicine and public health in both Japanese and American literature. Dr. Slingsby graduated with honors from Brown University, earned master's and doctorate degrees from Kyoto University and the University of Tokyo, and received his medical doctorate from the George Washington University.

Anthony So, MD, MPA, is Professor of the Practice of Public Policy and Global Health and Director of the Program on Global Health and Technology Access at Duke University's Sanford School of Public Policy and the Duke Global Health Institute. He also oversees the Strategic Policy Program of ReAct—Action on Antibiotic Resistance; served on the Lancet Infectious Disease Commission on Antibiotic Resistance; served on the Institute of Medicine's Committee on Accelerating Rare Disease Research and Orphan Product Development; chaired a WHO expert working group on fostering innovation to combat antimicrobial resistance; and was part of the Antibiotic Resistance Working Group of the U.S. President's Council of Advisors in Science and Technology. In a 6-year, combined program at the University of Michigan, he received his BA in philosophy and biomedical sciences and his MD. He earned his MPA as a Woodrow Wilson Scholar at Princeton University and subsequently trained in internal medicine at the Hospital of the University of Pennsylvania. He completed his fellowship as a Robert Wood Johnson Clinical Scholar at the University of California, San Francisco/Stanford and studies antibiotic innovation as a current recipient of the Robert Wood Johnson Investigator Award in Health Policy Research.

Samba Sow, MD, MS, is Director General of the Center for Vaccine Development–Mali and a Professor of Medicine at the University of Maryland School of Medicine. At the Center for Vaccine Development, Dr. Sow heads the implementation of field and hospital-based epidemiologic studies and clinical trials in the study of vaccine-preventable diseases. Previously, Dr. Sow has served as the coordinator for WHO Multi-Center Field Trial on Leprosy Chemotherapy. He received his MD in medicine from the National School of Medicine and Pharmacy of Mali and his MSc in epidemiology from the London School of Hygiene & Tropical Medicine. Dr. Sow's honors include the 2000 Paul Laviron Prize in Tropical Medicine from the University of Marseille, France. He was also named the Commemorative Fund Lecturer of the American Society of Tropical Medicine & Hygiene in 2006.

Mel Spigelman, MD, is the President and Chief Executive Officer of the Global Alliance for TB Drug Development (TB Alliance). Prior to being appointed President and CEO in 2009, Dr. Spigelman served for more than 5 years as the Director of Research and Development at the TB Alliance. Dr. Spigelman previously spent a decade as Vice President of R&D oversee-

ing all research and development at Knoll Pharmaceuticals (a division of BASF Pharma). Dr. Spigelman holds board certifications from the American Board of Internal Medicine, the American Board's Subspecialty Board of Medical Oncology, and the American Board of Preventive Medicine, and was the recipient of the American Cancer Society Clinical Oncology Career Development Award (1985-1988). He served on the full-time faculty at the Mount Sinai Medical Center in New York City upon completing his subspecialty fellowships. Presently, Dr. Spigelman serves on the Coordinating Board of the Stop TB Partnership, is co-chair of the Working Group on New Drugs of the Stop TB Partnership, and is a member of the Governing Board of the Tres Cantos Open Lab, GSK. He also serves on the boards of The Medicines Company and Synergy Pharmaceuticals.

Paul Stoffels, MD, is Chief Scientific Officer and Worldwide Chairman, Pharmaceuticals, at Johnson & Johnson. In his role as Chief Scientific Officer, he works with R&D leaders across Johnson & Johnson to set the enterprise-wide innovation agenda and is a member of the Johnson & Johnson Executive Committee. Dr. Stoffels chairs the Johnson & Johnson R&D Management Committee and provides oversight to the Johnson & Johnson Development Corporation and the Johnson & Johnson innovation centers, with the goal of catalyzing innovative science and technology. Additionally, Dr. Stoffels has oversight for product safety of all products of the Johnson & Johnson Family of Companies worldwide. Dr. Stoffels is also Worldwide Chairman of Janssen Pharmaceutical Companies of Johnson & Johnson, with responsibility for expansion of the company's therapeutic pipeline through global R&D and strategic partnerships, licensing, and acquisitions. He leads teams across Janssen to discover and develop treatments for unmet medical needs in the therapeutic areas of cardiovascular and metabolism, immunology, infectious disease and vaccines, neuroscience, and oncology. Prior to his role as Worldwide Chairman, he served as Global Head, Johnson & Johnson Pharmaceutical R&D from 2009 to 2011, as Company Group Chairman, Central Nervous System & Internal Medicine, from 2006 to 2009, and as Company Group Chairman, Global Virology, from 2005 to 2006. Dr. Stoffels joined Johnson & Johnson in 2002 with the acquisition of Virco and Tibotec, where he was Chief Executive Officer of Virco and Chairman of Tibotec, and he led the development of a number of leading products for the treatment of HIV. Dr. Stoffels studied medicine at the University of Diepenbeek and the University of Antwerp in Belgium, as well as infectious diseases and tropical medicine at the Institute of Tropical Medicine in Antwerp, Belgium. He began his career as a physician in Africa, focusing on HIV and tropical diseases research.

Rajeev Venkayya, MD, is the President of the Global Vaccine Business Unit of Takeda Vaccines. He is responsible for Takeda's global vaccine business, including a long-standing business in Japan and a global development pipeline that includes vaccine candidates for norovirus and dengue, gained through the acquisitions of LigoCyte Pharmaceuticals and Inviragen Inc. Dr. Venkayya was previously the Director of Vaccine Delivery at The Bill & Melinda Gates Foundation, where he was responsible for the foundation's top two priorities of polio eradication and new vaccine introduction. This included the foundation's engagement and investments in the Global Polio Eradication Initiative and GAVI, and an investment portfolio of approximately $500 million per year. He also served as a member of the GAVI Board. Prior to the Gates Foundation, Dr. Venkayya was Special Assistant to the President and Senior Director for Biodefense at the White House, where he directed the development of policies to prevent, protect, and respond to bioterrorism and naturally occurring biological threats. He led the development and implementation of the National Strategy for Pandemic Influenza, as well as Presidential directives on medical countermeasures and public health preparedness. Prior to his positions at the White House, he was 1 of 13 individuals appointed by President Bush to the nonpartisan White House Fellowship program. Dr. Venkayya was previously an Assistant Professor of Medicine in the Division of Pulmonary and Critical Care Medicine at the University of California, San Francisco (UCSF). He was Co-Director of the Medical Intensive Care Unit and Director of the High-Risk Asthma Clinic at San Francisco General Hospital, and the principal investigator for a 5-year research grant from the National Institutes of Health to study the immunologic mechanisms leading to asthma. Dr. Venkayya completed his fellowship training in Pulmonary and Critical Care Medicine at UCSF. Prior to this, he was a Resident and Chief Medical Resident in Internal Medicine at the University of Michigan Medical Center. He completed his undergraduate and medical school education in the 6-year BS/MD program at the Northeastern Ohio Universities College of Medicine, where he was inducted into the Alpha Omega Alpha honorary medical society. He is a lifetime member of the Council on Foreign Relations.

Mike Ward, BSc, recently assumed the position of Coordinator, Regulatory System Strengthening, Essential Medicines and Health Technologies, Health Systems and Innovation Cluster, WHO Headquarters. Mr. Ward joined WHO in 2015 as the Coordinator, Prequalification Team in the same department. Mr. Ward previously worked within Health Canada for close to 30 years as a good manufacturing practice specialist, drug evaluator and manager, international policy analyst, and for the past 15 years as Manager of the International Programs Division of the Therapeutic Products Directorate. Mr. Ward has extensive experience in the area of international

regulatory cooperation, having served on numerous international harmonization steering committees. He was also responsible for helping launch the Asia-Pacific Economic Cooperation Regulatory Harmonization Steering Committee, the International Generic Drug Regulators Pilot, and the International Medical Device Regulators Forum. Mr. Ward started his professional career working in the areas of quality assurance and production for Burroughs Wellcome, a former multinational pharmaceutical firm based in the United Kingdom. Mr. Ward won the Regulatory Affairs Professional Society Global Leadership Award in 2012. Mr. Ward has a BSc in physiology from McGill University.

Tadataka (Tachi) Yamada, MD, is a Venture Partner with Frazier Life Sciences. Prior to joining Frazier he was Executive Vice President, Chief Medical & Scientific Officer and a Board Member of Takeda Pharmaceuticals. Dr. Yamada has served as President of The Bill & Melinda Gates Foundation Global Health Program. In this position, he oversaw grants totaling more than $9 billion in programs directed at applying technologies to address major health challenges of the developing world including TB, HIV, malaria and other infectious diseases, malnutrition, and maternal and child health. He was formerly Chairman, Research and Development, and a Member of the Board of Directors of GSK and before that he was Chair of the Department of Internal Medicine and Physician-in-Chief at the University of Michigan Medical Center. Dr. Yamada holds a bachelor's degree in history from Stanford University and obtained his MD from New York University School of Medicine. In recognition of his contributions to medicine and science he has been elected to membership in the NAM, the Academy of Medical Sciences (UK), and the National Academy of Medicine (Mexico) and he has received an honorary appointment as Knight Commander of the Most Excellent Order of the British Empire (KBE). He is a past president of the Association of American Physicians and of the American Gastroenterological Association and he has served as a member of the President's Council of Advisors on Science and Technology and the Advisory Committee to the Director of NIH. He is currently Vice Chair of the Council of the NAM and serves on the Board of Directors of the Clinton Health Access Initiative.