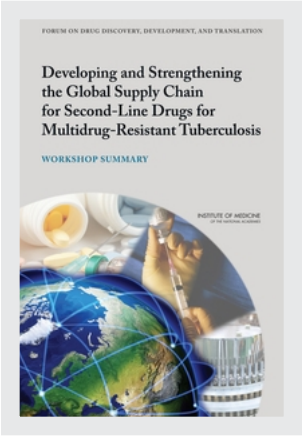


Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis: Workshop Summary

DETAILS

170 pages | 6 x 9 | PAPERBACK
ISBN 978-0-309-26595-9 | DOI 10.17226/13524

AUTHORS

Anna Nicholson, Rebecca A. English, Rita S. Guenther, and Anne B. Claiborne, Rapporteurs; Forum on Drug Discovery, Development, and Translation; Board on Health Sciences Policy; Institute of Medicine

Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis

WORKSHOP SUMMARY

Anna Nicholson, Rebecca A. English, Rita S. Guenther, and Anne B. Claiborne, *Rapporteurs*

Forum on Drug Discovery, Development, and Translation

Board on Health Sciences Policy

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW Washington, DC 20001

NOTICE: The workshop that is the subject of this workshop summary was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

This activity was supported by contracts between the National Academy of Sciences and Department of Health and Human Services (Contract Nos. N01-OD-4-2139 and HHSF223001003T), Abbott Pharmaceuticals, American Diabetes Association, American Society for Microbiology, Amgen Inc., Association of American Medical Colleges, Bristol-Myers Squibb, Burroughs Wellcome Fund, Celtic Therapeutics, LLLP, Critical Path Institute, Doris Duke Charitable Foundation, Eli Lilly and Company, Eli Lilly & Co. Foundation, FasterCures, Foundation for the NIH, Friends of Cancer Research, GlaxoSmithKline, Janssen Research & Development, LLC, March of Dimes Foundation, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, and Pfizer Inc. The views presented in this publication do not necessarily reflect the views of the organizations or agencies that provided support for the activity.

International Standard Book Number-13: 978-0-309-26595-9
International Standard Book Number-10: 0-309-26595-9

Additional copies of this workshop summary are available for sale from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

For more information about the Institute of Medicine, visit the IOM home page at: **www.iom.edu.**

Printed in the United States of America

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

Suggested citation: IOM (Institute of Medicine). 2013. *Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis: Workshop Summary.* Washington, DC: The National Academies Press.

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

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Advising the Nation. Improving Health.

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Charles M. Vest is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Charles M. Vest are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

PLANNING COMMITTEE FOR THE WORKSHOP ON GLOBAL DRUG SUPPLY CHAIN FOR SECOND-LINE ANTI-TUBERCULOSIS DRUGS[1]

BARRY R. BLOOM (*Co-Chair*), Harvard School of Public Health, Boston, MA
GAIL H. CASSELL (*Co-Chair*), Harvard Medical School (Visiting), Carmel, IN
RIFAT ATUN, Imperial College Business School, Imperial College London, England
PETER CEGIELSKI, U.S. Centers for Disease Control and Prevention, Atlanta, GA
LUCICA DITIU, Stop TB Partnership, World Health Organization, Geneva, Switzerland
GARY L. FILERMAN, Atlas Health Foundation, McLean, VA
HELLEN GELBAND, Center for Disease Dynamics, Economics & Policy, Inc., Washington, DC
MARK J. GOLDBERGER, Abbott Pharmaceuticals, Rockville, MD
DOUGLAS L. KEENE, Management Sciences for Health, Arlington, VA
SALMAAN KESHAVJEE, Harvard Medical School, Boston, MA
MONTSERRAT MEIRO-LORENZO, World Bank, Washington, DC
ELIZABETH (BETSY) MYERS, Doris Duke Charitable Foundation, New York, NY
PAUL P. NUNN,[2] World Health Organization, Geneva, Switzerland
ARIEL PABLOS-MÉNDEZ, United States Agency for International Development, Washington, DC
TRACY J. SIMS, Eli Lilly & Co. Foundation, Indianapolis, IN
BRENDA WANING, UNITAID, World Health Organization, Geneva, Switzerland
PRASHANT YADAV, University of Michigan, Ann Arbor

IOM Staff

ANNE B. CLAIBORNE, Forum Director
RITA S. GUENTHER, Program Officer
REBECCA A. ENGLISH, Associate Program Officer
ELIZABETH F. C. TYSON, Research Associate
ANDREW M. POPE, Director, Board on Health Sciences Policy
ROBIN GUYSE, Senior Program Assistant

[1] Institute of Medicine planning committees are solely responsible for organizing the workshop, identifying topics, and choosing speakers. The responsibility for the published workshop summary rests with the workshop rapporteurs and the institution.

[2] Paul Nunn was with the World Health Organization during the planning of the workshop.

FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION[1]

JEFFREY M. DRAZEN (*Co-Chair*), *New England Journal of Medicine*, Boston, MA
STEVEN K. GALSON (*Co-Chair*), Amgen Inc., Thousand Oaks, CA
MARGARET ANDERSON, FasterCures, Washington, DC
HUGH AUCHINCLOSS, National Institute of Allergy and Infectious Diseases, Bethesda, MD
CHRISTOPHER AUSTIN, National Center for Advancing Translational Sciences, Bethesda, MD
LESLIE Z. BENET, University of California, San Francisco
ANN BONHAM, Association of American Medical Colleges, Washington, DC
LINDA BRADY, National Institute of Mental Health, Bethesda, MD
ROBERT CALIFF, Duke University Medical Center, Durham, NC
C. THOMAS CASKEY, Baylor College of Medicine, Houston, TX
GAIL H. CASSELL, Harvard Medical School (Visiting), Carmel, IN
PETER B. CORR, Celtic Therapeutics, LLLP, New York, NY
ANDREW M. DAHLEM, Eli Lilly and Company, Indianapolis, IN
TAMARA DARSOW, American Diabetes Association, Alexandria, VA
JAMES H. DOROSHOW, National Cancer Institute, Bethesda, MD
GARY L. FILERMAN, Atlas Health Foundation, McLean, VA
GARRET A. FITZGERALD, University of Pennsylvania School of Medicine, Philadelphia
MARK J. GOLDBERGER, Abbott Pharmaceuticals, Rockville, MD
HARRY B. GREENBERG, Stanford University School of Medicine, CA
STEPHEN GROFT, National Center for Advancing Translational Sciences, Bethesda, MD
LYNN HUDSON, Critical Path Institute, Tucson, AZ
MICHAEL KATZ, March of Dimes Foundation, White Plains, NY
PETRA KAUFMANN, National Institute of Neurological Disorders and Stroke, Bethesda, MD
JACK D. KEENE, Duke University Medical Center, Durham, NC
RONALD L. KRALL, University of Pennsylvania Center for Bioethics, Steamboat Springs, CO
FREDA LEWIS-HALL, Pfizer Inc., New York, NY
MARK B. McCLELLAN, The Brookings Institution, Washington, DC
CAROL MIMURA, University of California, Berkeley

[1] Institute of Medicine forums and roundtables do not issue, review, or approve individual documents. The responsibility for the published workshop summary rests with the workshop rapporteurs and the institution.

ELIZABETH (BETSY) MYERS, Doris Duke Charitable Foundation, New York, NY
JOHN ORLOFF, Novartis Pharmaceuticals Corporation, East Hanover, NJ
AMY PATTERSON, National Institutes of Health, Bethesda, MD
MICHAEL ROSENBLATT, Merck & Co., Inc., Whitehouse Station, NJ
JANET SHOEMAKER, American Society for Microbiology, Washington, DC
ELLEN SIGAL, Friends of Cancer Research, Washington, DC
ELLIOTT SIGAL, Bristol-Myers Squibb, Princeton, NJ
ELLEN R. STRAHLMAN, GlaxoSmithKline, Research Triangle Park, NC
NANCY SUNG, Burroughs Wellcome Fund, Research Triangle Park, NC
JANET TOBIAS, Ikana Media and Mount Sinai School of Medicine, New York, NY
JOANNE WALDSTREICHER, Janssen Research & Development, LLC, Raritan, NJ
JANET WOODCOCK, Food and Drug Administration, White Oak, MD

IOM Staff

ANNE B. CLAIBORNE, Forum Director
RITA S. GUENTHER, Program Officer
REBECCA A. ENGLISH, Associate Program Officer
ELIZABETH F. C. TYSON, Research Associate
ANDREW M. POPE, Director, Board on Health Sciences Policy
ROBIN GUYSE, Senior Program Assistant

Reviewers

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

Colin Boyle, University of California, San Francisco, Global Health Sciences
Jennifer Furin, Case Western Reserve University School of Medicine
Robert Matiru, UNITAID
Owen Robinson, Partners In Health

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 **Enriqueta C. Bond,** QE Philanthropic Advisors. Appointed by the Institute of Medicine, she 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.

Contents

APPENDIXES

Table, Figures, and Boxes

TABLE

FIGURES

BOXES

Acronyms

ACT	artemisinin-combination therapy
AIDS	acquired immune deficiency syndrome
AMC	advance market commitment
AMFm	Affordable Medicines Facility-malaria
AMRH	African Medicines Regulatory Harmonization
APC	advance purchase commitment
API	active pharmaceutical ingredient
ARV	antiretroviral
BMGF	Bill & Melinda Gates Foundation
BRICS	Brazil, Russia, India, China, and South Africa
CDC	U.S. Centers for Disease Control and Prevention
CHAI	Clinton Health Access Initiative
DOT	directly observed treatment
DOTS	Directly Observed Treatment-Short course
DR TB	drug-resistant tuberculosis
DST	drug susceptibility testing
EMA	European Medicines Agency
EMR	electronic medical record
FDA	U.S. Food and Drug Administration
FLD	first-line anti-TB drug

FPP	finished pharmaceutical product
GDF	Global Drug Facility
GHC	Global Health Committee
GLC	Green Light Committee
HCP	health care professional
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFFIm	International Finance Facility for Immunization
IOM	Institute of Medicine
IQA	internationally quality-assured
MDR TB	multidrug-resistant tuberculosis
MSF	Médecins Sans Frontières
MSH	Management Sciences for Health
M.tb.	*Mycobacterium tuberculosis*
NGO	nongovernmental organization
NRA	national regulatory authority
NTP	national TB control programme
OpenMRS	Open Medical Record System
PAS	4-aminosalicylic acid
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PMDT	programmatic management of drug-resistant tuberculosis
PQ	prequalified (by WHO)
PRI	Program-Related Investment
QA	quality-assured/quality assurance
QC	quality control
SCM	supply chain management
SCMS	Supply Chain Management System (PEPFAR/USAID)
SLD	second-line anti-TB drug
SLDAII	Second-Line Drug Access Improvement Initiative
SMS	short message service
SRA	stringent regulatory authority

TB	tuberculosis
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization
WHO PQ	WHO prequalification
WHO PQP	WHO Prequalification of Medicines Programme
XDR TB	extensively drug-resistant tuberculosis

1

Introduction[1]

To effectively treat patients diagnosed with drug-resistant (DR) tuberculosis (TB) and protect the population from further transmission of this infectious disease, an uninterrupted supply of quality-assured (QA), second-line anti-TB drugs (SLDs) is necessary. Patients diagnosed with multidrug-resistant tuberculosis (MDR TB)—a disease caused by strains of *Mycobacterium tuberculosis* (*M.tb.*) resistant to two primary TB drugs (isoniazid and rifampicin)—face lengthy treatment regimens of 2 years or more with daily, directly observed treatment (DOT) with SLDs that are less potent, more toxic, and more expensive than those used to treat drug-susceptible TB. From 2000 to 2009, only 0.2–0.5 percent of the estimated 5 million MDR TB cases globally were treated with drugs of known quality and in programs capable of delivering appropriate care (Keshavjee, 2012). The vast majority of MDR TB patients either died from lack of treatment or contributed to the spread of MDR TB in their communities. A strengthened global supply chain for SLDs could save lives by consistently delivering high-quality medicines to more of the people who need them.

When SLDs are unavailable to a national TB control programme (NTP) and medical providers in a particular country, patients miss critical doses of medicine or never start treatment—risking the escalation of disease and

[1] The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the Forum or the Institute of Medicine (IOM), and they should not be construed as reflecting any group consensus.

amplification of drug resistance, enhanced infectivity and transmission of disease to others, and death. Ensuring a reliable and affordable supply of high-quality SLDs is a complex public health intervention that, thus far, has not been organized or implemented in a way that allows all providers and patients access to SLDs when they are needed. Some MDR TB patients without access to SLDs through a Green Light Committee (GLC)-approved program may receive appropriate treatment through a government-run or other QA program. However, it is estimated that approximately 90 percent of patients with DR TB are not receiving treatment through a government-run or QA program. In other words, these patients are likely receiving treatment from sources of unknown quality or no treatment at all. In recent years, many countries have been working to scale up MDR TB treatment programs but, as mentioned by several workshop participants, efforts by international organizations and institutions to ensure SLDs are delivered to patients have not kept pace with global MDR TB needs. Challenges facing the global supply chain for SLDs, and the efficient delivery of drugs to patients, include

- The overall market for SLDs is relatively small due to limited diagnostic capacity at the country level.
- Demand-forecasting mechanisms do not fully capture patient needs for SLDs.
- Markets are opaque, with high barriers to entry that may deter manufacturers.
- Drugs to treat MDR TB carry high prices and have a short shelf life (24 months) compared with treatments for drug-susceptible TB.
- Once drugs are ordered, there are lengthy time lines to reach the country.

The July 31–August 1, 2012, workshop was convened by the Forum on Drug Discovery, Development, and Translation ("the Forum") of the Institute of Medicine (IOM) in Washington, DC, to explore options and opportunities to improve the effectiveness of the global SLD supply chain in delivering drugs to patients. Titled "Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant TB," the workshop was part of a series sponsored by the Forum to gather information from experts around the world on DR TB prevention, diagnosis, treatment, and management.

The Forum held a foundational workshop in Washington, DC, in 2008. The summary of that workshop, *Addressing the Threat of Drug-Resistant Tuberculosis: A Realistic Assessment of the Challenge: Workshop Summary* (IOM, 2009), and the accompanying white paper (Keshavjee and Seung, 2008) provided background for and informed the development of four

subsequent workshops in countries with a high burden of DR TB. The first workshop in the international series was held in Pretoria, South Africa, on March 3–4, 2010 (IOM, 2011a). The second workshop was held in Moscow, Russia, on May 26–27, 2010 (IOM, 2011b). The third workshop was held in New Delhi, India, on April 18–19 and 21, 2011 (IOM, 2012), and the final workshop in the series is being planned for January 2013 in Beijing, China. Box 1-1 includes some key themes related to the drug supply chain that emerged from the workshops in Washington, DC, South Africa, Russia, and India.

The workshop summarized in this volume was convened by the Forum to provide a setting for fostering a dialogue on the needs and opportunities for a global supply chain for TB SLDs. The workshop brought together members of the international TB community—including individuals from U.S. federal agencies, international health authorities, nongovernmental organizations (NGOs), the private sector, academia, and advocacy groups, for 2 days of informative presentations and robust discussion. Box 1-2 lists the objectives of the workshop.

In her opening remarks, Gail Cassell, Visiting Professor, Department of Global Health and Social Medicine, Harvard Medical School, warned that failing to address current SLD supply issues would perpetuate the present situation in which the majority of MDR TB patients are undiagnosed and untreated while simultaneously fostering the development of rapid resistance to new TB drugs in the pipeline. Since the 2008 workshop (IOM, 2009), data have emerged to suggest that the burden of MDR and extensively drug-resistant tuberculosis (XDR TB) is underestimated (Wallengren et al., 2011) and has not only reached global pandemic proportions, but is being fueled by patients who are undiagnosed or who are receiving inadequate treatment (Keshavjee and Farmer, 2012). Data from KwaZulu-Natal, South Africa, show that 88 percent of XDR TB cases are untreatable with drugs currently available in South Africa.[2] China has the highest annual number of MDR TB cases in the world; a survey published by the Chinese Center for Disease Control and Prevention indicated that 10 percent of Chinese TB patients have MDR TB, and 8 percent of those with MDR have XDR TB (Zhao et al., 2012). The same survey in China also revealed that primary transmission, or person-to-person spread, of DR TB accounted for 78 percent of new MDR TB cases and 86 percent of new XDR TB cases. In sum, Cassell noted that there has been an increasing recognition in recent years that DR TB strains are just as easily transmissible from person-to-

[2] Data provided via personal communication, October 15, 2012, with Kristina Wallengren, KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH), Nelson R. Mandela School of Medicine, University of KwaZulu-Natal.

BOX 1-1
Key Drug Supply Chain Themes from Previous IOM Forum Publications[a]

- Diagnosing, treating, and managing DR TB is a complex public health intervention presenting multiple opportunities to improve the scientific, clinical, and organizational aspects of the intervention. Improvements to the efficiency and effectiveness of the global supply chain for SLDs represent a significant opportunity to speed medicines to patients and avoid preventable morbidity and mortality from DR TB.
- The arrival of drugs into beneficiary countries ordered through the GLC mechanism can be delayed for months, during which time patients are transmitting DR TB and dying.
- Limited, inconsistent, and unpredictable demand for SLDs is a key challenge for manufacturers of QA SLDs that results in backlogs, delays, and high prices.
- Increased market volumes could attract more manufacturers of QA drugs to the global SLD market and increase competition, reduce prices, and increase availability.
- Greater transparency and visibility for manufacturers with regard to demand, QA processes, and financing could improve the SLD supply chain.

person as drug-susceptible strains, which was previously not believed to be the case, heightening the need to prioritize MDR TB infection control.

BACKGROUND AND HISTORY OF THE CURRENT GLC MECHANISM

History Prior to the Formation of GLC[3]

The GLC mechanism was developed in response to the widespread emergence of resistance to first-line anti-TB drugs (FLDs) that began in the 1980s and that has gained momentum rapidly since the 1990s. Peter Cegielski, Team Leader for Drug-Resistant TB, International Research and

[3] This subsection is based on the presentation by Peter Cegielski, Team Leader for Drug-Resistant TB, International Research and Programs Branch, Division of Tuberculosis Elimination, U.S. Centers for Disease Control and Prevention (CDC).

- The forecast and demand management aspects of procurement have a high degree of uncertainty.
- Procurement processes for drug provision mechanisms could be improved and streamlined.
- Regulatory processes, quality standards, and treatment regimens could benefit from harmonization among countries in order to reduce barriers to suppliers entering the SLD market.
- Information management systems could improve tracking of operational activities of DR TB supply chains.
- Ensuring the timely delivery of high-quality SLDs to patients is part of a complex health care challenge that includes several steps, from initial testing, diagnosis, and treatment protocols to drug manufacturing and delivery to initiation and completion of treatment.

[a] Based on remarks from Gail Cassell, Visiting Professor, Department of Global Health and Social Medicine, Harvard Medical School; and *Stemming the Tide of Multidrug-Resistant Tuberculosis: Major Barriers to Addressing the Growing Epidemic* (Keshavjee and Seung, 2008); *Addressing the Threat of Drug-Resistant Tuberculosis: A Realistic Assessment of the Challenge: Workshop Summary* (IOM, 2009); *The Emerging Threat of Drug-Resistant Tuberculosis in Southern Africa: Global and Local Challenges and Solutions: Workshop Summary* (IOM, 2011a); *The New Profile of Drug-Resistant Tuberculosis in Russia: A Global and Local Perspective: Workshop Summary* (IOM, 2011b); and *Facing the Reality of Drug-Resistant Tuberculosis in India: Challenges and Potential Solutions: Workshop Summary* (IOM, 2012).

Programs Branch, Division of Tuberculosis Elimination, U.S. Centers for Disease Control and Prevention (CDC), provided historical background about the formation of the GLC initiative in the late 1990s. The history and design of the GLC mechanism provides context and a basis for understanding the current challenges facing efforts to supply SLDs to the global MDR TB population.

According to Cegielski, the period spanning the 1940s to the 1970s was a "golden era" for TB drug development, in which dozens of new compounds were developed into commercial products. Concurrently, microbiological methods to test for susceptibility to those new drugs were developed. By the early 1970s, the superior efficacy of the three-drug regimen of isoniazid, rifampicin, and pyrazinamide had been established by extensive clinical trials. The establishment of this efficient regimen consequently engendered a sense of optimism that TB had been conquered. Cegielski noted that this optimism led to a general complacency that left the world unprepared for the emergence of strains resistant to the regimen. Efforts to discover and

BOX 1-2
Statement of Task for the Workshop

This public workshop explored innovative solutions to the problem of how to get the right SLDs for MDR TB to people who critically need them. More specifically, the workshop examined current problems and potential opportunities for coordinated international efforts to ensure that a reliable and affordable supply of high-quality SLDs is available. The workshop objectives were to consider

- To what extent and in what ways current mechanisms are or are not effectively accomplishing what is needed, including consideration of bottlenecks
  - The advantages and disadvantages of centralization in the management of the global drug supply chain, and potential decentralized approaches to improve operations of the supply chain
  - What can be learned from case studies and examples from other diseases (e.g., the Affordable Medicines Facility-malaria [AMFm] and the U.S. President's Emergency Plan for AIDS Relief [PEPFAR])
- The current allocation of responsibilities and roles of the private (including industry and nonprofit public health organizations) and public sectors, and examination of opportunities for enhancing and optimizing collaboration
- Identification of potential innovative solutions to the problem

develop new drugs ended, and drug production was massively curtailed as the spread of disease slowed, particularly in wealthier countries. This period coincided with many nations' development into middle-income countries with their own domestic pharmaceutical industries. Because those industries often lacked stringent QA/QC (quality control) standards, the volume of substandard and counterfeit drugs infiltrating the market rose, and an incipient resistance to the standard TB drug regimen resulted. By the 1980s, rifampicin resistance had emerged as a serious problem in many areas of the world. In the 1990s, the Global Drug Resistance surveys carried out by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease ("The Union") demonstrated the magnitude of the worldwide MDR TB burden. The consequent surge in demand for SLDs revealed widespread supply, cost, and availability problems.[4]

[4] An exception is fluoroquinolones. They are effective against TB, but because they were developed for other indications, production is robust and pricing and supply are therefore not an issue.

MDR TB has persisted for 20 years, suggested Cegielski, because during the 1990s and into the 2000s, TB experts, public health leaders, and leadership organizations were polarized about how to respond to MDR TB outbreaks. One faction held the view that services for MDR TB should not be integrated into TB control programs; the other faction held the opposite point of view, that the MDR TB problem should be addressed head on through an MDR-specific strategy. Cegielski stated that the effect of this polarization was an overall ambivalence, with a lack of strategic guidance and policy setting due largely to "a failure of leadership to respond vigorously to the MDR TB problem." Consequently, low- and middle-income countries failed to develop sufficient diagnostic capacity, clinical expertise, markets, or regulatory capacity to treat MDR TB successfully. Lack of technical expertise therefore became a barrier to MDR TB treatment. Also during this time, many NTP managers did not develop adequate systems to procure SLDs or develop sufficient laboratory capacity.

Cegielski suggested that price also emerged as a primary barrier to expanding MDR TB treatment. He attributed this issue in part to national policies guided by public health leadership organizations opposed to treating MDR TB, which had the result of allocating insufficient resources from ministries of health to NTPs. This landscape began to change slowly in the late 1990s and early 2000s, when GLC; the Global Fund to Fight AIDS, Tuberculosis and Malaria ("the Global Fund"); and other initiatives were developed to address MDR TB by mitigating the barriers of expertise and price.

Formation of GLC[5]

Salmaan Keshavjee, Director, Program in Infectious Disease and Social Change, Department of Global Health and Social Medicine, Harvard Medical School, described the formation of GLC in response to evidence of the emerging MDR TB epidemic in the 1990s. Initially, GLC was designed as a pilot project mechanism to provide affordable SLDs and to gather data about those projects to inform global policy on the treatment of MDR TB. He also explained the structural and functional evolution of the GLC mechanism, from its initial development as a multi-institutional partnership composed of global stakeholders to its current configuration as an advisory committee to WHO.

[5] This subection is based on the presentation by Salmaan Keshavjee, Director, Program in Infectious Disease and Social Change, Department of Global Health and Social Medicine, Harvard Medical School.

Rationale for Formation of GLC

In the 1990s, WHO introduced promotion of the Directly Observed Treatment-Short course (DOTS) treatment strategy. The DOTS approach in the 1990s included five components: political commitment with increased and sustained financing; case detection through sputum smear microscopy; standardized treatment with supervision; an effective drug supply and management system; and a monitoring and evaluation system and impact measurement.[6] In many ways, the introduction of DOTS followed the framework of the selective primary health care movement of the 1980s, which focused on providing low-cost, highly effective interventions for diseases that were identified as particularly threatening to public health (although the primary health care movement itself excluded TB, categorizing it as category II [Walsh and Warren, 1979]). However, the rollout of the DOTS intervention, which was designed specifically for treating drug-susceptible TB, did not address the rising specter of MDR TB. At that time, WHO had advised against treating DR TB, particularly in low-income countries, citing a concern that such a treatment strategy would detract attention and resources from the treatment of drug-susceptible disease. Thus, resistant disease was progressively transmitted and the epidemic continued to grow. In 1993, WHO began conducting annual global surveys to assess drug resistance, which indicated the presence of resistance to TB drugs in all 35 countries reviewed.

In response to an MDR TB epidemic in Lima, Peru, Partners In Health carried out a pilot project for community-based treatment of MDR TB. The project was based on the approach used by New York City to address their MDR TB epidemic in the late 1980s, which had resulted in positive outcomes for MDR TB patients. The success of that pilot project started a movement leading to the creation of the "DOTS-Plus" framework for the treatment of MDR TB, which extended the existing DOTS program to include treatment of MDR TB with second-line anti-TB agents. DOTS-Plus pilot projects were designed to collect data from low-income countries with the objective of enabling WHO to change its policy on the treatment of MDR TB in resource-limited settings.

A mechanism was needed to make SLDs available at a low cost to those projects. GLC was therefore created between 1998 and 2000 as a multi-institutional partnership to address the high cost of MDR TB drugs. Modeled on an approach to make meningitis vaccines available in resource-limited settings, GLC provided access to low-cost SLDs exclusively to DOTS-Plus pilot projects that were meeting certain programmatic bench-

[6] See http://www.who.int/tb/dots/en/index.html (accessed October 18, 2012).

marks. The rationale for this selectivity was to ensure that the drugs were used properly in controlled settings in the pilot programs.

System of Pilot Projects

Keshavjee stressed that the GLC mechanism was not intended for scale-up, but was designed to facilitate a series of pilot projects intended to provide data to change global policy about MDR TB. Between 2000 and 2009, the number of pilot projects grew rapidly (Figure 1-1).

Organizational Structure of GLC

GLC's multi-institutional partnership was hosted by WHO's TB department as part of one of its working groups and was transferred to the Stop TB Partnership when that partnership was formed in 2001. As the number of pilot projects began to increase in 2005, the Global Drug Facility (GDF) was brought into the system beginning in 2007 to purchase the increasing volume of SLDs through procurement agents, based on a formal agreement with the GLC Secretariat that year.[7]

Keshavjee noted that the GLC mechanism had many positive aspects—most notably the success in encouraging programs to provide a high standard of care to patients, and encouraging countries to view the pilot projects as models for national scale-up. However, Keshavjee added, the fact that GLC functioned as a "centralized node of control" (Figure 1-2) had some negative implications. For example, instead of seeing MDR TB as an urgent need that must be rapidly addressed as a public health concern, countries applied to GLC seeking permission to treat their MDR TB patients in a pilot project format. Applications were evaluated on a program's capacity to diagnose patients and deliver appropriate care. Approved applications were then passed on to the GLC Secretariat, hosted by WHO, which functions in an administrative capacity. WHO's Stop TB Department provides technical assistance in starting, evaluating, and monitoring beneficiary countries' MDR TB programs and connects with countries and partners.

Keshavjee noted that all the components of the current system are actually situated within the WHO mechanism (including the Stop TB Partnership, which has no legal identity of its own). He added that eventually WHO's legal department ruled that GLC could no longer exist as a multi-institutional partnership because GLC and the entire Stop TB Partnership were legally part of WHO, and the current system of involvement of multiple non-WHO institutions was not consistent with WHO rules. As a result, the original system was disbanded. An advisory body to WHO

[7] Médecins Sans Frontières (MSF) purchased drugs for GLC in 2001 and 2002.

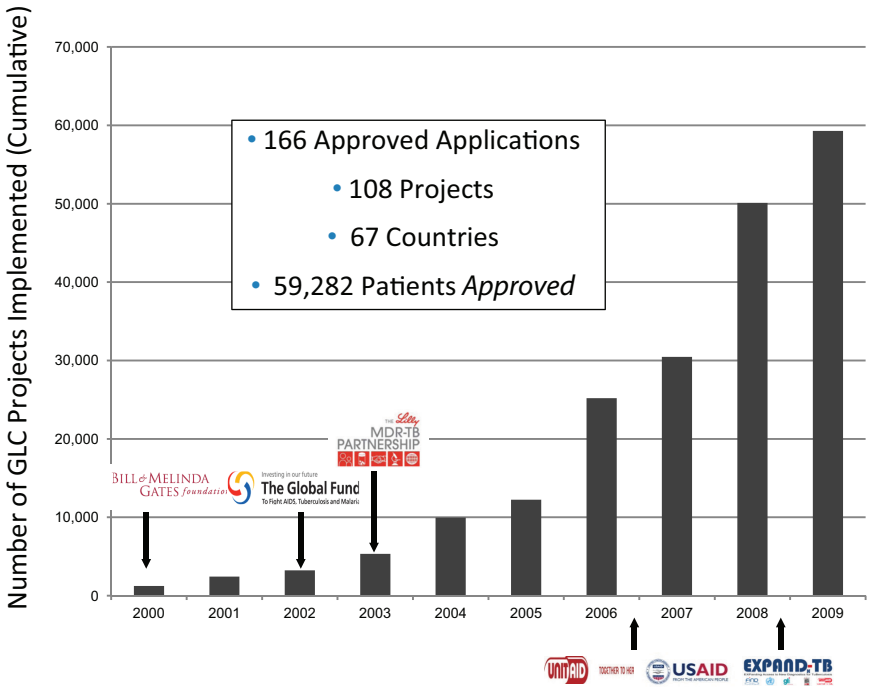


FIGURE 1-1 Number of GLC pilot projects implemented around the world between 2000 and 2009.
SOURCE: Keshavjee, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis, adapted from Dr. Ernesto Jaramillo, WHO, Geneva.

with a similar name—designed to keep the GLC "brand" but composed of individual experts, not stakeholders or partners—now exists instead.

Financing and Procurement Requirements

Currently, GLC MDR TB projects are financed by grants from the Global Fund, UNITAID, and other public and private sources of funding. Since 2002, the Global Fund has required that all SLD procurement for MDR TB programs that it funds go through GLC. This policy seeks to control the emergence of SLD resistance by ensuring the use of only QA drugs. Keshavjee emphasized that beneficiary countries are not allowed to use Global Fund or UNITAID monies to purchase SLDs directly from manufacturers, regardless of the QA status of the supplier. He also noted

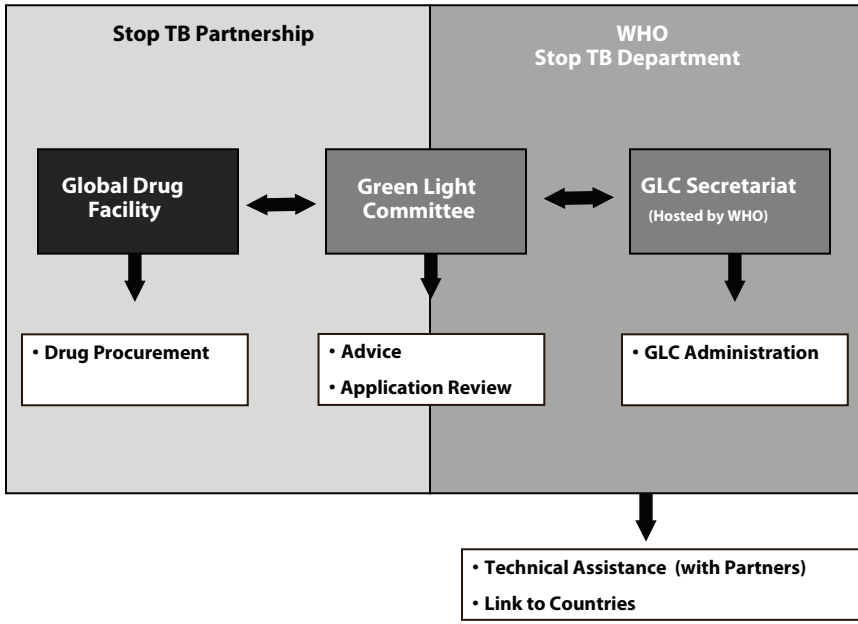


FIGURE 1-2 Creation of a centralized node of control for the GLC-approved SLD supply chain.
SOURCE: Keshavjee, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

that the WHO system, including use of GDF to oversee procurement, has not successfully optimized pooled procurement—it places orders only when funds are made available by countries/programs. Likewise, it also does not optimize direct price negotiation with manufacturers, and little active negotiation occurred after the initial lowering of prices in 2000.

Change in WHO Policy

Keshavjee stated that GLC's initial objective of gathering data from pilot programs to effect change in WHO's MDR TB policy was achieved in 2006. He described how WHO's global treatment and program recommendations were changed to apply the standard of MDR TB care used in places like New York City in the early 1990s to all countries worldwide. The standard of care included the use of drug sensitivity testing to diagnose drug resistance, the provision of SLDs, and the delivery of care with appropriate monitoring and treatment of adverse events (WHO, 2006).

PRINCIPLES OF DRUG SUPPLY CHAINS[8]

Understanding the fundamental principles and processes that underlie the efficient operation of drug supply chains in general is a critical first step in developing targeted, concrete strategies for addressing the specific problems that impede the effective operation of the current SLD supply chain. Prashant Yadav, Director, Healthcare Research Initiative, William Davidson Institute, University of Michigan, and Sana Mostaghim, MDR TB Drug Access Project Manager, Clinton Health Access Initiative (CHAI), delivered presentations that provided a technical overview of the structure and principles of drug supply chains. They described the mechanics of scaling up to deliver increased volumes and the effects of limited or "lumpy" demand on manufacturers and on prices. They also explained how market-shaping strategies can improve the efficiency of drug supply chains. In addition, the relationships between key market drivers and elements of price were examined in the context of potential strategies for improving access to treatment by mitigating the barriers of high prices and limited availability of SLDs.

SLD Supply Chain Structure[9]

A key characteristic of the supply chain for a predominantly donor-funded drug market, such as the current SLD market MDR TB, is that its two components, the "upstream" segment and the "downstream" segment, are decoupled from one another. This has important implications with regard to issues such as demand, pricing, scale-up, and financing (Figure 1-3).

The structure of the global, or "upstream," segment of the supply chain comprises

- manufacture of starting material, active pharmaceutical ingredient (API), and finished pharmaceutical product (FPP);
- procurement, financing, and forecasting; and
- warehousing of drugs (prior to shipment to countries).

The domestic, or "downstream," segment includes the in-country warehousing components, delivery of drugs to clinics, and treatment of patients.

[8] This section is based on the presentations by Prashant Yadav, Director, Healthcare Research Initiative, William Davidson Institute, University of Michigan, and Sana Mostaghim, MDR TB Drug Access Project Manager, Clinton Health Access Initiative (CHAI).

[9] This subsection is based on the presentation by Prashant Yadav, Director, Healthcare Research Initiative, William Davidson Institute, University of Michigan.

Challenges of Scaling Up: The "Sequence Question"[10]

The structure of a well-functioning upstream SLD supply chain should be able to fulfill existing demand and be able to scale up as needed to serve a larger number of patients if there is an increase in demand for SLDs. Two issues, if present, would raise concern about a global supply chain: (1) if the existing supply chain has structural problems (e.g., high prices, long lead times, and poor service levels) and (2) if only a small fraction of the potential demand is currently being served by the supply chain (i.e., when there is a potential latent demand for products that far exceeds the current actual demand).

The presence of those factors could indicate that the supply chain in question is not properly equipped to scale up and cope with that potential demand efficiently. Decisions about how to deal most effectively with this kind of supply chain inefficiency depend on what Yadav called the "sequence question." This question concerns the best way to bolster the supply chain's ability to serve a much larger number of people, and hinges on an understanding of the sequential relationship between increasing the demand for products and decreasing the price of those products.

The first option for answering the sequence question is to devote resources to diagnosing and treating the disease (i.e., demand creation) under the assumption that the resulting volume efficiencies will trigger decreases in product prices. The alternative option is a decrease in the price as a prerequisite for demand increase; that is, does the supply chain need to be improved (in terms of pricing, lead times, and service levels) before demand creation will have a "pay-off."

Price, Cost, and Volume Relationships[11]

In considering the best way to sequence and optimally allocate resources, Yadav stressed that it is important to understand that the relationship between price and volume is not the same as the relationship between cost and volume. This is due to the market structure that comes in between the cost- and price-volume relationship. In product segments with few suppliers, only a fraction of a producer's decrease in cost is actually passed on to the buyer in the form of a price decrease. In other words, when producers' costs decrease due to an increase in volume, the extent to which that decrease in cost will be reflected in a price decrease is dependent on the market structure. The market structure is itself contingent on both

[10] This subsection is based on the presentation by Prashant Yadav, Director, Healthcare Research Initiative, William Davidson Institute, University of Michigan.

[11] This subsection is based on the presentation by Prashant Yadav, Director, Healthcare Research Initiative, William Davidson Institute, University of Michigan.

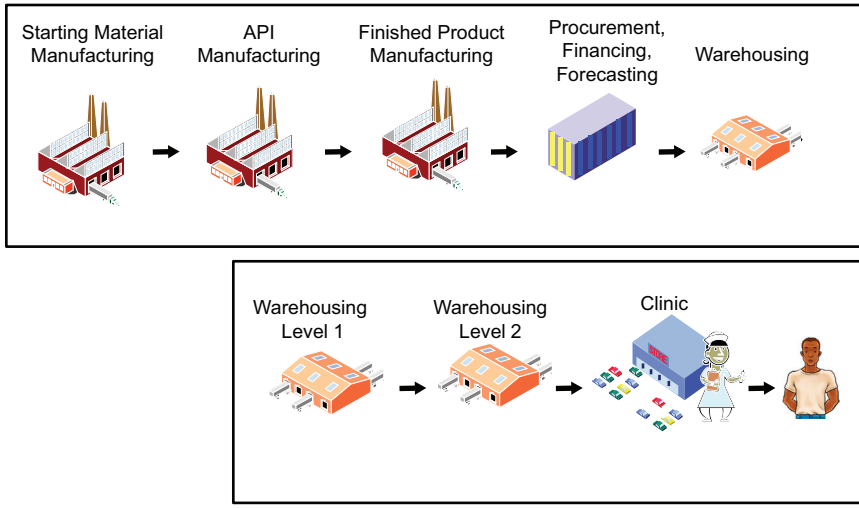


FIGURE 1-3 Existing supply chain for SLDs.
NOTE: API, active pharmaceutical ingredient.
SOURCE: Yadav, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

the degree of competitiveness in the market and the effectiveness of the procurement organization(s). Thus those two factors also determine the extent to which cost decrease due to volume increase will manifest as an actual price decrease.

Market Segmentation and Price Elasticity of Demand[12]

Yadav emphasized that the current SLD supply chain actually has two types of separately financed supply chains: the internationally financed supply chain operated by GDF and the domestically financed supply chain operated in a given country. The overall SLD drug market therefore faces a unique situation with regard to price and demand elasticity.

Yadav cited a modeling exercise for the market of an unspecified SLD treatment, which revealed that doubling the demand of that treatment led to a decrease in cost of approximately 17 percent. However, market structure dictated that only 50 percent of that decreased cost was reflected in the price, that is, there was a decrease of only about 8 percent as a result of doubling the volume. In the internationally financed portion of the sup-

[12] This subsection is based on the presentation by Prashant Yadav, Director, Healthcare Research Initiative, William Davidson Institute, University of Michigan.

ply chain, demand is relatively inelastic to small changes in price (in other words, small changes in price will not affect overall demand), whereas the domestically financed portion is a very price-elastic market. Thus when examining the overall market, with both supply chains, the demand curve is uniquely shaped. At the beginning it is extremely flat and unresponsive either to large volume changes or to small price changes, but at a certain point in the domestically financed portion of the market, volume will jump when the price point descends below a certain threshold. Yadav noted, however, that extensive modeling work would have to be performed to better understand what that threshold might be in a given market.

Use of Buffers or Stockpiles to Smooth Demand[13]

"Lumpy" demand patterns are a key structural challenge for small-volume SLD markets. Demand from NTPs is often very lumpy (i.e., erratic and inconsistent). This lumpy demand presents problems for pharmaceutical manufacturers with respect to costs, batch sizing, and changeovers. Yadav suggested that those problems could be addressed through the development of a buffer inventory or stockpile to smooth demand and thus to help increase batch sizes and decrease changeovers and costs (Figure 1-4). Whether those decreased costs would lead to significantly decreased prices ultimately depends on having the appropriate market structure.

Shifting the Push-Pull Boundary[14]

Yadav introduced the concept of the "push-pull" boundary in supply chain management (SCM), which delineates between those procedural steps in the chain that are based on forecasts and those that are based on actual orders. Processes in the supply chain include drug substance manufacturing, formulating and packaging, predelivery inspection, and shipping and transport. When most of those processes are order-driven as opposed to forecast-driven, manufacturers must contend with a suboptimal inventory-holding structure and batch-sizing calculus in which demand is low and lumpy, which in turn results in longer lead times and higher costs. In other words, the current market context is not conducive to planning ahead; manufacturers often wait for orders to arrive before initiating API production or FPP manufacturing.

Yadav suggested that to address the imbalance between order- and

[13] This subsection is based on the presentation by Prashant Yadav, Director, Healthcare Research Initiative, William Davidson Institute, University of Michigan.

[14] This subsection is based on the presentation by Prashant Yadav, Director, Healthcare Research Initiative, William Davidson Institute, University of Michigan.

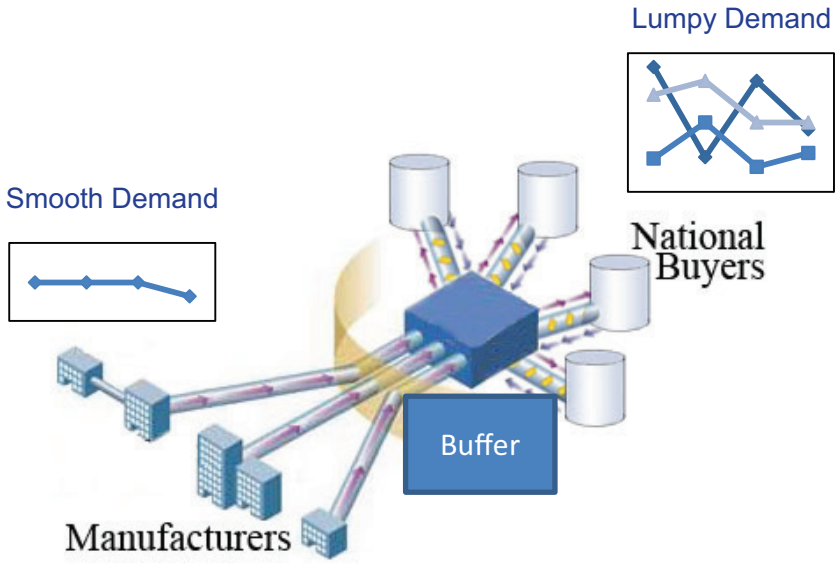


FIGURE 1-4 A "buffer" supply of SLDs smoothens the lumpiness of demand. Removing lumpiness in demand decreases changeovers, increases batch sizes, and decreases costs. If market structure facilitates, then it would also lead to decreased prices.
SOURCE: Yadav, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

forecast-driven processes in the supply chain, the push-pull boundary could be manipulated such that the interface point is shifted toward expanding the number of forecast-driven steps in the supply chain (Figure 1-5) and away from the number of order-driven steps.

Such a shift would enable manufacturers to plan ahead and facilitate improved inventory-holding patterns and batch sizing. Yadav added that shifting this boundary would require the development of both innovative supply-contracting structures and more accurate demand-forecasting techniques.

SLD Market Drivers and Elements of Price[15]

Mostaghim addressed two crucial barriers in the upstream portion of the MDR TB drug supply chain—high prices and limited availability of

[15] This subsection is based on the presentation by Sana Mostaghim, MDR TB Drug Access Project Manager, CHAI.

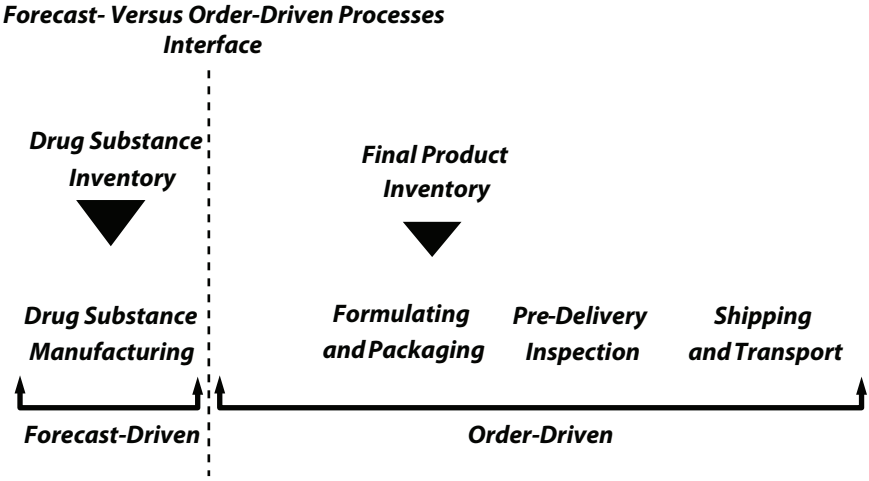


FIGURE 1-5 Shifting the push-pull boundary in the SLD supply chain. The current push-pull boundary leads to a suboptimal inventory-holding structure and a suboptimal batch-sizing calculus.
SOURCE: Yadav, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

QA SLDs. Mitigating those barriers and thus maximizing the operational efficiency of the supply chain could serve to increase the number of patients being treated and, ideally, ultimately contribute to controlling rates of DR TB. He also provided an illustrative case study on cycloserine (Box 1-3).

Four key elements factor into pricing of SLDs charged to procurement agents by manufacturers. They each have different market drivers (Figure 1-7). The first element that factors into pricing is the legitimate or "true cost" of manufacturing a given product, such as the costs of raw materials, labor, a reasonable margin, etc. Second, the "monopoly premium" element of price is driven by the lack of competition among manufacturers in the SLD market. Third, "risk premium" is the extent to which manufacturers (or partners) feel that they are in an ambiguous position with regard to investment decisions and confidence about, or visibility into, the market. The fourth element of price relates to economies of scale: the cost of subscale manufacturing, such as suboptimal batch sizes and production campaigns, which are driven by demand and order placement. The challenges facing the supply-and-demand structure for individual drugs in the SLD market are further elucidated with a case study of cycloserine (Box 1-3).

BOX 1-3
Cycloserine Case Study[a]

Examining the market for cycloserine is instructive for understanding the principles and challenges that underlie other major SLD markets (e.g., kanamycin, capreomycin, PAS [4-aminosalicylic acid] products), although each has unique characteristics. Upon examination, the market for QA cycloserine initially appears to be promisingly healthy and potentially competitive, with three formulators that are approved either by WHO prequalification (WHO PQ) or by a stringent regulatory authority (SRA) and more than one qualified API manufacturer. However, in reality its fundamental supply-and-demand structure is operating counter to the ultimate objective of affordable and sustainable access. For example, market fragmentation begins to occur at the drug packaging stage, where the same capsule formulation requires inner packaging in three different ways within four separate types of outer packaging. By the bottom level of the market, the eligible suppliers for each variety of packaged product have fragmented into four different silos that procurement agents must work with, effectively deteriorating the potential for healthy competition. A single manufacturer, Macleods, actually accounts for two of the silos, having developed a different variety of packaged product to comply with specific Indian requirements (Figure 1-6).

The upshot of this market fragmentation is effectively a monopoly situation. Despite having three eligible manufacturers of cycloserine, due to the incongruent technical specifications required by different treatment programs and countries, there is in practice only a single eligible manufacturer for each specific mode of packaging and tendering.

[a] This box is based on the presentation by Sana Mostaghim, MDR TB Drug Access Project Manager, CHAI.

BARRIERS, CHALLENGES, AND NEEDS

Cegielski moderated a multi-stakeholder discussion examining the specific barriers, challenges, and needs that prevent the SLD supply chain from operating at optimal efficiency to deliver drugs to MDR TB patients. The first part of this section sets forth an overview of the barriers and challenges that were raised during the individual presentations delivered by Keshavjee; Lucica Ditiu, Executive Secretary, Stop TB Partnership, WHO;

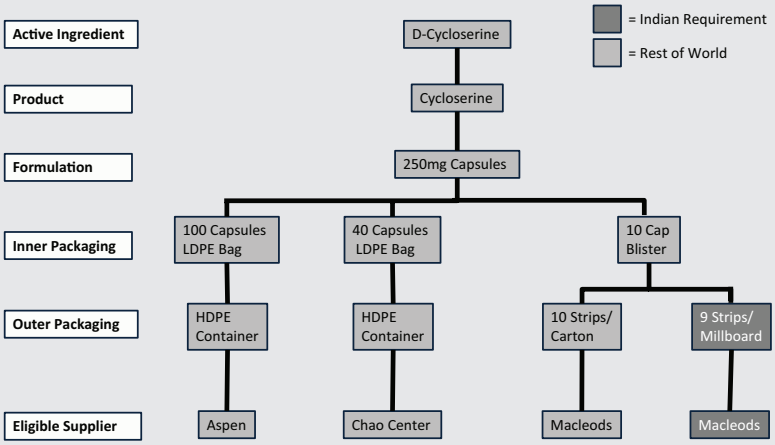


FIGURE 1-6 The current structure of supply and demand works against the goals of affordable and sustainable access.
NOTE: HDPE, high-density polyethylene; LDPE, low-density polyethylene.
SOURCE: Mostaghim, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

Yadav; Mostaghim; Rifat Atun, Professor of International Health Management, Imperial College London; and succeeding workshop discussions. The section is organized thematically to capture general topics covered by individual workshop participants, including the identification of bottlenecks and other supply chain structural issues; upstream supply chain barriers; financing needs; clinical challenges; and regulatory challenges. After covering these thematic issues, the section focuses on the perspectives of different stakeholders who elaborated on the specific supply chain barriers during

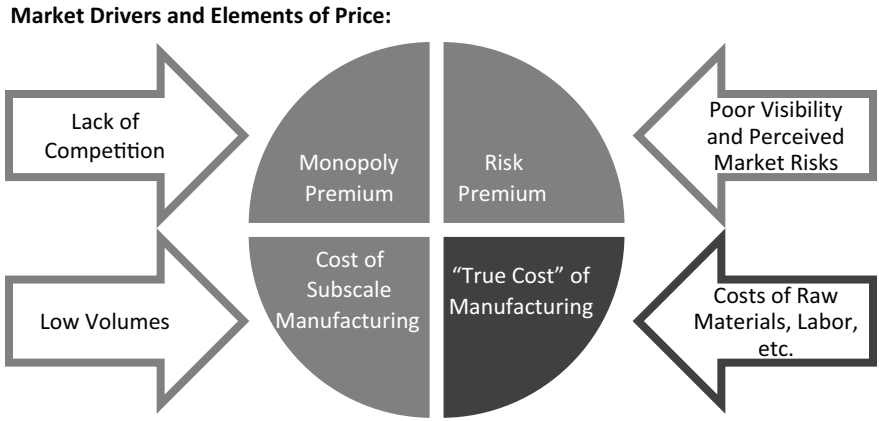


FIGURE 1-7 Key barriers to improving SLD access: high prices and limited availability of QA MDR TB drugs. Sufficiently deep volumes must be identified and leveraged to improve the situation and deflate the non-essential elements of price. SOURCE: Mostaghim/CHAI, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

panel discussions. Finally, the section compiles key messages and suggested ways forward as offered by the individual speakers and participants.[16]

Plenary Overview of Barriers and Challenges

Structural Challenges and Needs

Delay points. Keshavjee described an analysis carried out by GLC that identified multiple delay points for SLDs occurring within the GLC mechanism. The GLC analysis explored the average length of delays that occur among different cogs in the system, from the country's or TB program's initial application (which could be made by either the NTP directly, or an NGO working with NTP approval) to GLC, to the arrival of the drugs at treatment sites. For example, depending on when an application requesting permission to treat patients is received by the GLC Expert Committee,

[16] Although a few WHO employees were able to participate in the meeting, the leadership of the WHO Stop TB Department and the Global Fund, who had been invited to participate, were regrettably unable to attend. The viewpoints of stakeholders expressed in this summary are, per IOM guidelines, those views specifically expressed at the workshop. Several workshop participants noted that it will be important to follow up with and include WHO and the Global Fund in ongoing and future discussions.

it could take 1–3 months for a decision to be made and then referred to the GLC Secretariat to address any required technical issues. At that point there is a potential 2- to 6-month wait for the provision of WHO technical support (including receipt of a final report to the country). Once technical issues are resolved—and this sometimes takes months—there is often another delay averaging 1–4 months for the country or program to organize a procurement order with GDF, and a similar additional delay occurring between GDF and the GDF procurement agent. Keshavjee cited delays of days or months for the funding agency to release money, for the drugs to pass through customs and regulatory processes upon arrival in country, and for the drugs actually to be delivered to treatment sites (Figure 1-8).

Bottlenecks. Ditiu outlined a list of potential points in the system at which patients can face bottlenecks or barriers to receiving MDR TB treatment through the GLC mechanism. First, she noted, the patient must be empowered to seek help for his or her disease and have access to health care, diagnosis (testing, results, and follow-up), and good treatment advice; then the patient must receive appropriate therapeutic recommendations (e.g., drug

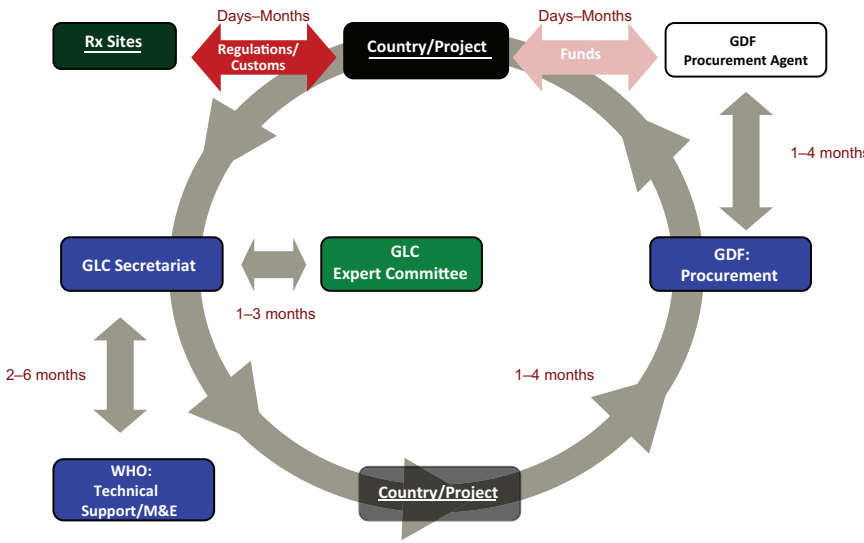


FIGURE 1-8 The GLC initiative flow through cycle.
NOTE: M&E, monitoring and evaluation.
SOURCE: Keshavjee, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

regimen). Patients in a given country must then have access to the SLD supply chain, and SLDs must actually be available to that country through the supply chain. The latter requires that national governments acknowledge the problem of DR TB and translate this into a political commitment to obtain SLDs.

Challenges of GDF/GLC system design. Keshavjee emphasized that GLC and GDF were initially designed to support pilot projects of DR TB programs (i.e., GLC was not designed for scale-up to meet global demand, and GDF was mandated to provide SLDs only to GLC-approved projects/cohorts). From that perspective, GLC accomplished its primary goal, which was to facilitate access to low-cost SLDs in order to collect data that could support WHO endorsement of a policy of treating MDR TB in resource-poor settings as part of an integrated TB treatment and management strategy. However, he noted, because much-needed operational changes to support conversion from a pilot project system were never made, the GLC mechanism became structurally incapable of facilitating treatment for the vast majority of MDR TB patients. He noted that GLC and GDF continue to function on a scale more consistent with pilot projects than with the scale of actual patient need. Keshavjee estimated that the GLC mechanism treated only 0.2–0.5 percent of the estimated number of patients in need of SLDs worldwide in the past 10 years (Figure 1-9). He noted that many of those patients who did not receive treatment with drugs of known quality and in programs capable of delivering appropriate care either died from a lack of treatment or have contributed to the spread of MDR TB in their communities.

Keshavjee noted that the spread of MDR and XDR TB is partly a consequence of the lack of scale-up of high-quality treatment programs. This has led to both ongoing transmission of drug-resistant strains in the community, and the acquisition of drug resistance through patients purchasing SLDs of unknown quality in the private sector and taking short and irregular courses of medicines without appropriate medical supervision and support.

Ditiu suggested that, in her opinion, as a consequence of the pilot project system, few countries—with the exceptions of Brazil, India, and South Africa—are currently aiming to diagnose all of their cases of MDR TB and enroll patients in treatment programs. She noted that the pilot project system has the result that countries often consider MDR TB to be a separate issue from the drug-susceptible TB issue and continue to focus on treating cohorts of MDR TB patients rather than addressing treatment of patients across the entire disease spectrum. She also noted that GDF was designed as an agency for preplanned orders, not as an emergency response

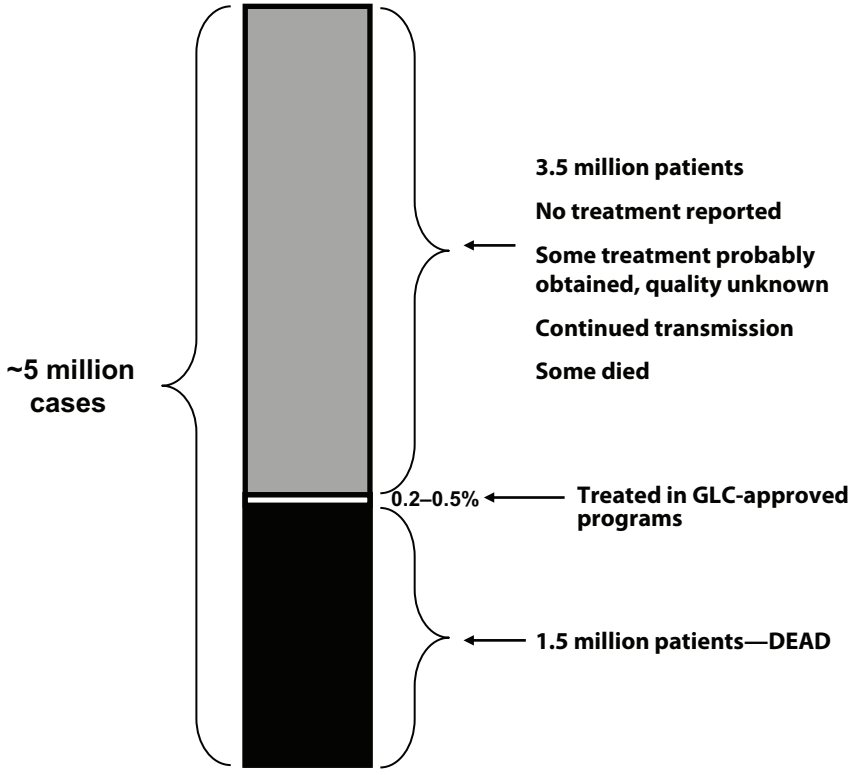


FIGURE 1-9 Of the estimated 5 million MDR TB cases that occurred between 2000 and 2009, only 0.2–0.5 percent were treated in GLC-approved programs.
SOURCE: Keshavjee, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

organization, which is a role that it is being called on to play with increasing frequency.

Prices. Keshavjee noted that prices for SLDs available through GLC-approved programs have increased significantly since initial negotiations with manufacturers in 2000 and 2001.[17] He argued that two factors contributed to this. First, as an institution WHO and the mechanisms sitting within it were not capable of undertaking the type of hard bargaining with

[17] Amikacin: +991 percent; kanamycin: +617 percent; cycloserine: 321 percent; capreomycin: +292 percent; ethionamide, prothionamide, PAS: stable (July 2001–March 2011) (MSF and IUATLD, 2011).

the pharmaceutical industry that has been the hallmark of the HIV drug supply. Second, the maintenance of high prices can be linked to the Global Fund's mandate that all MDR TB drug procurement for all its financed programs must go through the GLC mechanism (i.e., approval of the technical capabilities of a TB program followed by ordering of drugs to implement the treatment program). He noted that a motivation for this decision was to help contain the spread of broad-spectrum resistance that could arise if the Global Fund supported the provision of SLDs that were then used improperly.[18] Beneficiary countries were not permitted to purchase drugs directly from suppliers, regardless of their QA status, and could only purchase through WHO/GDF. Keshavjee characterized this as GLC being granted a "monopoly," which gave rise to what he deemed a "moral hazard" in the sense that "it created a monopoly, and a situation where the people buying the medicines and the people paying for them were different." He suggested that this moral hazard discouraged the development of a strategy to reduce the price of SLDs: "[s]omebody else was paying an unlimited amount, a check was coming to pay for it, and basically you could buy whatever you wanted at whatever price." He described a scenario whereby, on handing over purchasing of MDR TB medications to WHO/GDF, the Global Fund lost the ability to bundle the purchase of these drugs with its purchase of large volumes of HIV and malaria medications and to use this type of market mechanism to drive down prices while maintaining quality.

Structural procurement barriers. Keshavjee further suggested that because all procurement using Global Fund dollars is required to go through GLC, and GLC is an agency of WHO, WHO restrictions about conducting pooled procurement and the ability to negotiate prices with suppliers are key barriers to SLD price improvements. For example, because there was no real pooled procurement, nor were advance purchase contracts used, manufacturers had no idea about a given year's orders—no real forecast of the potential demand. These conditions, in turn, prevented manufacturers from being able to produce the necessary volumes to decrease prices. Keshavjee suggested that a significant barrier imposed by the current organizational structure of the global SLD supply chain is that there is no direct procurement relationship between countries and QA manufacturers.

Ditiu remarked that in July 2011, the GLC mechanism was reorganized. As a result of the reorganization, countries can procure directly from GDF, including purchasing partial regimens if necessary. She expressed concern, however, that countries currently are not availing themselves of this

[18] "To help contain resistance to second-line anti-TB drugs and consistent with the policies of other international funding sources, all procurement of medications to treat MDR-TB must be conducted through the GLC" (Third Board Meeting, October 10–11, 2002).

option, which could significantly scale up the number of MDR TB patients receiving treatment. She suggested improving communication to countries about this new, more open, option for SLD procurement.

Competing organizational incentives. Keshavjee cited the need to more clearly understand the differing incentives across the players in the supply chain and the potential implications of achievement of those disparate goals. He suggested that the search for solutions to the MDR TB problem requires examining and aligning the interests of all players. He presented a chart that elucidates his characterization of those incentives and the barriers to effective dispatch of their respective responsibilities (Table 1-1).

Upstream Supply Chain Barriers

Individual speakers described several key barriers to efficiency in the upstream SLD supply chain, which was defined by Mostaghim as the segment encompassing the point at which a company decides to produce a drug to the point an order is placed and the drug is tendered. The primary barriers identified include limited demand, restricted market structure, and low volumes of API and FPP production, all of which contribute to the key challenges of high prices and limited availability of SLDs.

Limited and unpredictable demand. Atun and Yadav noted that a major reason for the high prices of SLDs is that manufacturers are challenged by problems of limited and unpredictable demand from NTPs and procurement agencies, which stems from a lack of pooled procurement and poor forecasting results. Mostaghim noted that the range of product specifications, in terms of individual countries developing different DR TB treatment regimens, further fragments the already limited demand for specific SLDs.

Yadav explained that accurately estimating the point at which demand for SLDs would trigger the necessary price decrease is a challenge because it varies from manufacturer to manufacturer, depending on the plant configuration they use. Mostaghim elaborated that such a prediction is also highly product-dependent (e.g., fermentation- versus chemically-based products[19]). Moreover, the internationally and domestically financed segments of the SLD supply chain have very different price and demand elasticity, which combine to create a unique demand curve for the overall market.

Yadav noted that *potential* demand for SLDs far exceeds the demand fulfilled by the current supply chain. He estimated that, according to published sources (WHO, 2010), potential demand is likely at around 440,000

[19] This distinction is explained in the section "Perspectives of Suppliers/Manufacturers" later in this chapter.

TABLE 1-1 SLD Supply Chain Stakeholders: Responsibilities, Interests, and Barriers

	Responsibilities	Interests	Barriers
WHO	• Help countries • Set global standards	• Retain current system structure due to financial interests and "self-perception as central convener"	• Conflict of interest in reforming the system linked to receipt of substantial overhead from GDF funds • Control of funding provides leverage/ power over countries
Global Fund	• Help countries overcome barriers • Use donor funds appropriately	• Improve current system structure due to financial situation • Avoid blame for XDR TB	• Lacks in-house technical expertise on MDR TB • Fears conflict with WHO and resulting effect on donors
Stop TB Partnership	• Bring partners together to improve access to TB care • Use donor funds appropriately	• WHO connection facilitates access to countries • Benefits from size/scale of GDF operations	• Has operated essentially as a subsidiary of WHO rather than a true partnership • Coordinating board not responsive to MDR TB SLD problems
Donors	• Accountability to home taxpayers • Ensure good outcomes from funded projects	• Avoid perception of exerting overt/ undue influence on WHO, other multilateral bodies	• Political risk of backing away from existing strategy they have funded
Countries	• Protect citizens' interests • Deal with epidemics	• Support local industries and interests • Avoid hard currency	• Fear that complaining would lead to loss of WHO/donor funds • Funding TB not high priority
Patients		• Access high-quality treatment • Gain representation in the system • Avoid transmitting disease	• Access to adequate SLD regimens • Highly stigmatized • Unaware of their rights

SOURCE: Keshavjee, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

patients, numbers diagnosed at about 30,000, and current fulfilled demand at approximately 15,000 patients. Closing the gap between potential and currently fulfilled demand would require a significant scale-up of the existing SLD supply chain and the rapid diagnosis of more patients using drug susceptibility testing (DST). He suggested that the barriers of high prices, long lead times, and poor service levels[20] would need to be mitigated for such a scale-up to occur. Yadav suggested that bold, upfront financing would be required to facilitate both demand creation and the necessary scale-up to cope with that increased demand.

Restricted market structure. Restricted market structure—for example, having only one eligible supplier for a product—and lack of competition among suppliers in the SLD market are key barriers to improving price and availability. Mostaghim remarked that restricted market structure hinders price improvement in that even if sufficiently deep product volumes were attained, the extent to which that volume is channeled into a single-supplier market structure would curtail improvements in price.

Mostaghim and Yadav noted that the current market for SLDs is also severely restricted because the drugs are not typically used for any other indications in humans. Therefore, demand for QA versions of those products is limited exclusively to MDR TB treatment (e.g., kanamycin).

Low volumes of API and FPP production. Mostaghim noted that economies of scale with regard to batch sizing and production campaigns have a direct impact on production cost. Limited actual demand (i.e., drug orders) results in low batch sizes that are not cost-effective for manufacturers to produce, necessitating a higher price for the finished product. An overall lack of visibility into the SLD market also diminishes manufacturer confidence to produce greater volumes based on forecasts.

Yadav explained that another reason that prices for SLDs are inflated is because the API batch sizes that are currently produced by manufacturers are so relatively small[21] and therefore expensive to produce, and the cost of API manufacturing represents a significant portion of the FPP cost. He noted that the markets for producing APIs that are not used exclusively for manufacturing SLDs (i.e., that are also used for other types of FPPs) are healthier than those API markets that are linked only to TB drugs. Yadav suggested that a healthy API market requires specific one-time donor

[20] Service levels refer to the length of time between an NTP's order placement and receipt, and the fraction of those orders that can be fulfilled within a specified time frame.

[21] For example, an API batch size might run 5 out of 250 operating days per year, whereas a product with a "healthy" market might run for 2 or 3 months.

interventions to correct deficiencies and does not require ongoing donor support.

Financing and Systems Challenges

Atun identified a significant funding shortfall as the major challenge for MDR TB diagnosis and treatment. Projected funding requirements for MDR TB between 2011 and 2015 are estimated at $7.1 billion, around $3.6 billion of which has been approved by the Global Fund in 116 countries. However, the Global Fund's total TB control funding will decline substantially after 2012, despite the increasing prevalence of MDR TB in a number of countries around the world that depend on the Global Fund for financing their TB control programs.[22] Hence, if domestic funding is not mobilized to address the MDR TB emerging needs, the Global Fund may be the only funding source for MDR TB management and SLDs in countries such as Armenia, Bangladesh, Bulgaria, Georgia, Kyrgyzstan, Tajikistan, and Uzbekistan.

Atun suggested there is an urgent need to invest in innovative MDR TB financing and in appropriate push and pull mechanisms to use these funds for adoption of new medicines and health products for MDR TB. Push mechanisms are required to generate supply-side incentives for creating new innovations in TB control, new medicines and health technologies, and as new service delivery models; pull mechanisms are required for demand creation and market signaling to show that financing is available in countries and in health systems for adopting new innovations for TB control and MDR TB; and crosscutting initiatives are required for international- and national-level systems strengthening. For example, strengthening procurement and supply chains, building staff capacity, and developing appropriate regulatory policies can ensure that innovations that have been developed can be adopted when financing is available (Figure 1-10).

Atun noted that the current funding shortfall and state of unpredictable financing are detrimentally affecting the employment of push and pull mechanisms. He explained that there is an imbalance in industrial, health, and financing policies whereby industrial policies encourage technology

[22] At the time of the workshop, a 16 percent cap on Global Fund financing for TB had been proposed. However, in September 2012, the Board of the Global Fund voted not to implement a funding cap but instead to develop a new funding model that would allocate funds to country "bands" according to income level and disease burden, among other factors. The model envisions greater predictability and flexibility in the funding application and allocation process. For more information, see http://www.theglobalfund.org/en/mediacenter/newsreleases/2012-09-14_Global_Fund_Adopts_New_Approach_to_Funding_Grants (accessed November 14, 2012) and http://www.stoptb.org/news/stories/2012/ns12_058.asp (accessed November 14, 2012).

push mechanisms, but regulatory policies and a lack of incentives for health systems constrain adoption of innovation. He suggested the following reasons for this imbalance:

- insufficient emphasis on demand-side factors that influence innovation adoption;
- inadequate incentives and downstream rewards for adopting innovation;
- toleration of inefficiency and ineffectiveness in service delivery, where much waste exists; and
- no incentives for innovation.

Another barrier is that crosscutting initiatives, such as training of human resources and development of appropriate regulatory policies, which are critical for strengthening platforms for adoption and scale-up

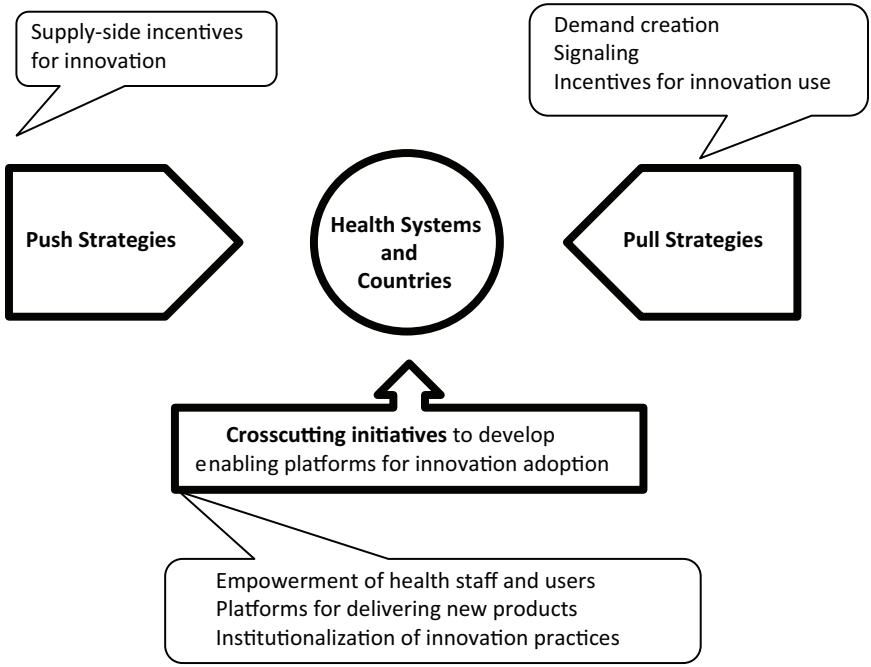


FIGURE 1-10 Push and pull mechanisms for adopting innovations for MDR TB. SOURCE: Atun, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis (edited).

of innovations, are similarly underfunded. He warned that if resources are not devoted to achieving strengthened health systems, functional SCM systems, and adequate country-level capacity for delivering services, SLDs will continue to fail to reach the people who need them—regardless of whether funding is available for the purchase of innovative medicines and health products.

Yadav stated that the SLD supply chain is limited by an antiquated contracting structure between GDF and manufacturers that is based on public procurement rules from decades ago and that is no longer supported by current empirical or analytical research. He maintained that the contracting practices need to be modernized with more innovative structures, but that such efforts are often met with the response that institutional constraints and the nature of available financing do not allow such innovation.

Because financing is currently dominated by domestic investments, Ditiu stressed the need to engage with stakeholders in those countries to clarify, for example, the importance of scale-up and QA drugs. Yadav further asserted that concrete financing must back up demand forecasting. To achieve this, he suggested that the nature of that financing must be reorganized to allow for longer-term commitments.

Clinical Challenges

Regimen harmonization for MDR TB treatment is challenged by the lack of a clinically established standard/best regimen of SLDs, said Cegielski. Thomas Moore, GDF, Stop TB Partnership, WHO, noted that GDF carries out efforts to harmonize WHO-recommended regimens in the programmatic management of drug-resistant tuberculosis (PMDT) catalog, but that it is ultimately at the discretion of NTPs whether they follow WHO recommendations or not. Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières (MSF), suggested that a range of different regimen options is necessary because the drugs are weak and have to be adapted for each individual patient's treatment.

Mostaghim stated that lack of harmonization of treatment regimens for SLDs both within and among countries results in fragmentation of overall patient demand. For example, there are cases of countries with six standard approved regimens, or that have accepted the use of all existing WHO Prequalification of Medicines Programme (WHO PQP) SLDs in the treatment of DR TB.

Regulatory Challenges[23]

Vincent Ahonkhai, Senior Regulatory Affairs Officer, Bill & Melinda Gates Foundation (BMGF), described the existing drug QA regulatory mechanism for low-resource countries with donor-funded MDR TB programs. After development, a drug first acquires approval from the U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA). To be eligible for procurement with donor funding, the drug must then pass through the WHO PQ process to assure its quality, safety, and efficacy per WHO's standards. After WHO PQ, the drug must then be registered in the beneficiary country before it can be procured by a donor agency. There are thus multiple bottlenecks in this regulatory process, particularly with respect to WHO's central regulatory authority,[24] that affect the overall global availability of QA drugs. Limited availability of SLDs is causally linked with high prices, as multiple participants noted.

Regulatory pathways vary widely among countries and have a direct impact on MDR TB patients' access to SLDs. Ahonkhai remarked that the MDR TB burden primarily affects low-income countries that are highly dependent on donor-funded regulatory and procurement pathways to deliver drugs to patients, as opposed to the "one-step" national regulatory pathways that are typical of middle- and high-income countries. Companies wishing to distribute in low-income countries therefore face multiple regulatory steps after drug development and before they can deliver the product in countries (Figure 1-11):

- approval by stringent regulatory authorities (e.g., FDA, EMA);
- WHO PQ[25]; and
- national registration in the recipient country.

In the amount of time that often elapses to achieve the SRA and WHO PQ regulatory steps, patients in higher-income countries would have usually received their drugs already, yet in lower-income countries, the additional step of national registration remains. This lengthy regulatory process is not attractive to manufacturers or procurers because the delays at each regulatory stage—also termed "drug lag"—contribute to slow product uptake and inadequate coverage. Ahonkhai suggested that regulatory har-

[23] This subsection is based on the presentation by Vincent Ahonkhai, Senior Regulatory Affairs Officer, Bill & Melinda Gates Foundation (BMGF).

[24] As Lisa Hedman, Project Manager, WHO, noted, the WHO PQ process is dealing with a "bandwidth" problem that is causing delays in registering new suppliers.

[25] Ahonkhai noted that the SRA approval and WHO PQ processes are often not run in parallel, which can result in further delay.

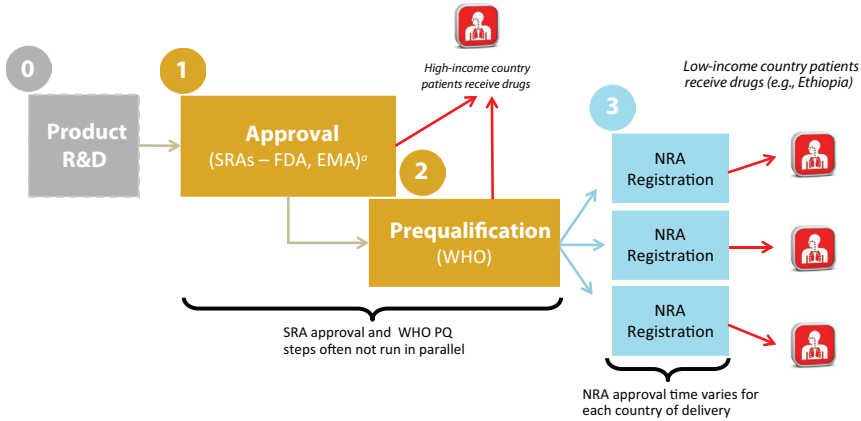


FIGURE 1-11 Regulatory steps from drug development to delivery. Typical time line for present-day medications.
NOTE: EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; NRA, national regulatory authority; R&D, research and development; SRA, stringent regulatory authority; WHO PQ, WHO prequalification.
[a] SRAs—typically FDA and EMA.
SOURCE: Ahonkhai, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

monization efforts (e.g., the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH], the Pan American Network for Drug Regulatory Harmonization) are needed to standardize and harmonize production regulation and registration.

The remainder of this section provides an overview of the specific barriers and challenges faced from the unique perspectives of different stakeholders in the SLD supply chain, as identified by individual presenters during Session I of the workshop and during discussions between the speakers and the audience. Moore delivered a presentation describing the perspective of GDF in its role as a procurement mechanism for GLC-supported programs. Iain Richardson, Senior Director, Global Supply Chain and Logistics, Eli Lilly and Company, and Robert Sebbag, Vice President, Access to Medicines, Sanofi, described challenges and barriers from the perspective of supplying and manufacturing SLDs. Anne Goldfeld, Professor of Medicine, Harvard Medical School, and Co-founder, Global Health Committee (GHC) (an NGO that has worked in Cambodia as the Cambodian Health Committee since 1994 and is based in the United States at Harvard Medi-

cal School), Henkens, and Andrew Gray, Senior Lecturer, Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal, offered their perspectives on the challenges faced by MDR TB providers and collaborating organizations operating in countries dealing with high MDR TB burdens.

Perspective of GDF[26]

Moore outlined the functions that GDF, as an initiative of the Stop TB Partnership launched in 2001, has fulfilled in coordinating and managing TB drug procurement. GDF has promoted harmonization of WHO's TB recommended treatment regimens, facilitated rapid DOTS expansion, and developed the market for FLDs. GDF strives to maintain stringent QA standards and by 2011 had increased the number of QA SLDs available for procurement for MDR TB treatment to 32 products, 75 percent of which have 2 QA suppliers. Through its commercial partners, GDF encourages competitive and sustainable pricing for SLDs through international bidding. More than 19,000 MDR TB patients were supplied with SLD treatment by GDF in 2011—with all these patients having been part of the previously approved GLC cohorts. GDF also monitors and provides technical assistance to TB management programs in-country.[27] GDF is an exclusively donor-supported system that does not derive profit from the funding it receives to procure SLDs.

GDF Procurement Cycle Barriers

Moore distinguished between two sections in the GDF procurement cycle—"pre-order" and "order" (Figure 1-12)—in describing specific supply chain barriers. Within the "pre-order" component, he noted that delays occur often within the country, including delays by the NTP in making the initial requests for medicines to GDF and in obtaining the necessary authorization and signatures from local government officials for grant and procurement agreements. Lack of funding from countries or donors to pay for the drugs is also a key barrier to an effective procurement cycle with GDF.

[26] This subsection is based on the presentation by Thomas Moore, GDF, Stop TB Partnership, WHO.

[27] Ditiu characterized GDF's role in this context as a kind of "call center" or reference point for drug management.

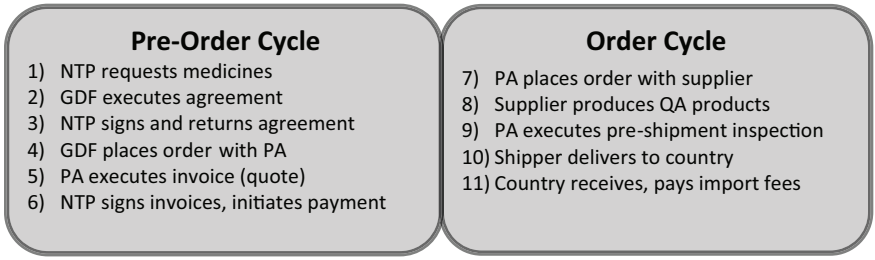


FIGURE 1-12 GDF procurement cycle. The cycle is made up of two components and normally requires 6–8 months.
NOTE: NTP, national TB control programme; PA, Procurement Agent; QA, quality-assured.
SOURCE: Ditiu, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

GDF's SLD Stockpile

To support the order segment of the procurement cycle, GDF established an SLD stockpile with UNITAID funding to expedite emergency orders (delivery within 30 days on average) and accelerated orders (delivery within 31–89 days on average). The stockpile consists of 5,800 patient treatments. Moore noted that the stockpile has been successful in reducing lead times thus far, with 60 programs ordering from the stockpile in 2011 (including 25 emergency orders placed by 20 different programs). Moore emphasized that the stockpile will require new funding if it is to continue after 2012, when its current UNITAID funding expires and, ideally, should consist of an increased number of patient treatments.

Expanding the SLD Market: GDF Role

Moore commented on GDF's potential ability to promote expansion of the global market for SLDs. Through its DOTS expansion effort, GDF was able to reach 41 percent of the FLD public market. A serious challenge for achieving similar results in the SLD market is the current lack of demand and resultant high prices. In 2011, the average price of drugs delivered through the GDF system ranged from $2,070 to $7,891 per patient. The high cost borne by suppliers to establish or upgrade production facilities and the lengthy (18- to 24-month) WHO PQ process remain significant barriers to growth in the SLD market. Because of the weak procurement systems of many NTPs and partners requesting QA products, Moore main-

tained that GDF's ability to support expansion of the SLD market would be contingent upon

- significant increase in demand;
- the provision of accurate information about numbers of patients, time lines, regimens, and patient enrollment rates from TB programs and partners;
- sufficient funding to allow NTPs to engage in direct procurement from GDF;
- whether funding is received from a donor, alignment of processes relating to the transfer of funds, paperwork, donor requests, and plans;
- new funding for the existing SLD stockpile; and
- attracting new suppliers to the SLD market.

Moore noted that GDF is actively attempting to recruit new potential SLD suppliers through direct meetings at their facilities, conferences, and workshops organized to engage suppliers in the SLD market.

Perspectives of Suppliers/Manufacturers

Perspective of Large Pharmaceutical Companies

Challenges for manufacturers in the SLD market.[28] Richardson reflected on key concerns from the manufacturer's standpoint about entering into and remaining in the SLD market, emphasizing that manufacturing SLDs is not yet attractive from an economic perspective. Absence of accurate demand forecasting makes it difficult to shape investment, production, and time lines. Richardson noted that Eli Lilly considers an adequate demand forecast to be one that is 80 percent accurate 2 months into the future, and projects at least 24 months. Currently, there is no forecast of SLD orders available, nor is the accuracy of the global annual forecasts measured in a meaningful way.

Information is lacking about product use in country and patient enrollment rates and plans, and data like these from in-country DR TB programs are not being fed back into any forecasting mechanism. Despite the usually ideal circumstance of having a single primary customer (WHO) for SLDs, the ordering process remains unpredictable with little to no forecast visibility. With no reliable forecast, in most cases manufacturers will not begin

[28] This subsection is based on the presentation by Iain Richardson, Senior Director, Global Supply Chain and Logistics, Eli Lilly and Company.

activities, or even order raw materials, until an order is received. This in turn leads to long lead times of several months to satisfy orders, which puts more pressure on countries to accurately forecast their demand up to a year or more in advance. The result is drug management challenges in-country, creating either shortages due to an inaccurately low forecast or the destruction of expired goods when a country forecasts its needs too high.

Richardson offered three suggestions for improving the operation of the SLD market, assuming significantly larger numbers of patients were to be enrolled in treatment and the demand for internationally quality-assured (IQA) drugs were to grow substantially:

1. attract more manufacturers to the market to avoid the monopoly premium effect;
2. develop improved forecasting mechanisms to make demand more predictable; and
3. improve supply chain design, including creating buffer inventories, which would allow manufacturers to produce larger, more economic production batches and reduce other lead times for customers.

More manufacturers would enter the market and engage in fruitful price negotiations, assuming the following conditions were met: substantial growth of overall demand, improvement of predictability of orders, and manufacturers' optimization of production scale.

Regulatory challenges.[29] Challenges to major manufacturers are also posed by an increase in regulatory barriers at the local and national levels in high–MDR TB burden countries. For example, at least 17 of the top 27 high-burden countries currently require at least one level of local registration (some countries also request that production information on the label be in the local language). Even for what are called "accelerated" regulatory approvals, there are still requirements for dossiers and filing fees, and such approval processes present opportunities for delays and market fragmentation. In contrast, countries that do not have additional local mechanisms, relying instead on the recognition of another regulatory authority's approval (e.g., WHO PQ), enjoy more rapid access to IQA medicines without generating additional costs.

Complexity of SLD manufacture. An important technical issue faced by manufacturers is the complexity of the manufacturing process for SLDs.

[29] This subsection is based on the presentation by Iain Richardson, Senior Director, Global Supply Chain and Logistics, Eli Lilly and Company.

Richardson clarified the distinction between chemically produced drugs (e.g., cycloserine), which are relatively straightforward to scale up in terms of volume of production, and injectable drugs, which are fermentation-based and require freeze-drying of the active ingredient. Fermentation chemistry and freeze-drying are expensive and complex processes. Cassell remarked that such injectable MDR TB drugs are made by microorganisms and have associated problems with batches, reproducibility, and yields (and thus QA). Patrick Lukulay, Vice President, Global Health Impact Programs, U.S. Pharmacopeial Convention (USP), noted that manufacturing the API for SLDs is also very complicated and extremely expensive due to the crystallization steps required.

Need for systems strengthening and capacity building.[30] SLDs for MDR TB are a particular challenge for pharmaceutical companies. Small volumes are required, they are expensive, and they are difficult to manage and to ensure proper treatment compliance. Sebbag stressed that reliable diagnosis and ensuring compliance are crucial for protecting SLDs from misuse, which can lead to further spread of MDR and XDR TB. In that vein, drugs are only one part of the MDR TB challenge, in that education and enhanced patient communication are also needed, calling for systems strengthening and capacity building, such as training programs, at all levels of the supply chain.

Using malaria treatment as an example, Sebbag described how a complex organizational structure of institutions, partners, and funding entities (which is similar to the MDR TB structure) makes facilitating communication among the multiple partners a challenge. One strategy for systems strengthening that is used in malaria treatment is capacity building to implement best practices at the local supply chain and case management levels to ensure that patients have access to QA drugs. Sebbag noted that this would require both workforce training and active partnership of all players in the SLD supply chain.

Perspective of a Midsize Pharmaceutical Company

Paul Ryu, Dong-A Pharmaceutical Co., Ltd., provided the perspective of a midsize pharmaceutical company. According to Ryu, Dong-A is currently producing drugs to meet 80 percent of the world's demand for cycloserine; the company has made investments of about $3 million to upgrade its facilities and has already been inspected by WHO. He commented that the company is willing to make the investment to enter the

[30] This subsection is based on the presentation by Robert Sebbag, Vice President, Access to Medicines, Sanofi.

Sidebar:
Eli Lilly's SLD Technology Transfer[a]

In 2003, Eli Lilly and Company launched the Eli Lilly MDR TB partnership (the "Partnership"). As part of the Partnership, Eli Lilly committed to transfer the technology necessary to manufacture two SLDs (cycloserine and capreomycin) to partners globally, some of whom would be located in countries with the highest MDR TB burden. In this way, Eli Lilly hoped to improve the availability of these drugs and the sustainability of their supply. In addition, between 2003 and 2011, Eli Lilly manufactured and supplied these two medicines to the WHO mechanism at concessionary prices. Eli Lilly stopped supplying cycloserine in 2006 and stopped manufacturing capreomycin in 2011, by which time several of its partners were able to supply the market.

To illustrate the rationale behind Eli Lilly's decision to transfer the technology for the manufacture of capreomycin, Iain Richardson, Senior Director, Global Supply Chain and Logistics, Eli Lilly and Company, explained that by 2011, despite having already doubled the company's internal capacity, manufacturing was "running flat out" and still only supplying sufficient medicine to treat approximately 7,000 patients. However, the installed capacity across Eli Lilly's partners far exceeds Eli Lilly's own capacity, thereby better assuring supply. Richardson also illustrated that Eli Lilly's cost structure for cycloserine manufacture was simply not competitive when compared with other manufacturers that had different scale and overhead drivers.

Such factors drove Eli Lilly's decision to transfer the technology for the manufacture of those two drugs, with the intention of creating a sustainable long-term supply and increasing market volume, by shifting production to low-cost manufacturing partners in high-burden countries. Richardson described how that technology was transferred via the Partnership to seven manufacturers, including several in high-burden countries (China, India, Russia, and South Africa). All of those manufacturers now have regulatory approvals, six have stringent regulatory approvals or WHO PQ, and one has national regulatory authority (NRA) and pending WHO PQ approval. Eli Lilly has continued its involvement with those partners in their ongoing attempts to expand the SLD market and provide treatments to patients.

[a] This box is based on the presentation by Iain Richardson, Senior Director, Global Supply Chain and Logistics, Eli Lilly and Company.

SLD market, despite its small size. However, it is currently facing a regulatory barrier, delay in WHO registration, and is seeking options to expedite the process. Lisa Hedman, Project Manager, WHO, commented that the Expert Review Panel process can grant a provisional prequalified (PQ) status while registration processes are pending. She noted that WHO is dealing with a "bandwidth" problem due to the large number of pending applications and inspections. This, compounded by the percentage of poor applications received from facilities deemed unacceptable (all of which must be processed and inspected), exhausts WHO resources and generates further delays.

Perspective of Providers and Collaborating Organizations

Challenges of Implementing a New MDR TB Program in a Country That Went Through the Proper GLC Mechanism[31]

Goldfeld related her experiences about how GHC initiated an MDR TB treatment in Ethiopia in 2009 in partnership with the Federal Ministry of Health. Ethiopia is a high TB- and MDR TB–burdened country. The GHC program employed a hospital and community-based MDR TB care model that GHC has pioneered in Cambodia, and in so doing overcame major obstacles, including the delay of WHO/GLC-approved SLDs from GDF and issues of diagnostic lab capacity, human resources, isolation beds, and access to traditional funding mechanisms such as the United States Agency for International Development (USAID).

Until this GHC program initiated treatment in February 2009, no MDR TB treatment was available in Ethiopia despite its large estimated burden and a successful application by the country for SLDs. Forty-five patients were approved for treatment, and the drugs had been anticipated for delivery in October 2008; however, they did not arrive until almost a year later. In this vacuum, by leveraging an initial donation of 18 doses of capreomycin from Eli Lilly, GHC, with the support of the Jolie-Pitt Foundation, purchased additional SLDs, provided funds for the inpatient and outpatient management of patients, and performed the first countrywide MDR training, including training personnel in its program in Cambodia. The South-to-South partnership that GHC established, with ongoing technical and program design input and funding for additional SLDs, ancillary medication, food baskets, social support, laboratory tests, and procedures, was supported by charitable contributions, including a grant from the Eli Lilly MDR-TB Partnership, continued support from the Jolie-Pitt Founda-

[31] This subsection is based on the presentation by Anne Goldfeld, Professor of Medicine, Harvard Medical School, and Co-founder, GHC.

tion, 305 courses of capreomycin from Eli Lilly, a donation of cycloserine from the Chao Foundation, and paser from Jacobus. These resources, in addition to the leveraged expertise, were key in removing bottlenecks to drug procurement from the Ministry of Health. When GLC drugs finally arrived, in-country expertise in treatment and management of MDR had been established, allowing rapid adoption.

The Ethiopian/GHC MDR TB treatment partnership has been scaled up and was expanded to Gondar in northern Ethiopia in August 2010. As of July 2012, 500 patients had been initiated on therapy, with only 6 defaults and a death rate of less than 10 percent in a very sick population (24 percent HIV co-infection and the majority of patients with bilateral cavitary disease). Though some GLC-imposed procedures (e.g., requirements that patients be hospitalized in isolation wards that were not yet completed at program initiation) were extremely problematic due to lack of funding and capacity limitations, Goldfeld noted that it was possible to find "work-arounds," such as setting up interim isolation wards in unused facilities and receiving drug donations. Goldfeld reported that scale-up of the MDR TB program, countrywide training programs, and health systems capacity building are ongoing in Ethiopia, with outstanding program results. She also noted that of the original 221 patients who were waiting for therapy in fall 2008, her team was able to find and initiate only 66 (30 percent) on MDR therapy; 42 had died waiting for drugs (20 percent), and the team was unable to find 110 (50 percent) of those on the list despite a house-to-house search, many of whom thus presumably died. She emphasized the urgency of providing access to high-quality MDR care to interrupt preventable death from a curable infectious disease and to interrupt further transmission.

Challenges of Supplying QA SLDs (MSF)[32]

Henkens described MSF's role in providing MDR TB treatment worldwide. In 1999, MSF became involved with procuring SLDs. The organization committed to pooling procurement of 2,000 treatments from QA sources by negotiating a price drop with manufacturers and buying drugs to guarantee complete treatment.[33] MSF currently treats approximately 1,200 patients in 17 countries, using both the GDF procurement mechanism and its own pooled procurement mechanism for certain projects. MSF maintains a stringent QA structure by adhering to the requirements for SLDs deter-

[32] This subsection is based on the presentation by Myriam Henkens, International Medical Coordinator, MSF.

[33] After 2,000 treatments were attained, procurement was taken over by IDA in 2002 and transferred to GDF in 2006.

mined by approved regulatory bodies (e.g., WHO PQ, SRA registration, U.S. FDA tentative approval, Global Fund/GDF Expert Review Panel) or evaluated following its own internal qualification scheme. Henkens also suggested that countries should commit to using only QA drugs, noting that given the relatively low efficacy of current treatment protocols and given the high rate of adverse reactions, patients have the right to be sure that at least the quality of drugs is not questionable.

A major challenge facing the supply chain for QA SLDs is that despite an increase in the number of QA manufacturers, the prices of QA products have not improved since 2001. Henkens suggested that the fact that Eli Lilly no longer subsidizes capreomycin and cycloserine could account for the increases in price of those drugs, noting that the prices for products that had the same manufacturers in 2001 and 2011 (ethionamide, prothionamide, and PAS) are the ones that have remained stable. Improved coordination among countries and producers could help ensure that increased competition does not lead to increased prices, given limited availability. Henkens suggested that "breaking the vicious cycle" would require strategies such as improved forecasting, transparent market allocation, and implementing a revolving fund and rotating stockpile.

Challenges for South Africa's MDR TB Policy[34]

Decentralizing MDR TB care. The South African National Department of Health has announced that every facility treating MDR TB will have a GeneXpert® machine for diagnosing *M.tb.* and rifampicin resistance by the end of the 2012 financial year. Gray speculated that the expected significant increase in the number of diagnoses and the number of patients requiring MDR TB treatment will present a serious challenge to the current treatment capacity in the country. Only 2,500 beds are available in specialist TB hospitals in the country (for a population of 50 million). To address this problem, South Africa has developed a new policy aimed at decentralizing the management of MDR TB patient care. Gray expressed his concern that the policy also includes, in certain cases, treating patients on an ambulatory basis even in the intensive phase of treatment.

Challenges of public tendering. Most TB drugs in South Africa are procured on a competitive basis through the public sector, which generates a specific set of problems. First, there is a dearth of domestic producers, despite the tender system being geared toward nationally registered products. Second, many tenders for first- and second-line products go unawarded; for

[34] This subsection is based on the presentation by Andrew Gray, Senior Lecturer, Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal.

example, in view of the limited number of products available, a company might opt not to put forward a tender in the hope that the government would then approach the company to negotiate a price higher than the one the company would have offered in a tender. Third, there is a concentration of suppliers—particularly suppliers of API. Though there are multiple formulators, the current market is overreliant on a single, limited supplier. It was also noted by several workshop participants that individual countries have different approaches for managing MDR TB and the SLD drug supply; country-specific experiences can inform efforts to improve the global supply chain (Box 1-4).

Need for New SLD Formulations and Regimens

The individual panelists offered the following additional concerns and problems relating to SLD formulations and regimens:

- prevalence, severity, and lack of diagnosis of SLD-related adverse reactions (e.g., ototoxicity due to injectable agents);
- problems with the effectiveness of existing SLDs;
- absence of pediatric formulations for SLDs; and
- lengthy and complex nature of treating DR TB with SLDs.

In light of such disadvantages, several panelists suggested there is an urgent need to develop new and improved regimens. Over the course of the session identifying barriers and challenges to the supply chain, individual speakers and participants also identified potential ways forward to address some of the key barriers (Box 1-5).

BOX 1-4
Country Approaches to the MDR TB SLD Supply Chain[a]

Several speakers delivered presentations describing the approaches of specific countries with a high burden of MDR TB. Norbert Ndjeka, MDR TB Director, Department of Health, South Africa, described the challenges faced in South Africa's approach to MDR TB management. Joël Keravec, Brazil Country Program Director, Management Sciences for Health (MSH), explained Brazil's model for TB treatment and drug management. Andreas Seiter, Senior Health Specialist, Pharmaceuticals, Health, Nutrition, and Population, World Bank, described India's approach to cofinancing its NTP with the World Bank.

South Africa

Ndjeka addressed South Africa's approach to the challenges it has faced in treating MDR TB patients and its attempts to shift from pilot projects to a nationally owned program. With the highest TB burden in the world, South Africa still struggles with a gap between diagnosed and treated MDR TB patients and a treatment success rate of less than 50 percent.[b] A first step is the standardization of treatment guidelines throughout the country, along with a means of ensuring compliance. To address the current bed shortage for MDR TB patients (due to an inadequate number of specialized facilities), South Africa has adopted a national strategic plan to transition to a decentralized model of MDR TB management. The essence of the policy is to de-institutionalize care of MDR TB patients, to "bring treatment to the communities where they live." A parallel objective is to implement nurse-initiated MDR TB treatment to further facilitate early diagnosis, initiation of treatment, community DOT, and patients' education about their disease. Under this policy, drug procurement[c] and quality testing are performed by the Department of Health and universities, not through global mechanisms of QA (e.g., WHO PQ, GLC, GDF).

A huge discrepancy remains between the cost of treating an MDR/XDR TB patient and the cost of treating a drug-susceptible TB patient in South Africa; approximately 100 drug-susceptible TB patients can be treated for the cost of treating a single MDR/XDR TB patient. This gives rise to challenges of prioritization, in that arguments exist for focusing on drug-susceptible TB and for questioning the high cost of treatment for MDR TB. A further issue is that TB funding in South Africa is not securely dedicated to TB only, and funds are often used for other health-related programs. Patients' high pill burden (especially when co-infected) and antipathy toward receiving injections is also a challenge, as is problem-

continued

BOX 1-4 Continued

atic packaging of medicines. Ndjeka outlined another stream of systemic challenges related to the supply chain for MDR TB drugs, specifically stock-outs. Poor forecasting leads to drug stock-outs, and there are no effective mechanisms to track those stock-outs or drug usage in general; "unreal" stock-outs often occur when there are drugs available at pharmaceutical depots but not at treatment facilities.

Brazil

In Brazil, the state is the key player in all aspects of drug management. In his presentation, Keravec explicated Brazil's national policy for TB management and control, which could provide a model for protecting the effectiveness of new TB drugs as they enter the market. Brazil currently carries a relatively low level of DR TB burden. Despite ranking 17th of the 22 highest-burdened countries for drug-susceptible TB, only 700 DR TB patients are notified and treated each year. All TB drugs are available only in the public sector, free to patients, and QA; both TB and DR TB treatment is similarly restricted only to the public sector. A system of reference centers is responsible for creating and monitoring DR TB treatment centers.

Keravec noted that Brazil's NTP quantifies need and the Ministry of Health's pharmacy department is responsible for procuring QA drugs. Local procurement is prioritized via direct agreements with public government manufacturers and via an open-tendering process at market prices for SLDs that are produced by local private-sector manufacturing firms.[d] However, he described the following major challenges facing Brazil's public SLD manufacturers: manufacturers have limited access to APIs that are not produced in the country, tax burdens and production costs are high compared to India and China, and the small internal DR TB market makes investment in SLD production by local manufacturers less attractive. Such barriers have led to the need to procure some SLDs that are not produced in-country (i.e., capreomycin, cycloserine, PAS, and clofazimine). In such cases the GDF/GLC mechanism is employed using the Pan American Health Organization as a mediator. To enable improved demand forecasting, procurement, and distribution, all DR TB

patients and SLDs are managed within a single integrated, Web-based platform (e-TB Manager/Site TB). This platform integrates all levels of TB control within the public sector and reference centers treating DR TB patients, including information on diagnosis, clinical management, and drug supply components. The system contributes to multiple programmatic aspects of DR TB control including, pharmacovigilance and precise drug consumption monitoring.

India

India is employing a different type of approach to financing its TB program, as described by Seiter. The World Bank finances loans (not grants) to the Indian government that are used to procure drugs, but in a way that is implemented within India's own national policy and in accordance with its own set of regulatory standards. The World Bank is not involved in any phase of procurement except for financing. This strategy is aimed at system strengthening, essentially functioning as a bridge between scale-down of the prior Global Fund program and scale-up of Indian investment in its own national program. The World Bank itself does not have the in-house technical expertise to help achieve such goals, but it can partner relatively flexibly to bring in the appropriate technical and organizational support as required. This financing framework could serve as an example of how countries might transition from external grants to autonomous financing and in the process build a stronger NRA. In India, pharmaceutical manufacturers are regulated at the state level, but the central authority plays a role in ensuring quality for centrally procured medicines. Neither the state regulators nor the central Food and Drugs Authority are yet accepted as "stringent regulatory authorities" by the international community.

---

[a] This box is based on presentations by Joël Keravec, Brazil Country Program Director, Management Sciences for Health (MSH); Norbert Ndjeka, MDR TB Director, Department of Health, South Africa; and Andreas Seiter, Senior Health Specialist, Pharmaceuticals, Health, Nutrition, and Population, World Bank.

[b] A new national strategic plan has a target of 60 percent within the next 5 years.

[c] Ndjeka noted that the companies that supply the drugs to the Department of Health are the same ones supplying those drugs for WHO PQ.

[d] All manufacturers are validated and registered by Anvisa, Brazil's NRA.

BOX 1-5
Suggested Ways Forward[a]

Over the course of the session identifying barriers and challenges to the supply chain, individual speakers and participants also identified potential ways forward to address some of the key barriers. A number of their suggestions are also addressed later in this report. Those suggestions are compiled here in an integrated summary of those individually identified themes. These suggestions should not be construed as reflecting consensus or endorsement by the planning committee, the Forum, the workshop participants, or the IOM.

- Implementation of a rotating stockpile or buffer stock could smooth demand and improve predictability in manufacturing and delivery processes.
- Improved demand forecasting and predictability could help to attract new manufacturers to the market and improve competition.
- Donors should consider increasing the allocation of funding toward program implementation and improvement and/or shortening of the current treatment regimen.
- Pooled procurement and direct procurement from manufacturers employed within the GLC mechanism could alleviate the problems of limited availability and high prices.
- Taking steps to accelerate registration, adoption, and uptake could reduce drug lag in the regulatory process.

Key Messages[a]

- Failure to address the current SLD supply chain issues will lead to increased drug resistance, morbidity, and mortality.
- GLC was designed to foster pilot projects and was not meant as a mechanism for scale-up.
- Market-shaping strategies, including shifting the push-pull boundary, may improve the drug supply chain.
- Crucial barriers to addressing SLDs include high cost, limited supply, and manufacturing complexities.
- Difficulties in meeting multiple, complex regulatory requirements contribute to delays in delivery of SLDs.

[a] Identified by individual speakers.

- Training programs implemented at all levels of the supply chain could strengthen systems and build in-country capacity.
- Development of innovative financing and contracting structures to shift the push-pull boundary SLD supply chain toward forecast-driven manufacturing processes could improve efficiency and cost.
- Market fragmentation could be addressed by consolidating and harmonizing product specifications.

Mostaghim offered four strands of market structure adjustments that might help to facilitate patients' access to QA SLDs. He noted that successful implementation of these types of structural adjustments would require tight coordination among all partners and stakeholders, including donors, procurers, manufacturers, NTPs, regulators, and so on.

- *Demand-side activities*: Consolidating and harmonizing NTPs' technical specifications for products and facilitating in-country registrations.
- *Manufacturer engagement*: Providing clear guidance regarding entry and eligibility for key product specifications.
- *Regulatory engagement*: Expediting priority dossiers for key products by maximizing the number of eligible participants in a tender.
- *Procurement and supplier selection*: Proactively splitting tenders, ensuring transparency, and providing clearer demand forecasting.

[a] Identified by individual speakers.

2

Logistics, Supply, and Demand

This chapter describes issues related to logistics, supply, and demand in the MDR TB SLD supply chain discussed at the workshop. The first section provides an overview of issues revolving around national- and international-level QA regulation of SLDs. The next section focuses on the importance of improved demand-forecasting methodology and improved information management systems in strengthening the SLD supply chain. The final section explores issues concerning national- and international-level drug shortages.

QUALITY ASSURANCE

The function of QA for pharmaceuticals is to help guarantee that patients receive medicines that are safe, effective, and of acceptable quality. Technical as well as managerial activities (i.e., staff training and supervision) are included in comprehensive QA programs and span the entire supply chain process (MSH, 2011). During the workshop, speakers and participants discussed the definitions of "quality" with respect to SLDs, examined the benefits and limitations of existing SLD regulatory processes including WHO PQ, and discussed potential applications and lessons to be learned from other programs. This section first describes the existing international regulatory pathway for SLDs in the donor-funded market and then provides an overview of issues with respect to the national regulation of SLD. The section then summarizes the country-specific perspectives of India's QA structure and Brazil's model of a national QA program. Last,

the section examines the "vicious circle" of SLD supply and the effect of the limited supply of QA API on the structure of the SLD market.

International- and National-Level QA Regulation[1]

WHO Prequalification of Medicines Program

Lisa Hedman, WHO, explained that the WHO PQP serves as an international standard for stringent QA regulation of TB and MDR TB drugs. WHO PQ is a voluntary mechanism that does not supervene on an NRA's decisions. Hedman noted that the WHO PQP can perform the function of an SRA proxy for manufacturers in countries without a SRA.[2] Though WHO PQ does not provide automatic market access in individual countries, the PQ designation is a procurement requirement for many donor-funded procurements.

There are currently 12 formulations on the WHO list of PQ SLDs for MDR TB, from only 3 manufacturers (Figure 2-1).[3] The small supplier pool for PQ SLDs exposes the global supply chain for MDR TB drugs to a significant risk of drug stock-outs should a single supplier stop production.

The essential medicines list has a policy-based function, whereas the WHO PQ list has a regulatory function. WHO PQ is renewed every 2 years and is intended as a model list to guide countries in the procurement of SLDs. The next review of first- and second-line anti-TB drugs will be carried out in March 2013, which, Hedman said, could provide an opportunity to renew outreach to countries and identify potential ways to "consolidate around logical and rational use of medicine."

Scarcity of Data Linking QA and Treatment Outcomes

Hedman expressed her concern that although procurement of non-QA (i.e., not quality-assured by a recognized SRA) MDR TB products might secure better prices and provide wider coverage, it is not worth the risk of a trade-off in quality and efficacy. In a study carried out by WHO that tested PQ and non-PQ medicines for API and dissolution, an average of 10 percent of non-PQ products failed due to non-extreme deviations and

[1] This subsection is based on the presentation by Lisa Hedman, Project Manager, WHO.

[2] Hedman added that there are certain situations in which WHO requires PQ for a product that has already been approved by an SRA. This is because some countries use WHO PQ status as a "fast track" into their own approval systems. In such cases the PQ process usually has a fast turnaround time, she noted.

[3] Of those 12, 4 have ≤1 SRA sources, and 6 have 2 or fewer.

Prequalification available:	PQ suppliers	Other SRA suppliers	Total
Amikacin, solution injection 500 mg/2 ml vial, amp; powder for injection 1g vial, amp	1	4	5
Capreomycin, powder for injection 1g, vial	0	1	1
Cycloserine, capsule 250 mg	2	1	3
Ethionamide, tablet /capsule 250 mg	2	1	3
Kanamycin, powder for injection 1g, vial	0	2	2
Kanamycin, powder for injection 500 mg, vial	0	2	2
Levofloxacin, tablet /capsule 250 mg, tablet 500 mg, tablet 750 mg	2	25	27
Moxifloxacin, tablet /capsule 400 mg	1	4	5
Ofloxacin, tablet /capsule 200 mg; 400 mg	2	20	22
Prothionamide, tablet /capsule 250 mg	0	0	0
Para-Aminosalicylic Acid (PAS) sachets, 4 g granules	1	0	1
PAS Sodium 100 g jar granules, 4g / 9.2 g sachets granules; powder for oral	0	0	0
Other SRA suppliers include sources identified in the United States, Europe, and Canada. Numbers are approximate and do not count potentially redundant sources.			

FIGURE 2-1 WHO PQ second-line medicines as of the July 2012, IOM workshop.
NOTE: PQ, prequalified; SRA, stringent regulatory authority.
SOURCE: Hedman, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

1 percent failed due to extreme deviations.[4] Hedman suggested that the general scarcity of data linking patient outcomes to QA status of a particular product has inhibited the ability to derive accurate conclusions about the true risk of treatment with non-QA drugs or substandard drugs.[5] She therefore noted that there is a need to mine in-country primary data from MDR TB programs to inform the market and guide SCM. Joël Keravec, Brazil Country Program Director, MSH, commented that it is particularly difficult to link SLDs with treatment outcomes because MDR TB treatment regimens comprise multiple drugs and it is not possible to isolate the impact of one drug from another. A similar problem arises because patients are treated with drugs coming from different batches throughout the course of their lengthy treatment.

[4] WHO Survey of Quality of Anti-TB Medicines in Selected Newly Independent States of the Former Soviet Union; none of the samples were assumed to be counterfeit. Extreme deviation was defined as the content of API deviating by more than 20 percent from the declared content and/or the average dissolution of tested units lower than 25 percent below pharmacopoeia Q value.

[5] It would be unethical to systematically compare, or randomize in the context of a study, patients using substandard versus QA drugs.

Pharmacovigilance

Hedman described the TB environment as "fairly high-risk" with respect to the impact of shortfalls in quality, citing factors such as disease severity, challenges in patient follow-up, length of treatment, and the multiple drug regimens of MDR TB treatment as compounding the opportunities for drug failures. Few high-burden countries currently have (or are close to having) the capacity for pharmacovigilance, that is, the capacity to "monitor the quality of the medicines being made or imported," an important component of stringent regulation.

Andreas Seiter, Senior Health Specialist, Pharmaceuticals, Health, Nutrition, and Population, World Bank, suggested that a key barrier to QA in pharmaceutical procurements is that existing and established QA processes are not enforced. He cited the example of quality tests in pre- and post-shipment inspection and testing that are required in the contract but are not carried out.

Christophe Perrin, QA Pharmacist, The Union, remarked that double standards in the manufacture of SLDs exist as a result of variability in the stringency of regulatory authorities and in producers' commitments to quality. He cited anecdotal evidence that TB drug producers "are playing with some of the standards of what is inside a tablet" by using inadequately QA API for their FPPs. Andrew Gray, University of KwaZulu-Natal, expressed similar concern that some manufacturers, particularly large firms, might have WHO PQ status and adhere to stringent quality standards in only one of multiple plants that are producing the same drug.

National-Level QA

Noting that no international mechanism can "police" for QA if countries do not take ownership of the process, Keravec said the responsibility for QA should be transferred to countries. Countries should be supported to establish more stringent QA policies and procedures along with a mechanism for reporting problems that are detected, he added. Indeed, a strong in-country QA process should be able to detect production problems, including those of WHO PQ products when they arise. David Ripin, Executive Vice President, Access Programs, and Chief Scientific Officer, CHAI, agreed that moving countries toward self-regulation of products is important, and an important component of that ownership is agreement on bioequivalence for global products. Not all countries require bioequivalence as part of their QA programs, which might contribute to fragmentation of the market among drugs manufactured to satisfy different definitions of quality. Ripin expressed concern that many smaller countries need to rely on a common standard of quality, and that as countries move toward their

own levels of quality there needs to be "some mechanism for the smaller countries who aren't going to be able to reach that critical mass on their own even if they can define quality in a robust manner."

Participants discussed that some countries with non-donor-funded MDR TB programs opt not to procure PQ drugs. Meg O'Brien, Director, Global Access to Pain Relief Initiative, American Cancer Society, cited the need to determine those governments' rationale for choosing non-PQ suppliers. She speculated that if governments had access to better data about the quality difference between PQ and non-PQ drugs, then their procurement practices might change. Peter Cegielski, CDC, noted that in practical terms, most countries favor domestic manufacturers whenever possible. Norbert Ndjeka, MDR TB Director, Department of Health, South Africa, noted that South Africa's primary objective is better-quality drugs. He said that because the NTP does not have in-house technical expertise, it outsources QA to laboratories, academics, and experts. These advisory bodies determine the type and quality of drugs to be purchased by the government and also liaise with procurement agents. Thus QA in South Africa is largely dependent on separate, nongovernmental entities that advise the NTP.

Seiter suggested that emphasizing the commercial aspect—that it is easier to export products that adhere to a global quality standard—could serve as an incentive to national governments. Nina Schwalbe, Managing Director, Policy and Performance, GAVI Alliance ("GAVI"), remarked that a similar strategy was used by GAVI in India to address vaccine QA.

Cegielski suggested developing a system of regulatory reciprocity, in which one country accepts the regulatory processes and decision making of another, such that countries without SRA could accept approval from countries that do have stringent standards. Vincent Ahonkhai, BMGF, pointed out, though, that countries have a "statutory responsibility to regulate the product that circulates within their borders" and also that the reviews conducted by SRAs in other countries might not take into account factors specific to other countries, such as their health systems, environments, coincident diseases, and so on. Hedman remarked that regulatory reciprocity between countries does not exist anywhere except in the European Union via the EMA. In contrast to regulatory reciprocity, regulatory harmonization seeks to standardize methodologies, reduce the regulatory burden, and minimize delays.

Seiter explained that in the absence of stringent regulatory oversight, the buyer needs to ensure quality of the drugs procured. Usually a procurement agent is involved, and this agent has an in-house QC and QA system. A working group, under the leadership of WHO and participation of most relevant international funding and procurement agencies, has developed a tool for a standardized assessment of procurement agencies. This tool is based on WHO's Model Quality Assurance System for procurement agen-

cies and allows for the first-time benchmarking of procurement agents and making their otherwise proprietary quality systems comparable. The tool is currently being tested.

Hedman commented that although it is important to foster long-term initiatives of national QA regulation such as those discussed here, in the short term there is an "immediate need to make sure that we reduce the risk of non-QA drugs that are going into high-burden countries."

QA Regulation in India

As described in Chapter 1 (Box 1-4), the World Bank provides loans to the Indian government to cofinance its NTP, with the objective of building and strengthening India's overall health system. According to Seiter, part of that system strengthening, particularly with respect to the NTP, should also include development of India's own voluntary stringent regulatory pathway. This would enable the development of a recognized "seal of approval," both for the purpose of exporting SLDs to other countries and to allow domestic procurement financed by external donors. At present, the Indian government employs a procurement agent, with an independent QA process in place, to procure SLDs directly from manufacturers. Seiter reported that it would cost the government three times as much to purchase a PQ product from the same company.

Brazil's National QA Model

Brazil's model for QA and management of SLDs can be characterized as a "rationally established environment," whereby the NTP is responsible for maintaining and assuring the quality of its TB drugs. The majority of SLDs are produced in-country in the public and private sectors. Keravec explained how, in Brazil, product quality is assured through a national regulatory system of registration, documentation, monitoring, onsite inspections, testing, and enforcement that is specifically designed for TB drugs. Production consistency in terms of batch sizing is analyzed, postmarketing surveillance is performed, and inspections are carried out at non-domestic manufacturing sites that respond to international tenders.

In terms of capacity, Brazil has a National System for Sanitary Surveillance based on the model of an independent NRA, Anvisa. The system in Brazil includes a national laboratory institute, the National Institute for Quality and Control, responsible for quality and control testing, developing reference materials, and administering proficiency-testing programs to accredit labs in the 27 states that meet the appropriate technical standards. A specific TB Drug Quality Testing Program has tested all FLDs and SLDs in use since 2004, according to national regulation policies for sanitary sur-

veillance. The program is conducted with the support of a working group that carries out its activities and monitors results and regulatory measures. The initial findings of the program revealed quality and labeling defects in 32 percent of the 70 samples analyzed,[6] which were linked primarily to API quality and discrepancies among the analytical methods used by the NRA and the public manufacturers. The NRA notified manufacturers of products that failed to meet adequate quality standards, and the products were recalled.

Keravec maintained that the "working group" model has facilitated improved interactions between producers and regulatory authorities as they have undertaken efforts to improve drug quality and harmonize analytical methods by decentralizing quality testing to the state level. Transparency for stakeholders is ensured because reports on product quality are publicly and freely accessible. The implementation of the e-TB Manager database (described in Chapter 1, Box 1-4) has also enhanced the NTP's capacity for pharmacovigilance.

"Vicious Cycle" of QA SLD Supply

Patrick Lukulay, USP, depicted SLD supply as being plagued by a "vicious cycle" in which there is a limited supply of QA API and QA FPP, while QA FPP volumes are also affected by the limited demand for QA drugs, including the poor diagnosis of MDR.

Lukulay differentiated between two components of QA: QC and quality of the manufacturing process (Good Manufacturing Practices). The former encompasses the quality of the attributes of the product, that is, presence of impurities, dissolution profile, ingredient identification, and microbial content (for injectables). Manufacturing process control helps ensure that drugs that meet QC standards are also produced in an environment appropriate for drug manufacturing. A facility could, for example, be prone to contamination or a product might not have been provided with sufficient documentation to be tracked if problems arise. QA medicines satisfy both components.

Limited supply of QA API is a serious barrier that affects lead times, price, quality, and prequalification of FPPs. Lukulay suggested there is an urgent need for more API suppliers to voluntarily seek WHO PQ in spite of the capital and human resources investment that the process entails. Entry into the API manufacturing industry is severely restricted by the complexity and cost of production. Lukulay's analysis revealed that in terms of cost/reactor volume, China (followed by India) has the lowest current Good Manufacturing Practices (cGMP) and operating costs in the

[6] Thirteen percent failed due to labeling and 19 percent failed due to tests.

world. China is the world leader in fermentation chemistry in part because its petrochemical industry, on which API production technology relies, is relatively far advanced. The combination of fermentation technology and low cost per volume explains why China produces 80–85 percent of the world's TB APIs, including SLD TB APIs.[7] He noted that low capacity use for API plants causes significant price increases, underscoring the need to fill idle plant capacity with full batch sizes to reduce product costs. While QA depends on a number of factors related to manufacturing and capacity, the tension between assuring quality and speeding treatments to patients was also discussed by several workshop participants (Box 2-1).

FORECASTING AND INFORMATION MANAGEMENT

Workshop discussions included a focus on selected issues of demand that affect and impede the entry of SLDs into countries. This section of the report provides an overview of the key roles that improved demand forecasting will need to play in addressing demand-side challenges to the SLD supply chain. O'Brien provided a synopsis of demand-forecasting fundamentally, described ways in which SLD demand forecasting methodology could be improved, and explored the impact of accurate and credible demand forecasting for suppliers. Hamish Fraser, Assistant Professor of Medicine, Harvard Medical School, and former Director of Informatics and Telemedicine, Partners In Health, provided an overview of how information management systems could be employed to improve patient management, track demand, and strengthen and improve transparency of the supply chain.

Demand Forecasting[8]

O'Brien articulated several tendencies prevalent in the field that can hamper both the practice of forecasting and the way results are interpreted, and offered suggestions for establishing a more effective forecasting process. While it can be tempting for both the forecaster and the consumer to gloss over the details on which a forecast is constructed, it is important not to skip over them: multimillion dollar investments and delivery of treatment to huge patient populations can be predicated upon those details. It is less helpful to construe forecasts as either "right" or "wrong" than it is to strive

[7] Further advantages: China's petrochemical industry is able to generate the starting material, intermediates, and solvents necessary for API production, and its transportation infrastructure is able to support bulk material logistics. At present, 50 percent of starting materials and intermediates are imported from China to the Indian pharmaceutical industry.

[8] This subsection is based on the presentation by Meg O'Brien, Director, Global Access to Pain Relief Initiative, American Cancer Society.

to generate "more useful" ones. Applying the analogy of a complex calculator, the forecasting process should begin by understanding the consumer's needs[9] and follow with the construction of a logical framework to abstract reality into a simpler model. A good model should be "superficially simple and covertly complex." The framework can incorporate both recent experience and the impact of the specific market and demand drivers to account for future uncertainty. Also helpful is clarifying the consumer's time horizon and restricting the forecast primarily to that time frame. Relevant, carefully selected data (ideally collected in a standardized way) should then be used in the model to produce and check results. Finally, the results should be communicated to the consumer in a way that does the following:

- satisfies the consumer's main objective;
- explicates the logic behind the model;
- makes assumptions clear;
- anticipates questions; and
- establishes the forecast's credibility.

O'Brien noted that a properly designed and credible demand forecast can play a key role in aligning product prices with their true costs by reducing demand uncertainty and improving visibility into expected orders. It is important to distinguish among need, demand, and procurement in forecasting: *need* refers to volumes required to treat all patients, *demand* to volume that will actually be used, and *procurement* to volume that will actually be purchased.

There is a distinction between aspirational and realistic forecasts. Political and national program objectives can drive forecasting toward unrealistic outcomes. For example, an organization might choose not to release a forecast that undermines or contradicts a highly publicized treatment objective (e.g., the WHO "Three by Five" ARV [antiretroviral] forecast). Similarly, a forecast might be manipulated to align with an aspirational national program objective, but then fail to constitute a realistic forecast for suppliers. O'Brien maintained that forecasting should ideally be performed in conjunction with both market generation and serious commitments to seeing orders through, as well as following up on forecasts to check for accuracy. Such efforts can help to "make sure that reality looks like your forecast" when trying to attract new products and suppliers to a market.

Prashant Yadav, University of Michigan, suggested that a process of consensus forecasting could be useful in creating a platform to synthesize different forecasts that have been generated for MDR TB SLDs. He cited

[9] For example, does the consumer need a precise estimate, generally plausible estimate, minimum/maximum, plausible range, or a yes/no answer?

BOX 2-1
Considering Two Key Priorities in the Donor-Funded MDR TB Market: QA and Treatment Access

A theme that emerged during the workshop was the tension inherent in trade-offs among cost, access, efficacy, and QC in the provision of SLDs for MDR TB treatment. A focal point of the issue is how these factors are affected by the regulatory structures through which SLDs are channeled in the donor-funded supply chain.

Expanding Access to Treatment

One perspective, expressed by some, including Salmaan Keshavjee, Director, Program in Infectious Disease and Social Change, Department of Global Health and Social Medicine, Harvard Medical School, is that the system should be designed with a primary focus on ensuring that more patients in need receive "good-enough" quality drugs in the quickest possible way, arguing that the current focus on ensuring the most controlled and monitored treatment is a limitation of the system. He said the system should be redesigned to be decentralized, with a priority focus on lower prices, increased drug supply, and expansion of the number of patients who can access treatment. For example, he suggested that countries should be permitted to procure drugs directly from manufacturers as long as they are QA through a mechanism like the Global Fund's 90-day rule, which allows a country to use second tier–level drugs if optimal quality drugs are not available within 90 days. As Andreas Seiter, Senior Health Specialist, Pharmaceuticals, Health, Nutrition, and Population, World Bank, commented, significantly lower prices can be achieved through this type of direct procurement. Norbert Ndjeka, MDR TB Director, Department of Health, South Africa, noted that countries like South Africa procure drugs without WHO PQ status from the same manufacturers that supply the drug with WHO PQ to GDF. Several other speakers reinforced the point by noting that countries desire the authority to regulate their own QA.

More broadly, Keshavjee suggested that definition of quality should be put on a spectrum in such a way as to prioritize the provision of comprehensive access to treatment. That is, instead of "not treating people because we don't believe that the drugs that are available 10 feet away from them in their local pharmacy are good," he suggested engaging the private sector and in-country leadership to focus on providing quality treatment in the immediate term while employing mechanisms to "move those governments toward quality" in the longer term. Similarly, he suggested that determining a country's or program's eligibility for the

GLC mechanism in terms of compliance with QA standards should be framed as a process rather than an end point. That is, these countries or programs should be allowed to access drugs while being facilitated in working toward achieving compliance.

Avoiding a Double Standard of Treatment

The alternative perspective, expressed by several other workshop participants, maintains that the absence of stringent centralized regulation gives rise to an unacceptable "double standard" of MDR TB treatment, whereby some patients in some countries receive drugs of poor quality while those in other countries receive drugs of good quality. Myriam Henkens, International Medical Coordinator, MSF, stated that such a double standard is unfair because all patients deserve quality drugs. She argued that it is "our role to fight for that and make that clear" and suggested that patients should also be educated to insist on quality drugs and to hold their governments accountable for providing them.

Peter Cegielski, Team Leader for Drug-Resistant TB, International Research and Programs Branch, Division of Tuberculosis Elimination, CDC, said that in addition to a double standard in terms of drug quality, in a broader sense the TB control community has also promoted a double standard regarding the diagnosis and treatment of TB for the past 20 years that is finally being overcome. He suggested that this is one of the causes of the current difficulties in diagnosing and procuring drugs for MDR TB patients.

Amy Bloom, Acting Chief, Infectious Diseases Division, USAID, articulated two key pharmacoeconomic questions that will need to be addressed in order to reconcile the differing perspectives and inform the potential restructuring of the system. The first is to decide whether treating more patients with drugs of questionable quality at lower cost is worth the risk in efficacy. The second is to determine the "real" respective costs of treatment with drugs that have passed through established centralized QA regulatory pathways, drugs that have passed through decentralized QA processes, and drugs of poor quality.

Lisa Hedman, Project Manager, WHO, stated that an evidential link between drug quality and actual patient outcomes had yet to be concretely established and warned that current data are insufficient to support a "risk-based" approach to QA. She stated that available data show real problems, citing as an example a case study documented by CHAI in India in which QA policies for locally procured medicines and donor-funded procurement policies were operating as discrete systems within the same country, and a quality two-tiered market emerged between QA and non-QA products.

the field of malaria, where a tripartite consortium develops three separate forecasts using different assumptions, different data, etc., and then meets to compare results and reconcile their differences to generate a combined forecast that is communicated to manufacturers. O'Brien concurred, on the basis of her experience in group forecasting with shared data in other fields, that consensus forecasting has the potential to improve forecasting and coordination. She warned, however, that it is important to properly harmonize data via systematic comparison and to establish a collective means for evaluating different forecasts and their underlying assumptions.

Information Management[10]

The field of information management can be applied in multiple ways to address issues associated with the MDR TB supply chain. Fraser emphasized that improving the efficacy and breadth of information management systems could concomitantly increase demand-forecasting accuracy; increase supply chain transparency; and improve health system strength, scalability, and sustainability. He listed a number of core variables[11] that should be collected and quantified with respect to the SLD supply chain, adding that although they are not difficult to collect in principle, they can be challenging to implement without good tools and training.

Electronic Medical Record (EMR) Systems

In what represented an early move toward integrating information management into the broader health system, a Web-based EMR system was designed in 2000 to support a Partners In Health project to scale up MDR TB treatment in Peru. Data collected about laboratory results, including sputum smears, cultures, and drug sensitivity tests; treatment regimens; and other types of records were used for various clinical, programmatic, and clinical research purposes (Fraser et al., 2006). For example, collection of drug regimen data was prioritized and used to improve QC, and then aggregated to assess monthly requirements. The aggregated data could then to be linked to price lists and combined with recruitment rates as well as with time and length of treatment. Eventually, models based on these data were used to generate forecasts of drug requirements 6 months or more in

[10] This subsection is based on the presentation by Hamish Fraser, Assistant Professor of Medicine, Harvard Medical School, and former Director of Informatics and Telemedicine, Partners In Health.

[11] Such variables include demographics, program enrollment date, start date for drugs, drug regimen, treatment status, treatment outcome and date, smear and culture results, DST results, other lab data (hematological, biochemical), previous medications, adverse events, and socioeconomic factors.

advance. Fraser questioned why such established tools are not being further developed or implemented more widely.

Fraser cited Keravec's e-TB Manager as another important innovation in MDR TB drug and information management. The OpenMRS (Open Medical Record System) project is an example of a non-disease-specific EMR initiative[12] that permits redeployment of a horizontal approach to vertical uses. Its broad framework can be tailored to support the management of various diseases by customizing its language, concept dictionary, and open-source modular design.[13] Furthermore, a system like OpenMRS might provide an opportunity for private-sector health care professionals (HCPs) in countries like India, where they are not part of national MDR TB initiatives, to communicate more effectively with the public sector. An OpenMRS system could offer tools for a range of diseases but have embedded key functionality for MDR TB. As with all personal health data, however, confidentiality and ownership of data is an important concern. Well-designed systems using existing technology can ensure security and encryption, but it is essential to properly train and supervise staff, and to develop stronger national policies and laws to protect such data in developing countries that often lack such regulation.

Information Technology Suggestions for MDR TB Supply Chain

Fraser offered several concrete suggestions, or "low-hanging fruit," that might drive efforts to improve the MDR TB SLD supply chain, as follows:

- There is a need for better standardized national and international coding of medical products in order to track and map shipments.
- If products all bore internationally agreed-upon bar coding containing name, batch number, expiry data, and authentication ID data, accuracy and workflow could be dramatically improved.
- Standardized reporting formats for drug stocks and status could improve both private- and public-sector transparency and stock-out monitoring.
- The OpenBoxes shipment tracking and inventory management system[14] is another broad system covering a range of supply chain requirements that might integrate with the MDR TB SLD supply chain.

[12] Collaborative project between Partners In Health, Regenstrief Institute in Indiana, and the South African Medical Research Council (www.openmrs.org, accessed October 18, 2012).

[13] An example of OpenMRS customized for MDR TB can be viewed at www.openmrs.org/demo (accessed October 18, 2012).

[14] Open-source software developed by Partners In Health.

Lucica Ditiu, WHO, suggested there is potential for data collected to contribute to reporting and integrating TB care with other treatments such as HIV and malaria. Fraser commented that investments into systems for HIV (like PEPFAR) have unfortunately not developed into common tools for use beyond HIV. Fraser suggested that as a matter of priority, national health authorities and funding agencies should be made aware that the development of common tools is not that much more expensive than the more prevalent disease-specific ones, and that they provide a better mechanism for efficient drug supply and dissemination of information and reports.

Keravec suggested the strategy of translating country- and facility-level demand forecasts based on reliable data (e.g., pace of enrollment, consumption, and real number of patients being treated) from information systems into usable data for GDF. GDF could then supplement this with its own data (e.g., orders, lead times, production, and shipment schedules) to develop an early-warning stock-out system.

DRUG SHORTAGES

Workshop discussion included examination of supply-side issues affecting the entry of SLDs into countries, with specific focus on the causes, impact, and prevention of supply chain shortages. Perrin provided an overview of common problems that lead to supply chain shortages at both the country and global levels. Jim Barrington, Global Program Director, Novartis, described the SMS for Life model for preventing stock-outs of malaria medicines in African countries. Cegielski demonstrated that TB and MDR TB drug shortages are a problem not only for low-income countries by describing the effect of such shortages in the United States.

Causes of National- and Global-Level Supply Chain Shortages[15]

Perrin emphasized the importance of setting and maintaining international quality standards for drugs and the benefit that the WHO PQ program provides in that regard to low-income countries. He also acknowledged the Global Fund's and GDF's efforts to align their QA policy with WHO PQ and other SRAs. Purchasers and funders were urged to foster demand for QA SLDs in order to incentivize reliable manufacturing and limit risks to individuals and public health.

[15] This subsection is based on the presentation by Christophe Perrin, QA Pharmacist, The Union.

National-Level SLD Shortages

Perrin remarked that international donors and procurement agencies often fail to consider an NTP to be their main "customer," focusing instead on their own internal organization and procedures; this leads to the NTP not being appropriately informed and updated about the logistics of its procurement once the order has been placed. A participant elaborated that when NTPs in this situation are faced with unexpected drug shortages due to being kept "out of the loop" by international agencies, they are often unfairly blamed for the problem.

Another common issue described by Perrin is the lack of visibility by the NTPs into the supply chain, which can lead to disruption and necessitate emergency orders due to resulting shortages. NTPs often lack adequate human resource capacity, leading to a lack of harmonization among donors and further straining their staff, who attempt to manage different processing and quality requirements. Discrepancies between actual diagnoses and the volume of SLDs ordered can result from inadequate data collection and forecasting competencies and can also lead to shortages.

Potential country-level solutions that Perrin suggested include strengthening NTP leadership and centralizing SLD supply chain coordination, and increasing human capacity for consistent program management with training programs led by qualified staff from donor agencies.

Global-Level SLD Shortages

Perrin outlined common causes of SLD shortages on the global scale. Global reliance on a single source for QA API or on an extremely limited supplier pool can lead to shortages when demand far outweighs supply capacity. A related problem is that minimum volume thresholds for orders can cause unexpectedly increased lead times. He reported that in 2010, the majority (56 percent) of shortages in Global Fund grants for TB were due to weak procurement and supply management capacities.

Perrin offered potential global-level solutions aimed at different components of the system, as follows:

- QA manufacturers could be incentivized via demand forecasting and expansion, transparent bidding processes, advance purchase commitments (APCs), and smoother regulatory mechanisms.
- Donors could implement revolving fund mechanisms and harmonization initiatives to shorten delays.
- Donors and procurement agencies could allow manufacturers seeking to reach minimum production thresholds to access a centralized SLD stockpile.

- WHO and donors could provide financial and technical support for innovation (new compounds, shorter regimens, packaging allowing longer shelf lives, etc.).
- Donors, countries, and procurement agencies could work to streamline forecasts of needs, order planning, and disbursement of funds.

Several participants referenced the limited shelf life of SLDs (24 months) and how this affects availability of drugs within the global supply chain. Pre-made SLDs can sit in a manufacturer's warehouse for weeks or months before the appropriate paperwork is completed for shipment, all while an already short shelf life deteriorates further. It was also referenced that ministries of health can often require receipt of SLDs with a predetermined percent of the shelf life preserved (e.g., 70 percent shelf life), which heightens the challenge of efficiently procuring SLDs from a manufacturer and distributing in-country.

"SMS for Life" Model for Preventing Stock-Outs[16]

Barrington said the SMS for Life project[17] was formed in response to the huge problem of malaria drug stock-outs at health facilities in Africa, the major cause of which is a lack of adequate information management and provision. The program facilitates patient access to medicine and eliminates stock-outs by using an SMS system to monitor stock levels and to collect surveillance data at remote health facilities. Collected data are used to generate reports delivered via the Internet and mobile phone to the reporting hierarchy. Key design criteria for the solution were usability in the targeted environment, capacity for scale-up to an unlimited number of health facilities and countries, affordability,[18] availability as a subscription service with no requirement for initial or future technology investments or management, commercial sustainability for service providers, and reliability proven via initial implementation in the pilot country at scale.

To date, the program has been implemented in all public health and faith-based facilities in Tanzania and in pilot districts in Kenya and Ghana, with implementation planning in progress in Cameroon and the Democratic

[16] This subsection is based on the presentation by Jim Barrington, Global Program Director, Novartis.

[17] In partnership with IBM, Vodafone, Google, Ministry of Health in Tanzania, Novartis, and Roll Back Malaria Partnership.

[18] The system was designed to be affordable in the poorest countries without requiring donor funding. The overall total cost was capped at $100 per facility per year with procedural and training materials provided free of charge. The system also needed to be offered via subscription service with no investment required.

Republic of the Congo. Scale-up to more countries and/or to cover more products and commodities would require funders to redirect funding into strengthening systems and operational projects for improved stock management at the health facility level and management of drugs in-country and at health care facilities after they are received in-country.

On a broader level, Barrington suggested that funding mechanisms would have a greater impact if they reallocated more resources toward systems strengthening. To that same end, he asserted that funders should take on both the obligation and accountability for outcomes; that is, they should seek to ensure that drugs are actually received by patients, not just to ensure their procurement and delivery into the country.

Potential Consequences of Data Transparency

Participants addressed possible repercussions of total data transparency for the countries that are beneficiaries of programs like SMS for Life. Brenda Waning, Coordinator, Market Dynamics, UNITAID, WHO, commented that this program holds governments to a strict and public level of accountability, to which they may be resistant. She continued that the application of such a program to an MDR TB program could be even more risky because the criticism of public and press in response to stock-outs would fail to account for the complexity of SLD procurement. Although several participants agreed that information should be made available, there was some disagreement as to whether it would be feasible for the data to be fully disclosed (and not "owned," e.g., by a Ministry of Health), or whether there are limitations on the extent to which data can be made available at the health facility level due to its high value and resulting security concerns.

TB Drug Shortages in the United States[19]

Cegielski highlighted the issue of TB drug shortages in the United States to illustrate that the problem is not exclusive to low- and middle-income countries, nor is it limited in the United States to TB drugs alone.[20] He described the results of an unpublished survey that was undertaken in 2010 through the National TB Controllers Association to assess drug shortages

[19] This subsection is based on the presentation by Peter Cegielski, Team Leader for Drug-Resistant TB, International Research and Programs Branch, Division of Tuberculosis Elimination, CDC.

[20] Between 2001 and 2011, 1,190 shortages were recorded using FDA's voluntary reporting system.

in state and local TB programs. Of the respondents, 64 percent reported problems with MDR TB drug procurement in the preceding 5 years.[21]

Cegielski reported that the most common reasons for the shortages were nationwide shortages (95 percent), lack of funding and drug price (62 percent), shipping delays (71 percent), regulatory delays (50 percent), and payer issues (~30 percent). The number of shortages[22] increased from 70 to 211 between 2006 and 2010, and as of September 2011, kanamycin was not available, streptomycin was out of stock, and capreomycin and amikacin were very difficult to procure. The shortages had direct negative effects on patients, according to the same survey, including delays in treatment initiation (58 percent), treatment lapses and interruptions (32 percent), and the need to be prescribed a suboptimal treatment regimen (26 percent). Cegielski stressed that dealing with these shortages depletes the time and human resources of clinic management.

Key Messages[a]

- National regulation of SLDs is essential, as there is no international mechanism to monitor for and ensure QA.
- The SLD supply chain is characterized by a negative cycle arising from the limited number of suppliers of API and FPP coupled with decreased demand for QA SLDs from certain areas.
- There is a need for better demand forecasting, and there is a need to distinguish between aspirational forecasting and realistic forecasting.
- Innovations in information management may offer improvements across many aspects of the SLD supply chain, from tracking of treatment to demand forecasting to reduction of stock-outs.

[a] Identified by individual speakers.

[21] Cegielski cautioned that only 33 of 61 reporting areas responded, so the results might not be generalizable.

[22] Including isoniazid, rifampicin, cycloserine, ethambutol, rifabutin, amikacin, kanamycin, and streptomycin.

3

Financing of MDR TB SLDs

This chapter provides an overview of issues related to the financing of the MDR TB supply chain discussed at the workshop. The first section provides an overview of the experiences of organizations currently funding the MDR TB chain. The second section describes the financing models for supply and details specific innovative financing approaches and applications used by other programs to consider how those innovative models and approaches might be applied to financing of SLD supply.

FUNDING OF THE MDR TB SUPPLY CHAIN

Each step in the supply chain process, from selecting a pharmaceutical for manufacture to patient use, requires support and funding from multiple organizations in the public and private sector. During the workshop, speakers and participants from organizations that provide funding for SLDs described challenges and barriers that their respective organizations have faced in funding MDR TB and explained some of the funding strategies that they have used to address those issues.

USAID's Funding Perspective[1]

Cheri Vincent, TB Team Leader, USAID, described SLD supply chain challenges from the perspective of USAID. She characterized the lack of demand for SLDs as urgently essential because "it really means that patients

[1] This subsection is based on the presentation by Cheri Vincent, TB Team Leader, USAID.

are not getting lifesaving treatment," and she observed that resolving the problem would require concerted effort to scale up MDR TB treatment programs: WHO/Stop TB Department data indicate that only 19 percent[2] of the estimated MDR TB patients worldwide were initiated on treatment in 2011.

Funding Inflexibility and Loss to Use

Inflexibility and mismatch of funding for SLDs is another key concern. An analysis of a randomly selected set of countries that compared the number of available Global Fund or UNITAID SLD treatment regimens to the number of MDR TB patients enrolled in 2011[3] revealed that only 39 percent of the available funds were actually used by countries for MDR TB treatment regimens. In other words, of the selected countries, only 30 percent met their planned MDR TB treatment objectives. This situation makes for an unpredictable market for manufacturers, donors, and technical assistance providers. Unused Global Fund funding can be reprogrammed for other important activities, but most of the time the country loses these valuable resources to treat MDR TB. However, it is also clear that a few countries are scaling up MDR TB treatment faster than SLDs are available in the Global Fund grants. These countries are not able to benefit from the drugs not used in other countries so they can continue to provide diagnosed patients with the lifesaving drugs. Vincent argued that more flexibility for available funding would allow resources to be matched more appropriately with enrollment and allow some countries to scale up faster, saving more lives and reducing the amount of MDR TB funding lost.

Country Capacity Barriers

Another challenge centers on insufficient country capacities for scale-up, forecasting, procurement, and in-country logistics. Global scale-up trends are erratic; some countries are scaling up more quickly than expected and many others more slowly. Due to the slower and unpredictable rates of national MDR TB program scale-up in countries like India, estimates about the number of patients to be treated are often unrealistically optimistic. The resulting discrepancies between forecasted demand and actual orders placed are problematic for manufacturers. Vincent noted the need for more regular reporting on the pace of MDR TB enrollments by country. WHO and GLC are now starting to monitor MDR TB enrollments by country every 6 months instead of yearly.

[2] Representing approximately 55,000 MDR TB patients.
[3] Per WHO enrollment data.

Many countries also struggle with the complicated Global Fund procedural and financial requirements, increasing lead times in procurement and causing drug stock-outs, which suggests that the processes need to be harmonized and simplified. On the manufacturing side, limited production of QA API and FPP SLDs is caused by a lack of incentives for suppliers and a lack of competitiveness in the SLD supplier market, which yields higher prices.

USAID's Approach

Vincent described USAID's three-pronged approach for making affordable, quality SLDs available around the world. The first approach is to improve and expand the global SLD supply chain, which mainly involves

- coordinating with GDF[4] and other partners on SLD SCM at the global level;
- improving procurement procedures;
- harmonizing treatment regimens; and
- improving the data on SLD needs.

The second approach is to encourage the quality of QA SLDs by taking the following steps:

- supporting GDF in the market development of quality SLDs;
- providing technical assistance to FPP and API manufacturers to become PQ;
- developing public pharmacopeia standards; and
- improving diagnostic technology.

The third approach, technical assistance at the country level, involves

- reducing bottlenecks through better quantification and stock-out early warning systems;
- in-country and regional technical assistance in pharmaceutical management for MDR TB (SLDs and ancillary medicines);
- development of new training platforms and information systems for SLD management; and
- promoting active indicator-based surveillance of use of SLDs, the formularies, and co-medication safety.

[4] USAID is a major donor to GDF, providing 31 percent ($14.97 million) of GDF's budget in 2011.

Suggested Ways Forward

Vincent offered several suggestions geared toward accelerating progress in the MDR TB arena. NTPs would benefit from a sustainable, flexible, and pooled global SLD procurement mechanism, an approach that would need major support from the Global Fund as one of the largest funders of SLDs globally. She maintained that because the Global Fund is the major donor for SLD procurement outside of countries' direct procurement, it needs a restructured focus with new procedures and processes put into place.

Vincent suggested that there is a need for four interventions that the Global Fund and others should support through GDF, including

1. a revolving stockpile to expedite delivery to countries and provide flexibility to countries for scale-up;
2. an APC to motivate suppliers to place full-batch orders to bring prices down;
3. incentives to manufacturers of QA API by guaranteeing orders; and
4. incentives to BRICS countries (Brazil, Russia, India, China, and South Africa) to procure QA medicines by supporting domestic QA manufacturing.

These interventions, she estimates, would reduce procurement time delays from 6 to 8 months to 3 to 4 months.[5]

Vincent noted that continued communication and coordination among donors through existing working groups and entities should move from talk to action, citing the successful example of the Xpert® Buy-Down. In August 2012, Cepheid, along with partners BMGF, PEPFAR, USAID, and UNITAID, announced their agreement to support a buy-down of the price of the Xpert MTB/RIF (rifampicin) molecular test,[6] with the objective of improving diagnosis and identification of MDR TB patients, a key first step in patient management and treatment that can thus reduce transmission (Cepheid, 2012). The buy-down agreement makes the test available in 145 high-burden countries for less than $10 per test (down from $16.86). However, the important work of partners to scale up MDR TB treatment must happen at the country level with appropriate in-country technical assistance.

[5] Since the workshop, according to Vincent, there has been progress on moving some of these interventions forward with the Global Fund.

[6] Endorsed by WHO in 2010 for use in countries with high TB burdens.

Benefit of National-Level FLD Procurement

At the national level, countries (that are capable of doing so) could be helped to transition to taking over responsibility for FLD procurement, allowing more donor funds to be channeled toward SLDs. There were more countries with government budget line items for FLDs before the Global Fund started than there are now. Although the Global Fund has ensured the scale-up of FLDs, the effort may have also crowded out some governments from providing even their minimal levels of funding for anti-TB medicines. Vincent noted that all of her suggestions ultimately hinge upon PMDT scale-up, particularly in countries like China (1,000 of 50,000 estimated cases put on treatment in 2011) and India (3,300 of 64,000–100,000 patients treated in 2011), and that countries need intensified support and capacity building to scale up.

Perspective from BMGF[7]

Michael Kimerling, Senior Program Officer, Tuberculosis Global Health Program, BMGF, described two key challenges related to the overfragmentation of the market at multiple levels. The first is a "collective inability" to consolidate demand and ensure the predictable and timely treatment delivery needed to incite the necessary volume growth. The second challenge is to find a way for stakeholders and funders to cooperate more effectively and leverage their strengths to stimulate price competition in the market.

He suggested that three integrated strands of innovation are necessary to spur progress toward resolving these issues:

1. Continued development of the right diagnostics to include expanding laboratory infrastructure and investing in R&D for point of care and rapid DST.
2. Consideration of new drugs and improved therapeutic regimens currently under development (he suggested the need to shift focus from old drugs to inclusion of new drugs).
3. Regimen harmonization and standardization to improve forecasting, simplification of the complex MDR TB patient management system, and encouragement of deeper country ownership.

[7] This subsection is based on the presentation by Michael Kimerling, Senior Program Officer, Tuberculosis Global Health Program, BMGF.

Cost of Drugs Versus Cost of Delivery

Kimerling urged the MDR TB community to look beyond the price of SLDs to consider the overall cost of patient care and treatment (i.e., the price of delivery[8]), because the SLD pricing problem is only one factor. He noted huge variation in cost of delivery in different countries and warned that "we can't be naive and think that by solving the SLD-pricing problem we actually are solving the care and treatment problems."

Impact of New Drugs on Market Fragmentation

The SLD market is fragmented by country-to-country variations in treatment regimen, and in many cases multiple regimens within countries themselves. Therefore, achieving market stability and reliable forecasting is likely to be further challenged and fragmented by the introduction of new drugs and regimens that are currently under development as part of the existing pipeline (Figure 3-1).

Because, Kimerling said, at least two of the new drugs in Phases II and III of clinical development could be on the market in the next 1 or 2 years, there will be a need for forecasting and modeling about the impact of their market entry. Currently, there are three key funders in the MDR TB space: Global Fund, UNITAID, and individual governments. He suggested interacting directly with those governments that are developing economically and have their own resources and health budgets that could potentially be combined with funding organizations in an innovative way.

BMGF Program-Related Investments (PRIs)

Kimerling remarked that the model of BMGF-supported PRIs, which take the form of loans that must be repaid (not grants), could potentially serve as an innovative financial intervention to help break the price-inflation cycle in the MDR TB market (Figure 3-3). PRIs are financial mechanisms offered by foundations like BMGF in the form of equity or debt guarantee as a way of using endowments to support charitable market interventions. For example, PRIs could help to counteract monopoly premiums by facilitating competition. Volume guarantees could be used to offset the costs of subscale manufacturing and to address risk premiums. PRIs could help manufacturers by supporting a product's manufacturing line or by taking an equity position through a loan or direct investment.

To be implemented, these types of mechanisms must function in conjunction with all players involved. Therefore, Kimerling suggested,

[8] Including hospital and clinic care, training and personnel costs, lab tests, etc.

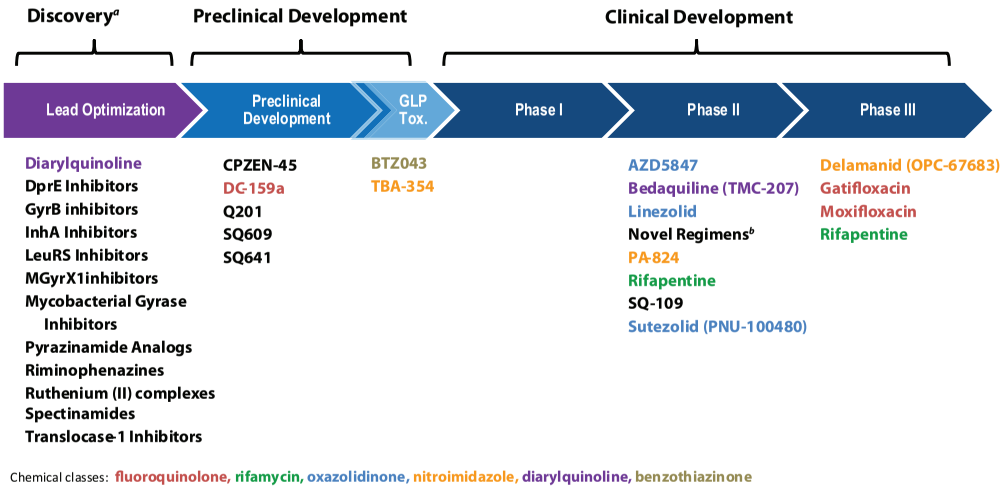


FIGURE 3-1 Global TB drug pipeline, as of June 18, 2012.
NOTE: GLP, Good Laboratory Practices; Tox., toxicity.
[a] Ongoing projects without a lead compound series can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php (accessed November 19, 2012).
[b] Combination regimens: first clinical trial (NC001) of a novel TB drug regimen testing the three drug combination of PA-824, moxifloxacin, and pyrazinamide was initiated November 2010 and completed in 2011 with promising results. The second clinical trial (NC002) of this regimen was launched in March 2012 and will test the efficacy of the regimen in drug-sensitive and multidrug-resistant patients. The third clinical trial (NC003) will evaluate PA-824, TMC-207, pyrazinamide, and clofazimine in combinations and is scheduled to begin September 2012.
SOURCE: Kimerling, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

they could usefully foster a needed shift from thinking about the cost-effectiveness of a single component of MDR TB treatment to thinking about aggregate affordability.

UNITAID's Financing and Spending Approaches[9]

Brenda Waning, UNITAID, WHO, presented two different functional characteristics of UNITAID: that the organization is itself funded through an innovative mechanism (the air ticket levy) and that the organization then spends those funds in an innovative way.

Innovative Funding Mechanism

The air ticket funding mechanism involves application of progressive levies[10] to all flights departing from contributing countries, levies from 9 of which represent 80 percent of UNITAID's funding[11] (the other 20 percent comes from various sources[12]). Air ticket levies have several advantages, including that they

- are equitable, predictable, and untied;
- are cost-effective to collect;
- do not affect airline profitability or sales; and
- have the unique characteristic of constituting a South-to-South cooperation.

Innovative Spending Approach

UNITAID's strategy for innovative spending consists of a market-only approach to increase access to the commodities used to prevent, diagnose, and treat TB, HIV, and malaria. Market conditions for those products are analyzed to expose their underlying causes and to seek opportunities to apply leverage and resources effectively. Although, as Waning noted, differences among individual markets can make it difficult to draw comparisons (e.g., between first-line ARVs and MDR SLDs), UNITAID's experience in

[9] This subsection is based on the presentation by Brenda Waning, Coordinator, Market Dynamics, UNITAID, WHO.

[10] Ranging from 1 euro for a domestic ticket to 40 euros for an international business class ticket.

[11] Cameroon, Chile, Democratic Republic of the Congo, France, Korea, Madagascar, Mali, Mauritius, and Niger.

[12] BMGF, Brazil, Cyprus, Luxembourg, Norway from a carbons emissions tax, Spain, and the United Kingdom. Waning quoted a leading group on innovative financing for development as strongly recommending an increase in the number of countries that pledge to UNITAID.

the second-line ARV and pediatric markets (implemented by CHAI), might be applicable to MDR TB SLDs. To that end, Waning offered the following as successful attributes of CHAI's pediatric ARV effort[13]:

- Drugs, treatment regimens, and product selections were harmonized within and among countries.
- Good cooperation with WHO was secured with regard to guidelines, consolidation agreements, and prioritization of WHO PQ registration for priority products.
- CHAI collaborated with multiple purchasing organizations (e.g., PEPFAR/USAID's Supply Chain Management System [SCMS], UNICEF [United Nations Children's Fund]) to improve quantification for country-level demand forecasting and global-level demand consolidation.

In that effort, it was important to understand supply chain cost structures in order to address their insufficiencies and also to understand interactions across markets (e.g., diagnostics, medicines, nutrition) and the impact of introducing new market entries. Manufacturers' confidence in the market was bolstered by UNITAID's coming to the table with a large pool of funding and resources, which resulted in successful price negotiations, improved price transparency, and development of new formulations. Procurement was innovative despite institutional constraints similar to those in the MDR TB supply chain.

Suggested Ways Forward

Waning offered her view on potential ways forward, emphasizing the need to minimize uncertainty as a crucial strategy for the SLD market. Adopting a proactive rather than reactive approach toward managing uncertainty could be a real opportunity in the SLD MDR TB market (e.g., improving clarity of funding and disbursements). Collecting both upstream and downstream data will help maximize efficiency and market certainty. Drawing on new diagnostic technology (e.g., GeneXpert) will help determine actual need more accurately. Connections with the private sector could be further strengthened (e.g., with IMS Health) to impact global market drivers.

Finally, she suggested creating new ways of working directly with those countries outside the donor-funded market (e.g., China and India) where products like API and FPP are being made and new technology is being developed. To deal with the global market space and "capitalize on the

[13] Treatment expanded from 60,000 to 360,000 patients within the UNITAID programs.

bigger world," UNITAID is making efforts to engage these middle-income countries that are dominating market anchors and not restricting its focus to the much smaller market of donor-funded programs.

MODELS FOR FINANCING AND SUPPLY

During the workshop, speakers and participants presented innovative models of financing and supply used by other organizations and programs to supply medical products for other diseases. The workshop discussions considered successes of and lessons learned from these other initiatives, the extent to which those lessons could or would not apply to MDR TB SLDs, and possible applications.

GAVI's Innovative Financing Mechanisms[14]

David Ferreira, Managing Director for Innovative Finance, and Head of the Washington, DC, Office, GAVI, provided an overview of GAVI, a public–private partnership founded in 2000 with the mission of increasing access to immunization in poor countries. In addition to increasing access, GAVI aims to serve as a developmental pathway for beneficiary countries toward "graduating" from the system and providing full access independently.

In contrast to the GLC mechanism, GAVI was initially designed and structured with the specific objective of not following a pilot model, but to roll out at the same scale as routine immunization. GAVI was originally part of UNICEF but broke off to become an independent foundation in 2008 and has sought to establish a diverse range of governing partners.[15] The inclusion of independent voices (e.g., investment bankers from Goldman Sachs) from outside the vaccine world better informs GAVI's planning and decision-making processes.

Ferreira introduced three innovative financing initiatives employed by GAVI to try to improve predictability and flexibility of funding, ensure sufficient and uninterrupted drug supply, aggregate and forecast demand accurately, and engage the private sector. The prevalent theme in those initiatives is market shaping, that is, creating a sustainable market with affordable prices and volumes sufficient for global coverage. Next, Nina

[14] This subsection is based on the presentations by David Ferreira, Managing Director for Innovative Finance, and Head of the Washington, DC, Office, GAVI; and Nina Schwalbe, Managing Director, Policy and Performance, GAVI.

[15] Among the partners are multilateral agencies, BMGF, developing country governments, donor country governments, civil society organizations, research institutes, and the vaccine industry.

Schwalbe, GAVI, described the GAVI vaccine market-shaping approach and its possible applications for MDR TB.

International Finance Facility for Immunization (IFFIm)

IFFIm is a vehicle for long-term legally binding government commitments. GAVI's donors (including Australia, France, Italy, the Netherlands, Norway, South Africa, Spain, Sweden, the United Kingdom, and soon-to-include Brazil) aggregate $6.3 billion in nominal terms, some of whom have made commitments for terms over 20 years. IFFIm uses these commitments to borrow money backed by those assets from bond markets in Australia, Japan, the United Kingdom, the United States, and elsewhere. This instrument's high degree of predictability over the long term enables GAVI to have the extreme flexibility to use money when needed. Ferreira noted that this also enables countries to plan more effectively and allows GAVI to make more sensible deals in the market, ultimately leading to improved public health outcomes.

Advance Market Commitment (AMC)

The AMC instrument is designed to incentivize manufacturers to move quickly from a low-volume, high-margin market (e.g., a three-dose pneumococcal vaccine being produced for rich countries at a very high price) to a business model with high volumes and low margins—in other words, to produce more, differently formulated, vaccines at lower prices. A "war chest" of donor funding ($1.5 billion) was created to present a feasible, sustainable, and attractive market for producers.

The AMC is essentially a long-term secure contract; manufacturers are offered a donor-funded[16] price guarantee and purchase commitment as a supply incentive to develop new formulations according to stringent quality standards. In exchange, manufacturers commit to supplying the product at a significantly lower price, long term, to developing countries (paid by both GAVI and beneficiary countries). The incentives to invest in R&D for new formulations stimulate innovation from manufacturers, and the contracting structure secures long-term supply. Ferreira noted that GAVI was able to achieve dramatic price reduction through the use of AMC and that rollout is proceeding rapidly (18 countries so far).

[16] Or in GAVI's case, a collective pool of donor funds.

GAVI Matching Fund

The GAVI Matching Fund was launched in 2011 with BMGF and the UK government. GAVI solicits funds from corporations or organizations with the promise that all funds raised within a given time frame will be doubled by the donors. This type of instrument is useful in diversifying the funding base and raising public awareness by encouraging participants to raise funds from their employers, suppliers, etc., which would also be doubled.

Ferreira noted that the GAVI Matching Fund has also been a useful tool for leveraging non-cash resources from partners, which are also matched with cash under certain conditions. By tapping into the core business skills of those partners, the supply chain is strengthened in various ways, such as logistics, delivery, and technology deployment to manage stock. This is a means of having the in-country logistics and in-country supply chain feed back to the global procurement part of the supply chain.

Market-Shaping Objectives

Schwalbe explained that because GAVI's initial strategy of pooling procurement of vaccines had not resulted in sufficient price reductions after 10 years, the organization adopted a market-shaping approach (in addition to pooling procurement). This approach has three key objectives: (1) to balance supply and demand to ensure sufficient uninterrupted market supply; (2) to control vaccine prices to minimize costs to GAVI and beneficiary countries; and (3) to ensure that the products are appropriate and QA and that innovation is fostered. Once the vaccines are procured, the countries have the full responsibility for actually delivering them, which also guides the market-shaping efforts.

Market-Shaping Tools

Maintaining the appropriate balance between those market-shaping objectives is dependent on the ability to communicate market information in a timely, transparent, and accurate way, and GAVI relies on certain tools to achieve that balance.

- *Predictability of funding* is enhanced through strategic long-term demand forecasting, which includes corroborating manufacturers' forecasts against GAVI's own forecasts.

- *Demand pooling*[17] among 73 countries allows leveraging of high demand volumes.
- *Flexible contracting* is achieved by adapting procurement tactics to the market environment (e.g., using AMCs to enter into multi-year contracts, demand guarantees, stockpiling, incentivizing new manufacturers).[18]
- *QA* is ensured through collaboration with WHO to strengthen national regulatory pathways and support the development of global quality standards.
- A *tiered pricing model* is used to scale prices according to a country's relative income.

Factors that influence GAVI's decisions about potential market-shaping interventions include the production complexity of vaccines (which has some similarities with MDR TB injectables), the market environment, and GAVI's relative market power. Schwalbe also cited the importance to suppliers of transparent and timely WHO PQ processes.

GAVI's Cofinancing Policy

Schwalbe detailed GAVI's financing policy, which falls under the auspices of the organization's objective to increase the predictability of global financing and improve the sustainability of national financing for immunizations.

Beneficiary countries cofinance with GAVI according to their ability to pay and in compliance with a very strict system. All countries must pay for at least a portion of every vaccine that GAVI funds. The copay for the lowest tier of countries is 20 cents per vaccine.[19] The next group of countries starts out paying 20 cents for the first year and then pays a progressive increase of 15 percent per year, and the final group includes "graduated"[20] countries that commit to a 5-year trajectory to full pricing. In other words, as countries develop economically, explained Ferreira, they are required to finance larger and larger proportions of their vaccines until they ultimately graduate out of the GAVI system and fully fund their own vaccines. Schwalbe noted that GAVI has ensured, through communication and connection with the pharmaceutical industry, that after graduation,

[17] In cooperation with procurement partner UNICEF.

[18] Countries can self-procure if they choose and are reimbursed for the price that GAVI pays.

[19] Established based on the cost of the DPT (diphtheria, pertussis, and tetanus) vaccine alone, which is what those countries were already paying for as a minimum.

[20] Countries with a gross national income (GNI) of $1,500 per capita or less are eligible for GAVI cofinancing.

countries will have guaranteed access to the same price they were paying within the program.

GAVI's disincentives for defaulting have thus far generally been effective. Ferreira explained that benefits of the cofinancing requirement include enabling country ownership and forcing the relative interests into alignment. Ministries of health and finance serve as signatories on grant proposals as a way of guaranteeing legislative accountability. Schwalbe also noted that within the cofinancing system, countries do not pay in cash but rather by procuring a proportion of the vaccines (using their own procurement systems or through UNICEF), which is aimed at establishing sustainable self-procurement systems.

Lessons from GAVI's Model

Schwalbe listed several suggestions for MDR TB that could be gleaned from GAVI's model:

- clarifying short- versus long-term objectives for each market;
- increasing funding predictability;
- improving demand transparency and credibility of forecasts;
- gathering forward-looking market intelligence on supply and suppliers; and
- engaging in partnerships and regular interaction with manufacturers.

Waning remarked, however, that an attempt to apply GAVI's people, systems, and resources to the Global Fund would yield very different results because of the Global Fund's structural and cultural constraints. Specifically, effecting change such as implementing pooled procurement would require the Global Fund to make procurement and SCM plans available. She praised GAVI's commitment to "sitting at the table" with industry in what she called a safe way, and suggested that WHO and UNITAID should seek a similar level of engagement with industry in order to move forward.

Supply Chain Management System[21]

SCMS Objectives

PEPFAR/USAID's SCMS was mandated to establish and operate a safe, secure, reliable, and sustainable supply chain and to develop country-level self-sustaining supply chain skills and capabilities. Gordon Comstock, Director, Global Supply Chain, Partnership for Supply Chain Management,

[21] This subsection is based on the presentation by Gordon Comstock, Director, Global Supply Chain, Partnership for Supply Chain Management.

noted that the challenges faced in the area of HIV/AIDS that led to the establishment of SCMS are similar to those faced in the MDR TB supply chain:

- poor coordination among governments, funders, and donors;
- insufficient long-range forecasting or planning capabilities;
- limited in-country SCM capacity;
- long procurement cycles;
- inability to place timely orders; and
- potentially inadequate infrastructure for warehousing and distribution.

SCMS Design

The impact of the barriers on treatment programs are also similar, including problems with product quality, cost, delays, delivery, and stock management. SCMS was designed to eliminate supply chain barriers, stock-outs, and overstocks by integrating the supply chain's four key levers:

1. *Financial structure* enables continuous product supply by pooling procurement through a USAID working capital fund.
2. The *business model* aligns the requirements of countries with the values of donors (in the case of SCMS, the U.S. government) to enhance flexibility in strategy, structure, people, and processes.
3. *Operational strategies* employ private-sector supply chain best practices, the key to which is knowing the "customer."
4. SCMS considers *quality systems* to be critical and thus adheres to stringent regulatory standards for public health.[22]

Working Capital Fund

The USAID working capital fund is critical to the SCMS procurement strategy and has the advantage of allowing countries to develop operating plans annually. Funds are deposited up-front and are not time-bound (thus they can be rolled over to the next fiscal cycle) or performance-restricted. Implementing partners are not charged until the product is actually delivered, allowing orders to be placed in advance according to a country's supply plan and enabling prompt vendor payment. The inventory methodology facilitates a blended inventory price to all countries rather than each country paying a unique price.

[22] The WHO model quality system for procurement agencies.

Regional Distribution Centers

SCMS's business model enables procurement decisions and tender splitting based on the best value for components, such as price, transportation costs, vendor performance, vendor lead time, product registrations, common harmonized labeling, and consideration of market dynamics. The logistics model integrates the global supply chain with local supply chains in each country to ensure that products reach their final destination. Central to this effort is prepositioning aggregated operating inventory in hubs or sustainable regional distribution centers to improve efficiency, to save costs (by moving product from the producer to the regional distribution center by sea transport), and to ensure an uninterrupted supply of ARVs by moving the product closer to its target market. Smaller, regular shipments protect local supply chain infrastructure and systems, and ensure the safe, secure, and timely transport of cold or cool chain commodities. The system also allows a rapid response to emergency requests.

Pooled Procurement

The in-country SCMS supply chain model aligns with health care services and strengthens national systemic infrastructure. It seeks to balance country ownership and pooled procurement through a national–organizational partnership. Through SCMS pooled procurement, central stock-outs have been virtually eliminated, and $1.3 billion was saved on procurement of nearly 700 million ARVs. The use of pooled procurement in SCMS, when appropriately aligned with national interests, also serves to increase flexibility, mitigate risk, implement QA requirements, strengthen the market, enhance purchasing power, and improve product availability and the ability to focus on harmonization.

However, SCMS has encountered challenges with pooled procurement that echo those faced by similar MDR TB efforts; examples include limited and fragmented demand, registration requirements leading to country-specific constraints, and a lack of harmonization regarding donor and procurement regulations. Comstock indicated that within SCMS a clear link was created between performance and results, noting that under PEPFAR, ARV stock-outs are not acceptable. He remarked that in the case of the market for MDR TB drugs like cycloserine and PAS, which feature a high supplier-to-buyer power ratio, market action such as pooled procurement could be warranted to gain supplier leverage and to shift the market toward a healthier equilibrium (Figure 3-2).

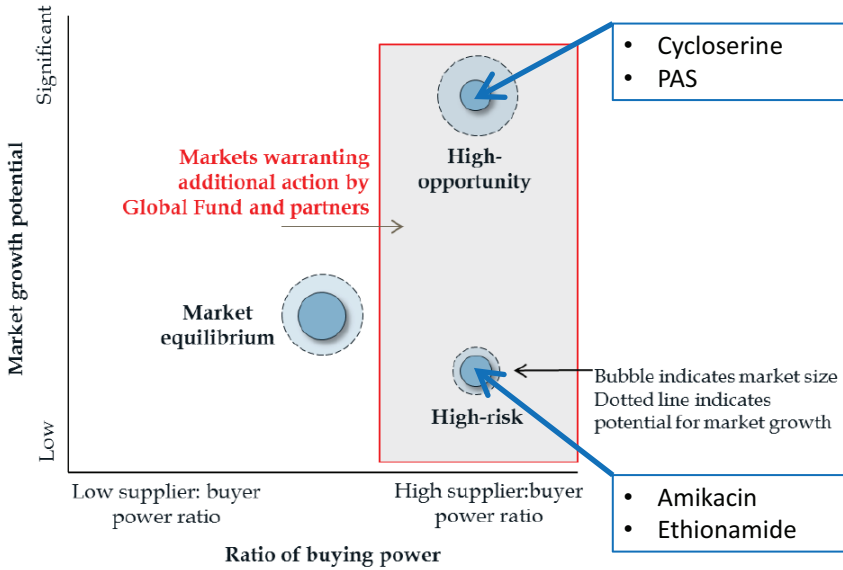


FIGURE 3-2 Global Fund product classification framework proposed by Results for Development Institute (R4D).
SOURCE: Comstock, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis, based on presentation to Global Fund Market Dynamics Committee by Results for Development Institute, March 28, 2011.

CHAI's Model for Improved Access to Pediatric HIV Treatment[23]

David Ripin, CHAI, recounted several procurement challenges faced by CHAI's UNITAID-funded project to scale up and catalyze the market for pediatric HIV treatment. When the project was implemented, there was a very low treatment coverage rate and a low-volume, fragmented market with few pediatric-friendly QA formulations or in-country product registrations. Noting that certain barriers to procurement existed that mirror those in the MDR TB supply chain, Ripin described the efforts that CHAI used to mitigate those barriers.

[23] This subsection is based on the presentation by David Ripin, Executive Vice President, Access Programs, and Chief Scientific Officer, CHAI.

Guidance for Prioritizing Regimens

As the market grew, the proliferation of unique treatment products fragmented a demand that was already relatively small, but the development and provision of clear normative guidance about regimen prioritization from WHO, through an IATT (Inter-Agency Task Team), was effective in reducing this fragmentation (e.g., creating a rationalized list to reduce the number of formulations from 45 to 15). CHAI also used that prioritization guidance to help specific countries and communities focus their formulary lists only on optimal products for regimens across all patient weight bands as well as for pediatric formulations.

Ripin remarked that a similar strategy of consolidation and rationalization could be used for MDR TB regimens, which are fragmented both between countries[24] and within the same country, noting that some countries have guidelines for more than five standard regimens. Product-level procurement data could be used to identify high-impact opportunities for harmonization of regimens (e.g., he noted that PAS and sodium PAS are the same active ingredient) and to make recommendations about packaging formats to improve market efficiency.

Aggregating Procurement

Another key challenge was the long lead times caused by low-volume individual orders from countries that would often fail to meet minimum production thresholds for manufacturers. In some cases, even aggregate global demand was insufficient for certain products. As the CHAI-UNITAID program transitioned funding and procurement responsibilities to countries, the program adopted the practice of aggregated (as opposed to pooling) procurement among a group of buyers through collaboration with PEPFAR and the Global Fund. CHAI coordinated and aligned orders in a predictable way, consolidated demand around fewer formulations, and reallocated product to manage shortages. Two or more suppliers were selected to supply products where demand was sufficient to support multiple suppliers. In some cases of low demand, where total market volume would not be greater than a few production batches, a single supplier was selected. The result was greater access to low-volume products, lower risk of stock-outs, and more consistent lead times. Feedback from suppliers indicated that they preferred tendering practices that split supply across more than one supplier in a predictable manner to allow higher confidence in allocating production capacity.

[24] He noted that countries have guidelines for regimens based on different drugs: kanamycin versus capreomycin, PAS-Acid versus sodium PAS, cycloserine versus terizidone.

Weighted Tender Review

Long and variable lead times were addressed by encouraging robust forecasting and considering non-price factors in evaluation of suppliers' tender bids. A weighted system was used to account for past performance factors such as supplier delivery metrics and breadth of country registrations (e.g., 70 percent weight on price, 15 percent weight on delivery metrics, and 15 percent on breadth of registration). The weighting strategy encouraged suppliers to improve their delivery performance and reduce delays in trying to improve their weighted scores for the next round of tendering.

Tender Splitting to Aid Market Entry

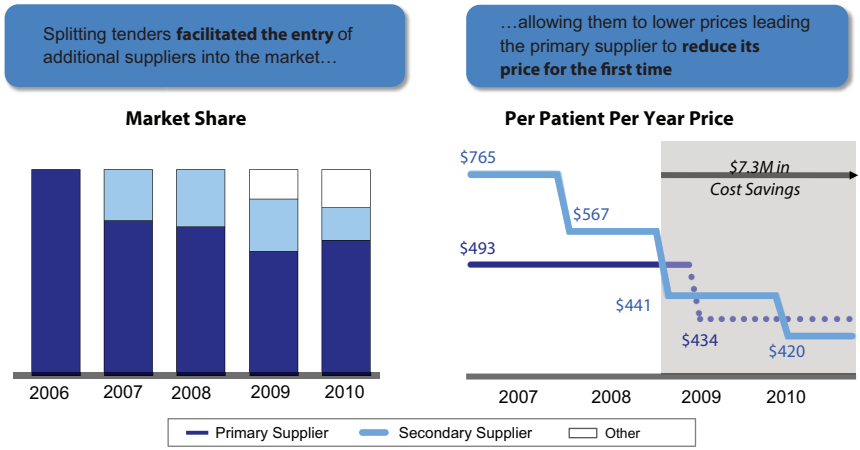
Ripin explained that minimum batch sizing is a particularly crucial barrier in the pediatric HIV market (as it is for MDR TB), both for new products and for suppliers seeking to enter the market. The batch-size requirements for validation purposes are often greater than preexisting volume of demand for a new product. This increases the risk that some of the material produced in the validation batches will expire before being sold, potentially resulting in higher pricing at the time of market introduction to offset this risk. The higher cost for a new supplier that has not yet achieved efficiencies of scale can put new market entrants at a disadvantage when entering the market. Therefore CHAI used a strategy of splitting tenders to encourage new market entrants; Ripin illustrated the benefits of that strategy on price using a case study (Figure 3-3).

For this product (LPV/r), there was a monopoly price in the market that was low enough to prevent new suppliers from entering the market at a competitive price. A second supplier was added to the program by splitting the tender award across a primary and a secondary supplier, with the secondary supplier paid a higher price than the primary supplier for the first 2 years. The investment in bringing additional suppliers into the market led to price declines for both the primary and secondary suppliers, which has resulted in an overall market savings. Ripin emphasized that though splitting tenders may result in a marginal increase in short-term spending, it can result in a long-term decrease in the amount that will be spent.

Affordable Medicines Facility-malaria (AMFm)[25]

AMFm was founded in response to the developing resistance to chloroquine and to the fact that the newer class of treatments (artemisinin-

[25] This subsection is based on the presentation by Olusoji Adeyi, Sector Manager, Health, Nutrition, and Population, World Bank.



Source: CHAI-UNITAID order data; price for LPV/r (200 mg/50 mg); cost savings based on patient volumes and price reductions relative to the innovator's original price ($500 per person/per year).

FIGURE 3-3 Price benefits of splitting tenders. Despite an initial investment of approximately $2 million for a premium price, this strategy led to a broader supply base and significant and sustainable price reductions.
SOURCE: Ripin, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

combination therapies, or ACTs) was too expensive to treat the large numbers of patients in need. Olusoji Adeyi, Sector Manager, Health, Nutrition, and Population, World Bank, offered some lessons from AMFm that could be relevant to the treatment of MDR TB. The functions of AMFm include

- reducing prices via negotiations with manufacturers;
- subsidizing buyers from the public, NGOs, and the private sector[26]; and
- providing in-country supporting interventions such as promoting uptake and ensuring proper use.

Public- and Private-Sector Interaction

The involvement of the private sector is crucial in provision of supporting interventions because 40–90 percent of treatment, depending on the country, is carried out in the private sector. Adeyi stressed that engag-

[26] Essentially, AMFm makes a copayment to registered suppliers on behalf of the buyer.

ing with the private sector has been very successful in reducing prices (thus increasing affordability) and increasing availability of subsidized ACT, even in remote areas, and it has facilitated an increased market share for ACTs.[27]

The public sector has also benefited from the private-sector involvement, as public-sector purchases of AMFm-subsidized ACTs from the private sector have served to offset public-sector procurement delays.[28] Adeyi warned, however, that a mechanism like AMFm, designed to work upstream to change the architecture of financing, cannot by itself change the downstream portion (the community level), which requires a reinforcement of quality at the case-management level.

Applications for MDR TB

Adeyi suggested that AMFm-style strategies that might improve access to MDR TB treatment include the use of wider public-sector channels for distribution, new approaches to financing and reducing prices, and determining the lowest-quality level of delivery system that should be eligible to participate in the system. He characterized the latter as constituting a necessary trade-off between "reach" and "richness" in the short term in order to progress toward the ideal extent of access to treatment. All of the above strategies would require pre-agreed scope, measures of success, and approaches to evaluation.

Adeyi emphasized the need to question and address the fundamental assumption that beneficiary countries necessarily have well-functioning central public medical systems. This assumption underpins the central medical store procurement approach that often causes major bottlenecks in the supply chain. As a possible alternative, he suggested taking advantage of and improving existing drug distribution systems in-country. Other efforts are under way to gather information and initiate improvements in the operation of the SLD supply chain, and workshop participants discussed these related efforts and their goals (Box 3-1).

[27] With the attendant effect of "crowding out" oral artemisinin monotherapy, which carries an increased probability of widespread onset of resistance.

[28] Adeyi remarked that concerns about middlemen taking advantage of the subsidy, rural areas being excluded from subsidized ACTs, and the private sector depriving the public sector of ACTs were ultimately unfounded.

BOX 3-1
Related Efforts in SLD Supply Chain and Access[a]

Second-Line Drug Access Improvement Initiative (SLDAII)

SLDAII is a joint effort of many leading organizations from the public, private, NGO, and allied fields that was founded on the vision that all patients would be able to access affordable, QA treatment within a sustainable MDR TB SLD drug market. SLDAII focuses on developing the technical information and knowledge needed to make rational decisions and to document why certain risks need to be taken.

The initiative comprises six workstreams, concentrated on the supply side, which are each tied to a goal or set of goals. The manufacturer scale-up and operational forecast workstreams are connected to the goal of increased affordability of IQA SLDs. Supply chain diagnosis and financing mechanisms aim to increase the supply of IQA SLDs. The IQA recommendation and private-sector engagement workstreams target greater operational efficiency. Each goal is also underpinned with a set of specific outcomes that need to be accomplished in order to achieve each goal itself (Figure 3-4).

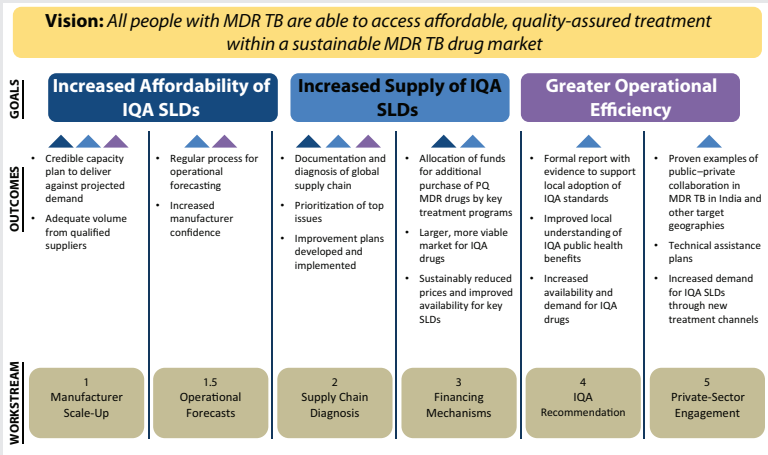


FIGURE 3-4 SLDAII vision and goals.
NOTES: Arrows represent connection between workstreams to different goals; IQA, internationally quality-assured; PQ, prequalified; SLD, second-line anti-TB drug.
SOURCE: Kimerling, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

Michael Kimerling, Senior Program Officer, Tuberculosis Global Health Program, BMGF, suggested that SLDAII fills an important niche in the current environment in helping to ensure coordination and action-oriented progress, but noted that it is open to revision; evaluation is currently underway with the view to ensuring that the right partners are being involved and properly engaged. He said that in moving forward strategically, a shift in focus is needed from identifying barriers to creating innovative solutions and from writing documents to writing business plans. Integrating the private sector will require learning its language and analyzing its needs, which will aid in adapting to a changing market. All efforts should be focused on working urgently and systematically toward a common and clearly established set of principles: ensuring uninterrupted and universal access to the QA drugs at affordable prices.

MDR TB Innovation Summit

Tracy Sims, Vice President, Eli Lilly & Co. Foundation, described ideas that were generated in an MDR TB Innovation Summit that was convened in May 2012.[b] The Innovation Summit tackled the following clearly defined problem statement:

> What innovative approaches/products can be implemented (either directly or indirectly) that would overcome the supply chain barriers that today prevent IQA SLDs from reaching the entire global population of MDR TB patients?

The Summit included participants from both within and outside the sphere of MDR TB expertise who were tasked with dissecting the problem, analyzing it, and producing actionable outcomes. The underlying strategic concepts driving the Summit were the need to take action, develop new approaches, involve new people, engage in partnership, and take well-informed risks.

The initial step in the process employed at the 2-day Summit was to clearly identify the problem and segregate the problem space into five pieces:

1. demand for care;
2. purchasing and procurement;
3. production, QA, and QC;
4. logistics; and
5. delivery of care.

Barriers to the delivery of medication from both the supply and demand sides were identified, and the participants were divided into teams to address each of the identified barriers separately. The teams devel-

continued

BOX 3-1 Continued

oped idea fragments, which were then accumulated into unique idea resumes against each barrier and ultimately refined into 12 idea platforms. Five of those platforms were identified as having the strongest potential for resolving major challenges and were developed into emergent, actionable strategies (Figure 3-5).

Sims explained how the five strategies might address their respective barriers in the SLD supply chain:

- Case Tracker: A mobile-enabled incident-reporting and treatment system to pool data, stimulate action, track demand for care, and enable more detailed forecasting.
- Global Connect: A mobile, Web-based system to support HCP adherence to recommended treatment and improve delivery of care.
- TB Impact Network: A moderated network of global efforts to treat and prevent TB and MDR TB and to improve collaboration.
- Health Express: A Web-based product-tracking and procurement support system to improve QA SLD supply chain visibility.
- New TB "Brand": Development of a consolidated voice or campaign for MDR TB to drive accountability and heighten awareness of the urgency of MDR TB nationally and internationally.

---

[a] This box is based on the presentations by Michael Kimerling, Senior Program Officer, Tuberculosis Global Health Program, BMGF, and Tracy Sims, Vice President, Eli Lilly & Co. Foundation.

[b] Partners included the Eli Lilly & Co. Foundation, the Stop TB Partnership, and the Innosight Consulting Firm.

Key Messages[a]

- Current barriers in access to SLDs include a lack of demand, inflexibility and a mismatch of expectations from stakeholders, and country capacity barriers.
- Collective inability to consolidate demand and a lack of collaboration among stakeholders, including funders, are key barriers to an effective SLD supply chain.

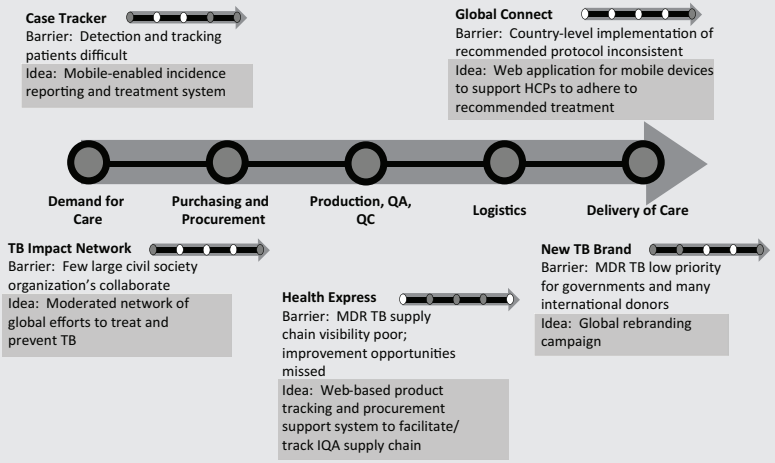


FIGURE 3-5 Owner/participant teams for the top five MDR TB Innovation Summit ideas.
NOTE: HCP, health care professional; IQA, internationally quality-assured; QA, quality-assured; QC, quality control.
SOURCE: Sims, 2012. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis.

- Unique funding mechanisms and spending strategies offered thought-provoking options for further consideration.
- Successful innovative funding mechanisms used in other disease programs were presented, including immunization, HIV/AIDS, and malaria.

[a] Identified by individual speakers.

4

Innovative Suggestions and Potential Solutions

As part of the final session of the workshop, several speakers, including session chairs, and workshop participants individually provided reflections on what they had heard during the 2-day meeting. They were encouraged to identify innovative suggestions and options offered by individual participants during workshop presentations and discussions. This chapter provides an integrated summary of the remarks and panel discussions during that session, organized thematically into three sections: mechanisms of purchase and supply; logistics, supply, and demand; and innovative financing. It should not be construed as reflecting consensus or endorsement by the workshop participants, the planning committee, the Forum, or the National Academies.

MECHANISMS OF PURCHASE AND SUPPLY[1]

Structural Reorganization and Accountability: Who Will Get It Done?

Analogizing to Other Supply Chains

A recurring topic throughout the workshop was the question of what structural and governance systems should be in place at the global level

[1] This section is based on reflections offered by Peter Cegielski, Team Leader for Drug-Resistant TB, International Research and Programs Branch, Division of Tuberculosis Elimination, CDC, and comments offered by individual workshop participants during an open discussion session moderated by Cegielski and Barry Bloom, Harvard University Distinguished Service Professor and Joan L. and Julius H. Jacobson Professor of Public Health, Department of Immunology and Infectious Diseases, Harvard School of Public Health.

to facilitate effective operation of the MDR TB SLD supply chain. The question of structure and governance to oversee this particular supply chain was, in turn, informed by a discussion among workshop participants about the extent to which the SLD supply chain shares characteristics of other supply chains. This discussion was framed by Salmaan Keshavjee, Harvard Medical School, who remarked that notwithstanding similar challenges (e.g., manufacturing complexity, limited market size, supply chain and access problems), strategies applied to other markets to improve their systems do not seem to work in the MDR TB context.

Olusoji Adeyi, World Bank, and several others expressed skepticism that the MDR TB market is in fact unique, arguing instead that more precise definition of the specific problems in the market could aid development of effective solutions. Other participants offered thoughts on ways that the MDR TB SLD supply chain could be viewed as unique. David Ripin, CHAI, noted that the MDR TB market faces a unique type of fragmentation among customers because the middle-income countries that represent large portions of demand are more difficult to aggregate effectively than, for example, the pediatric HIV market.

Nina Schwalbe, GAVI, suggested that the crux of the difference between MDR TB and other markets is its organizational and institutional establishment, which, she argued, needs significant restructuring. She cautioned that internal politics among the key players in the existing supply chain could impede effective reform and exhorted workshop participants to address and resolve those issues. Keshavjee added that complications and barriers that arise out of the present structural configuration of the supply chain justify the need for restructuring. He maintained that effective restructuring needs to be prefaced by properly examining and aligning the interests of all parties involved in the current system of SLD procurement. Amy Bloom, Acting Chief, Infectious Diseases Division, USAID, suggested that an evidence-based analysis of the hosting arrangements among GDF, the Stop-TB partnership, and WHO be conducted, noting that USAID is currently supporting such an analysis.

The remainder of this section reports individual participants' suggestions about the issue of the responsibility and accountability for a potential restructuring.

Consideration of WHO/GDF Hosting Arrangements

Participants considered the implications of GDF being hosted by WHO and the potential consequences of GDF's removal from WHO. In this discussion, individual perspectives were offered on the structural advantages and disadvantages of having a centralized supply chain mechanism like GDF, successes achieved by GDF, and needs for improvement if the cen-

tralized GDF-like structure is retained. The discussion was grounded in a general understanding among workshop participants that approximately 20 percent of SLDs procured worldwide are donor-funded and purchased through GDF, while the remaining 80 percent are procured independent of donor-funding mechanisms and GDF, typically by the governments of middle-income countries to serve their patients.

Some participants cited the importance of GDF or another centralized purchasing mechanism. For example, Andre Zagorski, Principal Technical Advisor for TB, Center for Pharmaceutical Management, MSH, suggested that the 20 percent of countries whose drug procurement is donor-funded and facilitated by GDF would not be able to acquire enough funding to develop sufficient procurement capacities to procure drugs autonomously (and not through a centralized purchasing mechanism) within the near term.

Several participants noted that the housing of GDF within the WHO structure—and bound by WHO procurement and hiring policies—has led to certain inefficiencies in procurement processes. On the other hand, some participants noted that the hosting of GDF within the WHO infrastructure might not be the principal impediment. Prashant Yadav, University of Michigan, commented, for example, that UNITAID is an example of a WHO-hosted partnership that has been successful at adopting innovative financing, procurement, and hiring practices. Robert Matiru, UNITAID, also noted that the GDF mechanism has seen success in the area of delivery of FLDs notwithstanding its being hosted by WHO, citing the benefits, networks, connections, and access to beneficiary governments that WHO provides GDF. Matiru further urged the participants not to focus solely on concerns about whether the hosting mechanism is optimal or not, because GDF's functions are only one segment in the supply chain; both he and Zagorski suggested that pooled procurement and other innovative financing tactics could address the fundamental inefficiencies without requiring structural reform. Similarly, Myriam Henkens, MSF, commented that the question of whether a centralized procurement mechanism is used, whether it is housed within or outside WHO, is not alone sufficient to address the many needs in improving the supply chain, as there are multiple other activities and responsibilities that must be allocated to other entities (e.g., countries), including product registration and development of treatment protocols.

Participants also discussed considerations arising due to the fact that the market is segmented into the 20 percent that are donor-dependent and the 80 percent that are not. Tracy Sims, Vice President, Eli Lilly & Co. Foundation, suggested that perceptions of these different populations have implications for decisions about issues such as logistics and forecasting. He offered three options for moving forward:

1. evolving the current structure to appropriately treat the population as it is currently segmented;
2. developing a parallel process that may or may not supplant the existing approaches; or
3. starting over with a new consolidated structural system.

Several participants noted that any redesign of the SLD supply chain should take the two systems into account in parallel rather than focusing solely on the donor-funded, GDF-routed sector. Yadav stated that unless the segment of the market currently served by the global donor-funded mechanism is directly interfering with efforts to provide QA drugs to the remaining approximately 80 percent of the market, the architecture of the market does not need to be addressed as a whole. That is, efforts should still be made to improve the donor-funded segment while simultaneously assessing how to address the larger segment. Along these lines, it was suggested that the 80 percent of the market that is not donor-funded could benefit from a separate mechanism by which to coordinate the currently independent approaches to procurement. Gail Cassell, Harvard Medical School, suggested that the donor-funded segment requires more urgent focus in the short term due to probable underestimates of actual burden and vast numbers of unserved populations in those countries.

Capacity Building and Accountability

In considering allocation of responsibilities, participants discussed the importance of clearly defining and assigning supply chain roles to appropriate entities and supply chain participants. For example, Henkens noted that manufacturers should be responsible for drug availability; a "GDF-like" structure should be responsible for supply; and countries should take responsibility for registration, scale-up, and monitoring of treatment programs in the public and private sectors. Some participants noted the need to strengthen capacity, including the leadership and technical capacities of NTPs to support and incentivize the creation, manufacture, and standardization of QA SLDs and the development of training methods for supply chain managers. It was suggested that directing funds toward crosscutting initiatives could strengthen existing infrastructural, QA, procurement, and SCM systems.

Once responsibilities are allocated, establishment of accountability is a next step. To facilitate accountability, some participants observed a need for alignment of performance incentives of organizational and program leaders with desired outcomes for countries and patients.

Mobilizing Public–Private Advocacy for MDR TB

Mobilizing public and private advocacy for MDR TB was identified as a means of accelerating progress through a more visible presence. MDR TB may not currently have the profile necessary to effect change; for example, it is not considered as one of the "big three" in Millennium Development Goal 6.[2] Schwalbe advocated garnering more public and high-level political commitment for MDR TB and overcoming political constraints impeding the establishment of new partnerships and models. She suggested, for example, that leadership of World Bank could be enlisted as a potential public ally. It was further suggested that a TB advocate within WHO could serve to encourage the leadership to more publicly highlight the growing MDR TB epidemic, particularly within high-burden countries. Another suggested strategy was the engagement of ministers of health and other appropriate leadership in high-burden countries and other BRICS countries.

Manufacture of SLDs

During the workshop, participants provided individual observations about key barriers regarding the manufacture and pricing of SLDs. This section provides an overview of the innovative suggestions and options offered by individual participants for overcoming those challenges.

Some participants discussed engagement of the SLD manufacturing industry, including both current and potential producers, in order to encourage competition, discuss and engage with demand forecasts, and resolve batch-sizing problems. Schwalbe suggested that GAVI's experiences convening manufacturers could serve as a model of productive engagement with manufacturers. Barry Bloom, Harvard University Distinguished Service Professor and Joan L. and Julius H. Jacobson Professor of Public Health, Department of Immunology and Infectious Diseases, Harvard School of Public Health, suggested that one way manufacturers could help drive progress is by sharing their supply chains to "piggyback" SLDs on chains that currently exist or by sharing their knowledge of SCM in specific countries.

Iain Richardson, Eli Lilly and Company, commented that there is will and interest on the part of manufacturers to contribute certain aspects of their experience as appropriate, adding that manufacturers need clearer guidance as to what the needs are and how they can most effectively deploy their resources and capabilities. He described by way of example how Eli Lilly has made continuing investments in supportive efforts to improve

[2] Millennium Development Goal 6 seeks to combat HIV/AIDS, malaria, and other diseases. The description of this goal includes tuberculosis but not MDR TB. For more information, see http://www.un.org/millenniumgoals/pdf/MDG_FS_6_EN.pdf (accessed November 14, 2012).

SLD supply, including deployment of subject-matter experts to contribute to SLDAII. Richardson also characterized Eli Lilly's technology transfer effort as a way of stimulating and sustaining the supplier market in the longer term.

Similarly, in considering the entry of new suppliers to the market (beyond provision of technical support or technology transfer), Sana Mostaghim, CHAI, noted that potential new suppliers would need clearer guidance to facilitate their entry into the market. Michael Kimerling, BMGF, described the mandates of a new strategic task force at WHO, which is funded by BMGF, on the issue of new drugs: to create an information sheet for drug manufacturers and people who produce regimens about what types of information materials WHO needs to provide guidance and guidelines; to provide information to countries about the process of adoption and introduction of new drugs and new drug regimens; to open a discussion with regulators about how this process can be facilitated; and to compile all of the above into a strategic framework and time line. Subsequent stages will involve separate meetings with the individual companies to understand their pricing strategies.

Procurement Strategies

Pooled Procurement

Many workshop participants noted that there is a need for development of a pooled procurement mechanism as a key priority. There was discussion about where the barriers to adoption of a pooled procurement system reside. Matiru stated that GDF's success with pooled procurement for FLDs was backed by consolidated, controlled financing and facilitated by an approval and review mechanism designed to survey and address the quantities of treatment required, which enabled demand aggregation. By contrast, MDR TB financing in the donor-funded market is channeled through GDF in a non-pooled, uncoordinated way, without the benefit of centralized fund management. This prevents effective up-front order planning, forecast-driven orders, and pooled procurement. Procurement quantities are limited by non-scaled, inadequate technical review and treatment distribution mechanisms. Keshavjee suggested the creation of a proper financing pool to be used by the procuring body. He also remarked that bundling SLD procurement with the well-established supply chains for other drugs, such as those for HIV and malaria, could drive prices down. Mostaghim and Ripin suggested that tender splitting is another mechanism to address procurement problems as well as to maximize the number of eligible participants in a tender to stimulate competition and reduce prices in the SLD market.

To address the emerging gap of middle-tier countries that lack access to

vaccines, GAVI and UNICEF are exploring the option of demand pooling in non-donor-funded markets in which the country is the buyer. A key need for such strategies to be effective is that the aggregated demand be backed by adequate financing to support the value proposition for manufacturers. GAVI and UNICEF are also working with the major BRICS-country buyers to establish pricing and volume commitments to resolve the problem of variable, unbacked marginal demand. Schwalbe suggested that such strategies might have potential to be implemented in the MDR TB market.

Tiered Pricing

Pricing is also an important issue that will help or hinder the procurement and distribution of SLDs, particularly with respect to novel drugs coming into the market. GAVI's use of a tiered pricing strategy was suggested as a possible model for the SLD pricing according to a country's ability to pay. According to Andreas Seiter, World Bank, a key problem is differentiation within countries; middle-income countries often have both a high-income population and large proportions of poor populations. He maintained that the high-income population in those countries should pay the same prices as high-income people in developed countries. A key task would therefore be finding a way to use access strategies like market segmentation and appropriate price differentiation that prioritize reaching those lower-income markets.

Yadav noted that while tiered pricing can be a good tool for improving access, it can be more challenging when there is a limited number of manufacturers because there are cases in which a generic entrant was paid a higher price than the incumbent manufacturer's tiered price (in order to encourage market entry). On the basis of his experience with ACT manufacturers through AMFm, Adeyi stated that downward negotiation of tiered prices for SLDs in developing countries is feasible, as is the potential for subsidizing purchases at the buyer level at reduced prices.

LOGISTICS, SUPPLY, AND DEMAND

Incentivizing and Regulating QA[3]

A number of participants emphasized the importance of QA for MDR TB drugs, particularly in light of the number of therapeutic regimens

[3] This subsection is based on reflections offered by Amy Bloom, Acting Chief, Infectious Diseases Division, USAID, and comments offered by workshop participants during an open discussion session moderated by A. Bloom and Barry Bloom, Harvard University Distinguished Service Professor and Joan L. and Julius H. Jacobson Professor of Public Health, Department of Immunology and Infectious Diseases, Harvard School of Public Health.

involved, the length of treatment, and the emergence of potentially untreatable TB. Establishing and maintaining such standards is a complex undertaking that affects manufacturing, supply, and national and international regulatory pathways.

Incentivizing Production of QA SLDs

Some workshop participants discussed approaches to implement incentives for manufacturers to produce SLDs according to specified quality standards (and removal of incentives to produce low-quality products). With respect to the BRICS countries in particular, Lisa Hedman, WHO, noted that encouraging the use of QA SLDs would require "supporting local production of QA SLDs, supporting regulatory and other procurement processes, and saturating the market at competitive prices." Christophe Perrin, The Union, suggested that international donors should not allow the use of non-QA drugs to be purchased with their funding.

Regulation of QA SLDs

The QA qualification process can also introduce backlogs and disincentives to producers. Particularly in light of the leading roles of China and India in API production, Patrick Lukulay, USP, suggested adjusting the stance of the WHO PQ process toward partnership. This approach could increase the number of API manufacturers willing to invest in the process of qualification. To deal with backlogs in the WHO PQ assessment and inspections processes, Lukulay suggested the possibility of establishing a secretariat at WHO that would accredit other agencies to grant PQ status.

Brazil's national SLD QA system was highlighted by A. Bloom. In Brazil, the national government takes an active role to procure local SLDs when possible, but avails itself of the GDF/GLC mechanism as required. Unlike many countries, Brazil employs a comprehensive, in-country QA process that includes registration and documentation, site inspections, drug sampling, postmarketing surveillance, and monitoring systems. It also includes an extensive lab network responsible for drug quality testing. Stakeholders are actively involved in a working group that monitors the process and is empowered to make necessary changes, and the development of the e-TB Manager tool has integrated information management about TB patients and SLDs.

Andrew Gray, University of KwaZulu-Natal, expressed concern about accepting SRAs and WHO PQ as the only arbiters of quality. He noted that SRAs must by definition be ICH members, which is "a closed shop." He suggested establishing a process by which national- or regional-level regulators could gain access to SRA status. Vincent Ahonkhai, BMGF, com-

mented that a fully functional regulatory system should have independence and complete oversight in the value chain of regulation, responsibilities that few countries can bear. He called for a shift of focus from a system that relies on formal designations to a system that assesses factors such as technical functionality, independence, and systems of governance needed to facilitate satisfactory oversight, checks and balances, and the elimination of poor-quality drugs.

Noting the generally inverse relationship between a country's income and the strength of the regulatory barriers to procuring QA SLDs, Ahonkhai emphasized that accelerating adoption of harmonized regulations could have a large impact on working through these barriers, citing the success of recent regional harmonization efforts in Africa. The African Medicines Regulatory Harmonization (AMRH) effort is a joint collaboration that aims to improve and streamline the product registration system for both regulators and manufacturers in each region of the continent.[4] Ahonkhai described recent efforts to engage the African Union to expedite regulatory harmonization efforts, which have been in progress for the past 3 years at the national, ministerial, and regional levels. He reported that the initiative is promising, though some regions are more aligned for collaboration than others.

Improved Demand Forecasting[5]

Throughout the workshop, multiple participants cited improved accuracy and credibility of demand forecasting as a crucial strategy for moving forward and strengthening various components of the SLD supply chain by improving transparency and predictability. The accuracy of demand forecasting has ramifications for various components in the MDR TB supply chain. In explaining how to improve demand-forecasting methodology, Meg O'Brien, American Cancer Society, described the importance of forecasters being more transparent and precise in their methodology. Ripin stated that the MDR TB market is not necessarily different fundamentally

[4] The AMRH initiative is a joint effort formalized in 2009 to improve the fragmented system of product registration in Africa by focusing on regions within the continent, thereby creating a platform on which to build African regulatory capacity. AMRH is focusing initially on generic drugs for infectious diseases and will extend to other product categories and regulatory functions over time. For more information, see http://amrh.org (accessed November 14, 2012) and http://www.who.int/medicines/areas/quality_safety/regulation_legislation/PL2_3.pdf (accessed November 14, 2012).

[5] This subsection is based on reflections offered by Owen Robinson, Program Manager, Partners In Health, and comments offered by workshop participants during an open discussion session moderated by Robinson and Barry Bloom, Harvard University Distinguished Service Professor and Joan L. and Julius H. Jacobson Professor of Public Health, Department of Immunology and Infectious Diseases, Harvard School of Public Health.

from other markets, but one of its unique challenges is the need to instill confidence among suppliers by reducing discrepancies between actual and projected procurement and increasing predictability of procurement. He suggested that doing this will require the development of smooth, reliable, and accurate forecasting techniques that suppliers view as realistic and credible.

Yadav suggested that developing more accurate demand-forecasting techniques is necessary for manipulating the push-pull boundary in SCM in order to shift a proportion of component processes from those that are order driven to those that are forecast driven. He noted that improved demand forecasting is essential to resolve the crucial disparity between the number of patients who need treatment and the number of patients who are actually diagnosed and treated.

Schwalbe suggested that improved interaction with manufacturers around that forecasting data would be productive and that it is important to forecast the "whole picture" (i.e., to not forecast the donor-driven and non-donor-driven markets in isolation).

Relatedly, some participants discussed the concept of a buffer inventory or stockpile to address SLD stock-outs and shortages. The buffer would shorten delivery times and increase predictability. Such a mechanism could assist manufacturers by smoothing demand and could help ensure that an uninterrupted supply of SLDs can be delivered where and when needed.

Information Management Systems[6]

Some participants discussed feasibility and opportunities for improved information management through Web- and mobile-based technology for managing patient care and drug supply. Hamish Fraser, Partners In Health, identified low-hanging fruit in the area of information management, suggesting adoption of universal bar coding in the short term. As a required first step, funders and international agencies would need to agree on standard naming, formatting, and coding conventions. Scanners or mobile phones that would be used to read the bar codes are already widely available, so Fraser suggested that the process would be relatively straightforward. Yadav commented, however, that although the *technology* for standardizing bar codes is simple, the standardization *process* itself would be complicated and lengthy, which could pose a serious barrier to the quick

[6] This subsection is based on reflections offered by Owen Robinson, Program Manager, Partners In Health, and comments offered by workshop participants during an open discussion session moderated by Robinson and Barry Bloom, Harvard University Distinguished Service Professor and Joan L. and Julius H. Jacobson Professor of Public Health, Department of Immunology and Infectious Diseases, Harvard School of Public Health.

establishment of such a system for SLDs entering developing country markets. Richardson remarked that although serialization of individual units may not be feasible in the short term, the option of printing established G10 numbers (containing either manufacturing or expiry date and batch number) could be adopted in the short term.

INNOVATIVE FINANCING[7]

Flexible Financing

Issues regarding how best to finance procurement of SLDs resonated throughout the workshop. From a practical standpoint, participants discussed expansion of the funding pool and improvement of its predictability and flexibility. Increased predictability of financing and funding could serve to facilitate program implementation and improve market health, while more flexible financing mechanisms could reduce the amount of funding lost to use. Vincent added that shifting the financing burden for FLDs to countries could free up funding from external donors for SLDs.

In addition to the possibility of pooling procurement processes (discussed earlier), participants also explored the possibility of pooling financing. A. Bloom suggested that under a pooled financing system, purchaser countries could withdraw funding from the broader pool at an appropriate time for purposes of making payment, rather than having to access funds far in advance, when needs may be uncertain due to less accurate forecasting. Several participants discussed the potential for a mechanism incorporating WHO data to monitor pooled financing, procurement, pricing, and drug distribution on a global level to ensure that drugs are being used at the appropriate time in the appropriate place. A. Bloom suggested, given that the Global Fund represents 85 percent of the funding in non-BRICS countries, coordinating with the Global Fund to try to obtain data about how it distributes those funds and how funds flow in and out of those countries, with the view to establishing a more pooled source of funds that could be better matched with the countries' needs.

[7] This section is based on reflections offered by Prashant Yadav, Director, Healthcare Research Initiative, William Davidson Institute, University of Michigan, and comments offered by workshop participants during an open discussion session moderated by Yadav and Barry Bloom, Harvard University Distinguished Service Professor and Joan L. and Julius H. Jacobson Professor of Public Health, Department of Immunology and Infectious Diseases, Harvard School of Public Health.

Innovative Financing Strategies and Mechanisms

"Push" and "pull" mechanisms were presented as potential novel financing strategies designed to strengthen the SLD market over the long term. Push mechanisms create incentives for new suppliers to enter the market. Rifat Atun, Imperial College London, suggested the following push strategies:

- reengaging public–private partnerships;
- providing R&D credits for investments in small markets; and
- accelerating regulatory approval.

Pull mechanisms create demand and signal a market both for new entrants and for current players to stay in the market. Atun commented that market signaling is as important as funding because potential suppliers prepared to undertake a 10- to 15-year commitment to invest in R&D and manufacture drugs need assurance that they will be able to recoup their investment. He suggested the following long-term pull strategies for the MDR TB market:

- long-term instruments such as a TB bond to provide 10- to 15-year funding;
- at the domestic level, expanded health insurance or catastrophic risk insurance to cover MDR TB;
- venture capital impact funds for development of new SLDs;
- value-based pricing; and
- outcome-based financing to reward successful novel approaches.

Yadav suggested two specific types of new contracting structures that could be employed to shift the push-pull boundary, leading to expansion of forecast-driven orders, as follows:

1. long-term contracting agreements with quantity flexibility that allow quantities to be adjusted, subject to specified restrictions, if actual demand turns out to be slightly different from forecasted demand; and
2. a volume increase–price decrease trajectory contract that can guarantee a supplier a 10 percent volume increase for each of the next 3 years in return for a reciprocal 10 percent yearly price decrease over the same period.

During the workshop, several participants suggested a number of specific innovative mechanisms that could potentially apply to MDR TB financing.

- *Net and Pledge Guarantees*: Brad Herbert, Managing Director, Brad Herbert Associates, emphasized the need to integrate public and private financing in innovative ways such as those implemented by UNITAID, GAVI, and BMGF. He suggested the use of net and pledge guarantees as mechanisms to guarantee advance payments to manufacturers. This could, for example, potentially address delays in procurement that occur during the 12–15 months required to sign a Global Fund grant agreement.
- *IFFim*: GAVI's IFFIm is characterized by both extreme predictability and flexibility. The vehicle raises funds by issuing bonds backed by long-term pledges ($20 million to $3 billion) from donor countries. It has the advantages of enabling both market shaping and long-range, multiyear planning in beneficiary countries; increasing financial efficiency; and generating better public health outcomes.
- *AMC*: AMCs can incentivize manufacturers and stimulate innovation by offering a long-term secure contract via donor-funded purchase commitment and price guarantee.
- *GAVI Matching Fund*: A matching fund can be used to raise financing and leverage non-cash assets as well as to increase public awareness.
- *Buyer Subsidy*: AMFm successfully used price negotiations with manufacturers, coupled with a buyer subsidy, to generate a price reduction of around 90 percent.
- *Balance Sheet Demand Guarantee*: Under GAVI's balance sheet demand guarantee, vaccine purchases are guaranteed using GAVI's balance sheet (in lieu of an up-front commitment) as the financial backing, which eliminates the need for new funding. It functions like a bank guarantee except that it does not accrue interest.
- *Working Capital Fund*: According to Gordon Comstock, Partnership for Supply Chain Management, a working capital fund like SCMS's could facilitate better up-front planning, less restrictive funding policies, and pooled procurement plans for liaising with manufacturers.
- *PRIs*: Kimerling suggested that PRIs could be used as a variety of SLD market interventions to address problems of limited drug availability and high prices.

REFLECTING ON THE WAY FORWARD

This final section is based on concluding remarks offered by the final panel of experts, who provided individual reflections on the ways forward to strengthen the SLD supply chain. An integrated summary of the key themes and suggestions that these individuals presented (as well as topics that arose in the subsequent discussion) is presented thematically in this section, covering approaches/methods, strategic messages, and new structures. The section concludes with Box 4-1, which compiles individual concrete suggestions and low-hanging fruit offered at the workshop. This summary should not be construed as reflecting consensus or endorsement by the workshop participants, the planning committee, the Forum, or the National Academies.

Approaches and Methodologies

Leadership

Herbert addressed the need for boldness, particularly within the new global GLC, in strategizing, tactical planning, and acquiring funding for MDR TB. He identified as key issues the need for improved decision making and stronger leadership to enact a paradigm shift toward producing good business plans. Strengthened leadership could support construction of a new strategy to achieve concrete results and to reach established goals. Strengthened in-country leadership is also important for capacity building.

Execution

B. Bloom stated that the key problem in the improving overall treatment of MDR TB is not a lack of ideas, but a lack of execution, that is, translating those ideas into action. He suggested that while collecting data and evaluating evidence are necessary before taking some risks, there is a worry that requiring an evidential basis for everything could preclude the type of risk taking that adopting an innovative new approach requires. Adeyi concurred, citing AMFm as an example in suggesting that the MDR TB program should be willing to explore new pathways and structures, with the appropriate checks and balances in place in execution and management, without being constrained by the need for certainty about the outcome at every step. Adeyi also urged application to MDR TB of lessons of successful aspects of other programs.

Trish Stroman, Principal, The Boston Consulting Group, suggested that a powerful strategy moving forward would be to quantify the impact of *no*

action on patients, HCPs, and the entire health care system—that is, "what happened while we were waiting for a drug."

Keshavjee observed that pooled funding mechanisms have been essential to support systems such as GAVI, AMFm, and SCMS to effectively procure drugs. He suggested applying these mechanisms to MDR TB, developing an available pool of money coupled with an efficient purchasing mechanism.

Jose Gomez-Marquez, Director, MIT Little Devices Lab, suggested that decentralizing the ways that patient-needs data are collected and shared to make information more freely available would improve transparency about the actual MDR TB burden and thus facilitate better demand signaling.

Engagement with Private Sector, Patients, and HCPs

Keshavjee proposed that engaging and penetrating the private market should be a primary approach for effecting change because it is in that market that the bulk of TB care is being provided and TB drugs are being sold. He suggested that many years spent focusing on the donor-driven market have eclipsed focus on private-sector engagement.

Gomez-Marquez maintained that there is a need to more systematically and deeply engage the perspectives and experiences of patients and HCPs, which could help to foster accountability about the tangible effect of issues like procurement delays. Similarly, he suggested encouraging greater input from both large- and small-scale manufacturers about their specific technical needs in terms of financing, forecasting instruments, and supply production.

Strategic Messages

Many workshop participants identified the importance of mobilizing influential advocates to take advantage of political leverage and effect change. Advocates could be enlisted from WHO, World Bank, and other high-level political leadership.

Adeyi cited the need for clarity about both strategic goals and the specific means of achieving those goals, noting that any structure adopted must make practical sense. A. Bloom also suggested that finding the right solution requires clarifying the problem to be addressed. She maintained that thinking broadly about a longer-term strategic vision should be accompanied by immediate concrete steps toward improvement and innovative changes in the short term.

New Structures

Several participants discussed the idea of forming an "Affordable Medicines Facility for TB" (AMFtb). Herbert suggested a move toward structural integration that could involve taking "everything of high value from the GDF and all the wonderful work they have done and moving it out of WHO into a better, more functional Global Fund," maintaining that the Global Fund is no longer functioning as the innovative financing mechanism that it was set up to be. Herbert recommended that the Global Fund serve as an implementing body, but suggested that alternative mechanisms be considered to design the new model. Seiter remarked that such a new mechanism might be beneficial in selectively identifying the buyers that are qualified to purchase the subsidized product. Furthermore, implementing a stringently controlled treatment program in the private sector could help prevent patients from purchasing uncontrolled SLDs.

In his concluding remarks, B. Bloom stated that an underlying tension throughout the workshop was the need to reinvent a system to do what the present one is not doing. He suggested three alternatives for moving forward. The first option is to reinvent the current way of thinking about matters such as supply chains and details of drugs for TB in general and MDR TB specifically. The second is to create a mechanism for renewing existing agencies that currently have such responsibilities. The third option is to establish the partnerships required to coalesce the multiple groups involved in different parts of the system. He stated that the success of partnerships, including their capacity to generate business plans, would be aided by the institution of external, transparent review processes by all partners within the MDR TB program.

Individual workshop participants offered concrete suggestions and potential low-hanging fruit, compiled in Box 4-1. Some participants noted that there is a further need for prioritization and identification of specific next steps by various stakeholders in the SLD supply chain.

BOX 4-1
Suggestions and Low-Hanging Fruit[a]

Suggestions

- Prioritize development of an operational strategy to improve demand forecasting.
- Develop a mechanism for pooled procurement to increase predictability and volume of demand.
- Maintain a buffer inventory of SLDs with optimal size, scope, and design to improve production efficiencies by smoothing demand, thereby reducing product costs and delivery lead times.
- Use innovative mechanisms to facilitate long-term financing commitments and improve contracting structures.
- Bundle SLDs with other well-established drug supply chains to lower costs and expedite delivery.
- Improve flexibility and predictability of funding; facilitate reallocation of unused funds to avoid loss to use.
- Develop in-country capacity and support system strengthening through training programs.
- Facilitate regulatory harmonization to reduce delays in drug qualifications and approvals.
- Increase level of engagement with private sector and governments in countries.
- Mobilize public and private advocacy for MDR TB.

Low-Hanging Fruit

- Develop a system of universal, standardized bar coding for products coupled with mobile information technology to track drug supply and prevent stock-outs.
- Implement an EMR system for MDR TB programs.
- Simplify regulatory dossiers and priority sequencing; consolidate and harmonize NTPs' technical product specifications.
- Facilitate regular interaction with manufacturers around demand forecasting.

[a] Identified by individual workshop participants.

References

Ahonkhai, V. 2012. *Regulatory issues affecting MDR-TB SLDs*. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis, July 31–August 1, Washington, DC.

Atun, R. 2012. *Challenges and barriers to efficient operation of existing supply chain*. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis, July 31–August 1, Washington, DC.

Cepheid. 2012. *Cepheid announces first phase of Xpert MTB/RIF buy-down for high burden developing countries*. http://www.cepheid.com/company/news-events/press-releases/?releaseID=698417 (accessed October 1, 2012).

Comstock, G. 2012. *Learning from other models: PEPFAR's supply chain management system (SCMS)*. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis, July 31–August 1, Washington, DC.

Ditiu, L. 2012. *GDF vision for SLD supply chain*. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis, July 31–August 1, Washington, DC.

Fraser, H. S., J. Blaya, S. S. Choi, C. Bonilla, and D. Jazayeri. 2006. Evaluating the impact and costs of deploying an electronic medical record system to support TB treatment in Peru. *AMIA Annual Symposium Proceedings* 264-268.

Hedman, L. 2012. *Quality of 2nd line medicines for tuberculosis*. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis, July 31–August 1, Washington, DC.

IOM (Institute of Medicine). 2009. *Addressing the threat of drug-resistant tuberculosis: A realistic assessment of the challenge: Workshop summary*. Washington, DC: The National Academies Press.

IOM. 2011a. *The emerging threat of drug-resistant tuberculosis in Southern Africa: Global and local challenges and solutions: Workshop summary*. Washington, DC: The National Academies Press.

IOM. 2011b. *The new profile of drug-resistant tuberculosis in Russia: A global and local perspective: Workshop summary*. Washington, DC: The National Academies Press.

IOM. 2012. *Facing the reality of drug-resistant tuberculosis in India: Challenges and potential solutions: Workshop summary*. Washington, DC: The National Academies Press.

Keshavjee, S. 2012. *Background on the Green Light Committee and the second line tuberculosis drug supply chain*. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis, July 31–August 1, Washington, DC.

Keshavjee, S., and P. Farmer. 2012. Tuberculosis, drug resistance, and the history of modern medicine. *New England Journal of Medicine* 367(10):931-936.

Keshavjee, S., and K. Seung. 2008. *Stemming the tide of multidrug-resistant tuberculosis: Major barriers to addressing the growing epidemic*. http://www.iom.edu/~/media/Files/Activity%20Files/Research/DrugForum/IOM_MDRTB_whitepaper_2009_01_14_FINAL_Edited.pdf (accessed September 15, 2011).

Kimerling, M. 2012. *SLD Financing Issues: IOM workshop on the global supply chain for second-line drugs for MDR-TB*. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis, July 31–August 1, Washington, DC.

Mostaghim, S. 2012. *MDR-TB drugs: Challenges and barriers to efficient operation of existing supply chain*. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis, July 31–August 1, Washington, DC.

MSF (Médecins Sans Frontières) and IUATLD (International Union Against Tuberculosis and Lung Disease). 2011. *DR-TB drugs under the microscope: Sources and prices for drug-resistant tuberculosis medicines*. http://www.msfaccess.org/our-work/addressing-medical-challenges/article/888 (accessed October 1, 2012).

MSH (Management Sciences for Health). 2011. *Quality assurance for pharmaceuticals*. http://www.msh.org/resource-center/publications/upload/MDS3-Ch19-QualityAssurance-Nov2011.pdf (accessed November 13, 2012).

Ripin, D. 2012. *Lessons learned from catalyzing and sustaining access to pediatric HIV treatments*. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis, July 31–August 1, Washington, DC.

Sims, T. 2012. *Creating innovative solutions for MDR-TB: Ideas from the MDR-TB innovation summit*. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis, July 31–August 1, Washington, DC.

Wallengren, K., F. Scano, P. Nunn, B. Margot, S. Buthelezi, B. Williams, A. Pym, E. Y. Samuel, F. Mirzayev, W. Nkhoma, L. Mvusi, and Y. Pillay. 2011. Drug-resistant tuberculosis, KwaZulu-Natal, South Africa, 2001-2007. *Emerging Infectious Diseases* 17(10):1913-1916.

Walsh, J. A., and K. S. Warren. 1979. Selective primary health care: An interim strategy for disease control in developing countries. *New England Journal of Medicine* 301(18):967-974.

WHO (World Health Organization). 2006. *Guidelines for the programmatic management of drug-resistant tuberculosis*. http://whqlibdoc.who.int/publications/2006/9241546956_eng.pdf (accessed October 1, 2012).

WHO. 2010. *Global Tuberculosis Control: WHO report 2010*. http://www.who.int/tb/publications/global_report/2010/en/index.html (accessed September 18, 2011).

Yadav, P. 2012. *Supply chain for MDR-TB: Challenges and ideas for improvement*. Presentation at IOM workshop on Developing and Strengthening the Global Supply Chain for Second-Line Drugs for Multidrug-Resistant Tuberculosis, July 31–August 1, Washington, DC.

Zhao, Y., S. Xu, L. Wang, D. P. Chin, S. Wang, G. Jiang, H. Xia, Y. Zhou, Q. Li, X. Ou, Y. Pang, Y. Song, B. Zhao, H. Zhang, G. He, J. Guo, and Y. Wang. 2012. National Survey of Drug-Resistant Tuberculosis in China. *New England Journal of Medicine* 366(23):2161-2170.

Appendix A

Workshop Agenda

DEVELOPING AND STRENGTHENING THE GLOBAL SUPPLY CHAIN FOR SECOND-LINE DRUGS FOR MULTIDRUG-RESISTANT TB: A WORKSHOP

July 31–August 1, 2012

IOM Keck Center
Room 100
500 Fifth Street, NW
Washington, DC 20001

Background and Meeting Objectives:

To effectively treat patients diagnosed with multidrug-resistant (MDR) tuberculosis (TB) (in 2010, WHO estimated that there were approximately 650,000 cases of MDR TB,[1] and there were 150,000 deaths in 2008), and protect the population from further transmission of this disease, an uninterrupted supply of quality-assured second-line anti-TB drugs (SLDs) is necessary. The IOM Forum on Drug Discovery, Development, and Translation has convened a multi-year international initiative on MDR TB, which began with a foundational workshop in Washington, DC, in 2008, and when completed will have included international workshops in the high-burden countries of South Africa (2010), Russia (2010), India (2011), and China (forthcoming 2013). The four workshops that have been held to date have each identified issues related to the global drug supply chain for quality-assured second-line drugs for MDR TB as major barriers to access to treatment.

When SLDs are unavailable to the national TB control programme (NTP) and medical providers, patients miss critical doses of medicine or

[1] WHO 2011/2012 Tuberculosis Global Facts, http://www.who.int/tb/publications/2011/factsheet_tb_2011.pdf (accessed October 18, 2012).

never start treatment—risking the escalation of disease/amplification of drug-resistance, enhanced infectivity and transmission of disease to others, and death. Also, compared to the 6–9 month treatment course for drug-susceptible TB, treatment of DR TB requires a daily regimen of less potent, more expensive and more toxic drugs over the course of 2 years or more. Ensuring a reliable and affordable supply of high-quality SLDs is a complex public health intervention that, thus far, has not been organized or implemented in a way that allows all providers and patients access to second-line anti-TB drugs when they are needed. In 2010, the Green Light Committee (GLC)-approved (and thus quality-assured) 42,033 SLD patient treatments,[2] reaching only about 6.47 percent of the estimated cases of MDR TB. Although some MDR TB patients not having access to SLDs through a GLC-approved program receive appropriate treatment through a government-run or other quality assurance program, it is estimated that 90 percent of patients with drug-resistant TB are not receiving treatment through a government-run or quality-assured program; thus they are likely receiving treatment from sources of unknown quality (e.g., the local pharmacy), or no treatment at all. The involvement of both the public and private sectors is important to ensure that patients receive effective second-line drugs in a timely and cost-efficient manner.

This public workshop will explore innovative solutions to the problem of how to get the right SLDs for MDR TB to people who critically need them. More specifically, the workshop will examine current problems and potential opportunities for coordinated international efforts to ensure that a reliable and affordable supply of high-quality SLDs is available.

The workshop objectives are to consider:

- To what extent and in what ways current mechanisms are or are not effectively accomplishing what is needed, including consideration of bottlenecks.
    - What are the advantages and disadvantages of centralization in the management of the global drug supply chain, and potential decentralized approaches to improve operations of the supply chain.
    - What can be learned from case studies and examples from other diseases (e.g., malaria/Affordable Medicines Facility and HIV/AIDS/PEPFAR).
- The current allocation of responsibilities and roles of the private (including industry and nonprofit public health organizations) and

[2] GDF Annual Report, 2010, available at http://www.stoptb.org/assets/documents/gdf/whatis/GDF%20Anuual%20Report%202010.pdf, p. 10 (accessed October 18, 2012).

public sectors, and examination of opportunities for enhancing and optimizing collaboration.
- Identification of potential innovative solutions to the problem.

Day One

8:00 a.m. Continental Breakfast Available

8:30 a.m. Opening Remarks

GAIL CASSELL, *Workshop Co-Chair*
Visiting Professor, Department of Global Health and Social Medicine, Harvard Medical School
Vice President, TB Drug Discovery, Infectious Disease Research Institute
Vice President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company (retired)

BARRY BLOOM, *Workshop Co-Chair*
Distinguished Service Professor, Department of Immunology and Infectious Diseases, Harvard University
Dean of the Harvard School of Public Health (former)

SESSION I: OVERVIEW OF THE BARRIERS IN THE SUPPLY CHAIN FOR MDR TB DRUGS

Session Objectives:

- Provide an overview of the history and current operational structure of the supply chain for SLDs for MDR TB.
- Examine barriers preventing the optimal operation of the current supply chain.
- Discuss implications for access to SLDs as they are approved and become available as new drugs on the market.

9:00 a.m. Overview, Background, and Session Objectives

PETER CEGIELSKI, *Session Chair*
Team Leader for Drug-Resistant TB
International Research and Programs Branch, Division of Tuberculosis Elimination
U.S. Centers for Disease Control and Prevention

9:15 a.m. Background on the Green Light Committee and the SLD Supply Chain for MDR TB

SALMAAN KESHAVJEE
Assistant Professor, Department of Medicine & Director, Program in Infectious Disease and Social Change, Department of Global Health and Social Medicine, Harvard Medical School
Associate Physician, Brigham and Women's Hospital, Division of Global Health Equity
Senior Tuberculosis Specialist, Partners In Health

9:35 a.m. GDF Vision for the SLD Supply Chain for MDR TB

LUCICA DITIU
Executive Secretary
Stop TB Partnership

9:50 a.m. Series of Presentations: Challenges and Barriers to Efficient Operation of Existing Supply Chain

PRASHANT YADAV
Senior Research Fellow and Director, Health Care Research
William Davidson Institute
University of Michigan

SANA MOSTAGHIM
MDR-TB Drug Access Project Manager
Clinton Health Access Initiative

RIFAT ATUN
Professor, International Health Management
Head, Healthcare Management Group
Imperial College London

10:35 a.m. Discussion Session with Speakers and Audience

Discussion Moderator:
- Peter Cegielski, CDC

11:05 a.m. BREAK

11:25 a.m. Speaker/Panel Discussion: Challenges and Barriers from the Perspective of Suppliers and Manufacturers

Panel Moderator:
- Peter Cegielski, CDC

Panelists:
- Iain Richardson, Senior Director, Global Supply Chain and Logistics, Eli Lilly & Co.
- Robert Sebbag, Vice President, Access to Medicine, Sanofi

11:55 a.m. Discussion Session with Panelists and Audience

12:15 p.m. LUNCH

12:45 p.m. Speaker/Panel Discussion: Challenges and Barriers from the Perspective of Countries and Providers/Collaborating Organizations

Panel Moderator:
- Michael Kimerling, Bill & Melinda Gates Foundation

Panelists:
- Anne Goldfeld, Harvard Medical School/Global Health Committee
- Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières
- Andy Gray, Senior Lecturer, Pharmaceutical Sciences, University of KwaZulu-Natal
- Norbert Ndjeka, MDR TB Director, National Department of Health, South Africa

1:45 p.m. Discussion Session with Panelists and Audience

SESSION II: DEFINING AND ASSURING QUALITY

Session Objectives:

- Discuss definitions of "quality" in determinations about quality of SLDs.
- Examine the benefits and limitations of the existing SLD prequalification requirement and process.

- Discuss applications and lessons learned from other programs and sectors.

2:15 p.m. Background and Session Objectives

AMY BLOOM, *Session Chair*
Acting Chief, Infectious Diseases Division
USAID

2:20 p.m. Series of Presentations: Setting Quality Standards

Speakers:
- Lisa Hedman, Project Manager, Essential Medicines and Health Products: Access and Rational Use, WHO
- Andreas Seiter, Senior Health Specialist, Pharmaceuticals, Health, Nutrition, & Population, World Bank
- Joël Keravec, MSH Brazil Country Program Director
- Patrick Lukulay, Vice President, Global Health Impact Programs, USP

3:00 p.m. Discussion with Speakers and Audience

Discussion Moderator:
- Amy Bloom, USAID

3:30 p.m. BREAK

SESSION III: SLD FINANCING ISSUES

Session Objectives:

- Discuss issues relating to financing. Who will support the supply and delivery of SLDs?
- Discuss potential innovative approaches and mechanisms that could be used for financing of SLDs.

3:50 p.m. Background and Session Objectives

RIFAT ATUN, *Session Chair*
Professor, International Health Management
Head, Healthcare Management Group
Imperial College London

3:55 p.m. Perspective from the Funders

CHERI VINCENT
TB Team Leader
USAID

MICHAEL KIMERLING
Senior Program Officer, Tuberculosis Global Health Program
Bill & Melinda Gates Foundation

4:25 p.m. Series of Presentations: Innovative Approaches to Financing

Speakers:
- Brenda Waning, Coordinator, Market Dynamics, UNITAID
- Andre Zagorski, Principal Technical Advisor for TB, Center for Pharmaceutical Management, MSH
- David Ferreira, Managing Director, Innovative Financing, GAVI Alliance

5:00 p.m. Discussion with Speakers and Audience

Issues for Discussion:
- What is lacking in the MDR TB drug supply system? Why do so few firms enter the SLD market?
- How can signaling be improved? What can the private sector do to encourage competition?
- What are imaginative new ways to raise funds for SLDs? To create healthy market expectations that make it possible to reduce prices?

Discussion Moderator:
- Rifat Atun, Imperial College London

5:30 p.m. Adjourn

DEVELOPING AND STRENGTHENING THE GLOBAL SUPPLY CHAIN FOR SECOND-LINE DRUGS FOR MULTIDRUG-RESISTANT TB: A WORKSHOP

July 31–August 1, 2012

IOM Keck Center
Room 100
500 Fifth Street, NW
Washington, DC 20001

Day Two

8:00 a.m. Continental Breakfast Available

8:25 a.m. Day 2 Welcoming Remarks

BARRY BLOOM, *Workshop Co-Chair*
Distinguished Service Professor, Department of Immunology and Infectious Diseases, Harvard University
Dean of the Harvard School of Public Health (former)

GAIL CASSELL, *Workshop Co-Chair*
Visiting Professor, Department of Social Medicine, Harvard Medical School
Vice President, TB Drug Discovery, Infectious Disease Research Institute
Vice President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company (retired)

SESSION IV: SELECTED ISSUES OF DEMAND AND SUPPLY

Session Objectives:

- Identify and discuss key issues affecting and impeding the entry of SLDs into countries.
- Discuss drug supply shortage issues.

8:30 a.m. Background and Session Objectives

OWEN ROBINSON, *Session Chair*
Program Manager
Partners In Health

Demand—Entry of SLDs into Countries

8:35 a.m. Presentation: Country-Specific Regulations

VINCENT AHONKHAI
Senior Regulatory Affairs Officer
Gates Foundation

8:50 a.m. Presentation: Demand Forecasting

MEG O'BRIEN
Director
Global Access to Pain Relief Initiative

9:05 a.m. Presentation: Information Management Issues

HAMISH FRASER
Assistant Professor of Medicine, Harvard Medical School
Director of Informatics and Telemedicine, Partners In Health

9:20 a.m. Discussion with Speakers and Audience

Discussion Moderator:
- Owen Robinson, Partners In Health

Supply—Drug Shortages

9:50 a.m. Presentation: Drug Supply Shortages at the Global/National Level

CHRISTOPHE PERRIN
QA Pharmacist
IUATLD

10:05 a.m. Presentation: Drug Supply Shortages at the Facility Level

JIM BARRINGTON
Global Program Director
Novartis

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

Discussant:
- Peter Cegielski, U.S. CDC

Discussion Moderator:
- Owen Robinson, Partners In Health

10:50 a.m. BREAK

SESSION V: LEARNING FROM OTHER MODELS

Session Objectives:

- Examine models and experiences from efforts addressing other diseases and supply chains.
- Explore how the supply chain for SLDs for MDR TB is different from and/or similar to other supply chains.

11:10 a.m. Background and Session Objectives

PRASHANT YADAV, *Session Chair*
Senior Research Fellow and Director, Health Care Research
William Davidson Institute
University of Michigan

11:15 a.m. Innovation in Practice: Lessons from the AMFm

SOJI ADEYI
Coordinator, Public Health Programs
World Bank

11:30 a.m. Series of Presentations: Learning from Other Models: Experience with Other Diseases

Speakers:

- Gordon Comstock, Director, Global Supply Chain, Partnership for Supply Chain Management
- David Ripin, Executive Vice President, Access, and Chief Scientific Officer, CHAI
- Nina Schwalbe, Managing Director, Policy and Performance, GAVI Alliance

12:15 p.m. Discussion with Speakers and Audience

Discussion Moderator:

- Prashant Yadav, University of Michigan

12:45 p.m. LUNCH

SESSION VI: CONCLUDING SESSION

Session Objectives:

- Identify and discuss key themes from the workshop.
- Consider promising and innovative suggestions and potential solutions.

BARRY BLOOM, *Session Chair*
Distinguished Service Professor, Department of Immunology and Infectious Diseases, Harvard University
Dean of the Harvard School of Public Health (former)

1:15 p.m. Presentation of Findings from the MDR TB Innovation Summit

TRACY SIMS
Vice President
Lilly Foundation

1:35 p.m. **Group Brainstorming Session: Innovative Suggestions and Options for a Way Forward**

The group brainstorming session will be broken down into four segments, grouped according to themes that roughly correspond to the workshop sessions. For each segment:

- A workshop session chair will first provide a 5-minute report of key issues discussed at the workshop relating to the theme.
- Then, during a 30-minute discussion period, audience members are invited to provide comments, innovative suggestions, and options for a way forward on key questions related to the theme.

1:35 p.m. **Segment One: Mechanisms to Purchase and Supply Drugs: Who Will Get It Done?**

Report from Session Chair

PETER CEGIELSKI, *Session I Chair*
Team Leader for Drug-Resistant TB
International Research and Programs Branch, Division of Tuberculosis Elimination
U.S. Centers for Disease Control and Prevention

1:40 p.m. Discussion with Session Chair and Audience

2:10 p.m. **Segment Two: Drug Quality Assurance**

Report from Session Chair

AMY BLOOM, *Session II Chair*
Acting Chief, Infectious Diseases Division
USAID

2:15 p.m. Discussion with Session Chair and Audience

2:45 p.m. BREAK

3:05 p.m. **Segment Three: Logistics, Supply, and Demand**

Report from Session Chair

OWEN ROBINSON, *Session IV Chair*
Program Manager
Partners In Health

3:10 p.m. Discussion with Session Chair and Audience

3:40 p.m. **Segment Four: Innovative Financing**

Report from Session Chair

PRASHANT YADAV, *Session V Chair*
Senior Research Fellow and Director, Health Care Research
William Davidson Institute
University of Michigan

3:45 p.m. Discussion with Session Chair and Audience

4:15 p.m. **Reflecting on the Way Forward/Next Steps**

Discussants

SALMAAN KESHAVJEE
Assistant Professor, Department of Medicine and Director, Program in Infectious Disease and Social Change, Department of Global Health and Social Medicine, Harvard Medical School
Associate Physician, Brigham and Women's Hospital, Division of Global Health Equity
Senior Tuberculosis Specialist, Partners In Health

BRAD HERBERT
Managing Director
Brad Herbert Associates

SOJI ADEYI
Coordinator, Public Health Programs
World Bank

Jose Gomez-Marquez
Director, Little Devices Lab
Massachusetts Institute of Technology

Trish Stroman
Principal
Boston Consulting Group

Amy Bloom
Acting Chief, Infectious Diseases Division
USAID

5:15 p.m. Key Themes and Closing Remarks

Barry Bloom, *Workshop Co-Chair*
Distinguished Service Professor, Department of Immunology and Infectious Diseases, Harvard University
Dean of the Harvard School of Public Health (former)

Gail Cassell, *Workshop Co-Chair*
Visiting Professor, Department of Social Medicine, Harvard Medical School
Vice President, TB Drug Discovery, Infectious Disease Research Institute
Vice President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company (retired)

5:30 p.m. Adjourn

Appendix B

Participant Biographies

Barry R. Bloom, Ph.D. (*Workshop Co-Chair*), is Harvard University Distinguished Service Professor and Joan L. and Julius H. Jacobson Professor of Public Health, Department of Immunology and Infectious Diseases, Harvard School of Public Health (HSPH). Dr. Bloom served as dean of HSPH from 1998 through 2008 and is a leading scientist in the areas of infectious diseases, vaccines, and global health. After more than 35 years as the Principal Investigator in the laboratory researching the immune response to TB, he recently shut down his Harvard lab to concentrate on teaching and lecturing. He is a member of the National Academy of Sciences, IOM, American Association for the Advancement of Science, and American Philosophical Society. While dean of HSPH, Dr. Bloom served as secretary/treasurer for the Association of Schools of Public Health. Prior to coming to Harvard, he served as Chair of the Department of Microbiology and Immunology at the Albert Einstein College of Medicine and as an Investigator of the Howard Hughes Medical Institute, where he also served on the National Advisory Board. In 1978, he was a consultant to the White House on international health policy. He is a past president of the American Association of Immunologists and the Federation of American Societies for Experimental Biology. He received the first Bristol-Myers Squibb Award for Distinguished Research in Infectious Diseases, shared the Novartis Award in Immunology in 1998, and was the recipient of the Robert Koch Gold Medal for lifetime research in infectious diseases in 1999. Dr. Bloom has been extensively involved with WHO for more than 40 years. He is currently chair of the Technical and Research Advisory Committee to the Global Programme on Malaria at WHO, has been a member of the WHO

Advisory Committee on Health Research, chaired the WHO Committees on Leprosy Research and Tuberculosis Research, and chaired the Scientific and Technical Advisory Committee of the United Nations Development Programme (UNDP)/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. He is also a member of the Innovation Working Group under the U.N. Secretary General's Joint Effort to Improve the Health of Women and Children. Dr. Bloom also serves on the Scientific Advisory Boards of the Earth Institute at Columbia University, the Doris Duke Charitable Foundation, the City University of New York School of Public Health at Hunter College, and the Howard Hughes Medical Institute–KwaZulu-Natal Research Institute for TB and HIV. In addition, he is an Expert Advisory Group member of the Global Fund–AMFm and Scientific Oversight Group member of the Institute for Health Metrics and Evaluation at the University of Washington, Seattle. He is a member of the Board of Trustees for the Tuberculosis Vaccine Institute (TBVI) and the first Chair of the Board of Trustees and now Chair Emeritus of the International Vaccine Institute (IVI). Most recently, he joined the Advisory Board of the Fogarty International Center at the National Institutes of Health (NIH). He is a graduate of Amherst College (B.S. 1958 and honorary D.Sc. 1990) and Rockefeller University (Ph.D. 1963).

Gail H. Cassell, Ph.D. (*Workshop Co-Chair*), is a Visiting Professor in the Department of Global Health and Social Medicine, Harvard Medical School, and Vice President of TB Drug Discovery of the nonprofit Infectious Disease Research Institute in Seattle. Dr. Cassell has recently retired as Vice President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company in Indianapolis, Indiana. In this capacity, among other things, she was responsible for initiating and leading the nonprofit Lilly TB Drug Discovery Initiative launched in 2007. In 2003, she was one of two individuals at Eli Lilly who initiated and developed the Lilly Multidrug Resistant Tuberculosis Partnership. The partnership has resulted in company support to date of $135 million and is the largest philanthropic effort in Eli Lilly's 125-year history. The partnership now involves more than 20 partners, including WHO and CDC. She is the former Vice President of Infectious Diseases Drug Discovery and Clinical Development of Eli Lilly, where she led the programs of a hepatitis C protease inhibitor from the discovery phase to clinical candidate (the compound is now in Phase III clinical trials) and the development of a new antibiotic from clinical development to product decision. Prior to moving to Eli Lilly in 1997, Dr. Cassell was the former Charles H. McCauley Professor and Chair of the Department of Microbiology at the University of Alabama Schools of Medicine and Dentistry at Birmingham, a department that ranked first in research funding from

NIH during the decade of her leadership. She obtained her B.S. from the University of Alabama in Tuscaloosa and in 1993 was selected by that institution as one of the top 31 female graduates of the 20th century. She obtained her Ph.D. in Microbiology from the University of Alabama at Birmingham and was selected as its 2003 Distinguished Alumnus. She is a past President of the American Society for Microbiology (the oldest and single largest life sciences organization with a membership of more than 42,000). She was named to the original Board of Scientific Councilors of the Center for Infectious Diseases, CDC, and served as Chair of the Board. She has served on the Advisory Board of the Director of NIH, the Director of CDC, the Secretary of Health and Human Services Advisory Council of Public Health Preparedness, and the FDA Science Board: Advisory to the Commissioner. Currently she is a member of the NIH Science Management Board, the newly appointed NIH Board of Trustees, and the Advisory Council of the Fogarty International Center of NIH. Since 1996 she has been a member of the U.S.–Japan Cooperative Medical Science Program responsible for advising the respective governments on joint research agendas (U.S. State Department/Japan Ministry of Foreign Affairs). She has served on several editorial boards of scientific journals and has authored over 350 articles and book chapters. Dr. Cassell has received national and international awards for her research in infectious diseases, including two honorary degrees; the CDC Honor Award in Public Health for exceptional leadership and contributions in the development and implementation of the CDC's Emerging Infectious Disease Plan 1997; a Citation from the FDA Commissioner for her role as Chair of the review of science and technology at FDA and the report *FDA: Science and Mission at Risk* in 2008; and the Emmy Klineberger-Nobel Award in 2008 by the International Organization for Mycoplasmology for outstanding and sustained research contributions to the field of mycoplasmology. She is a member of the IOM of the National Academy of Sciences and has recently completed a second 3-year term on the IOM Council, the governing board. She was elected in 2011 to membership on the U.S. Council of Foreign Relations. Dr. Cassell has been intimately involved in establishment of science policy and legislation related to biomedical research and public health. For 9 years she was chair of the Public and Scientific Affairs Board of the American Society for Microbiology; has served as an adviser on infectious diseases and indirect costs of research to the White House Office of Science and Technology Policy; and has been an invited participant in numerous congressional hearings and briefings related to infectious diseases, antimicrobial resistance, and biomedical research. She has served two terms on the Liaison Committee on Medical Education (LCME), the accrediting body for U.S. medical schools, as well as other national committees involved in establishing policies in training in the biomedical sciences. She is an Emeritus

Member of the Board of Research!America and a former member and Chair of the Board of Directors of the Burroughs Wellcome Fund. She has recently completed terms on the Leadership Council of the School of Public Health of Harvard University, the Executive Committee of Columbia University Medical Center Board of Visitors, and the Johns Hopkins School of Nursing. Currently she is a member of the Morehouse School of Medicine Board of Trustees, and the Advisory Council of the University of North Carolina Gillings School of Global Public Health.

Olusoji Adeyi, M.D., M.B.A., Dr.P.H., is the Sector Manager for Health, Nutrition, and Population (Eastern and Southern Africa) at the World Bank in Washington, DC. He is responsible for the World Bank's support for country-led policies, strategies, operations, and partnerships in the subregion. World Bank's work in Africa emphasizes improved governance, improved competitiveness of human capital, and reduction of vulnerabilities from short- and long-term effects of poor health. Dr. Adeyi was founding Director of AMFm at the Global Fund. An innovation in the architecture of financing medicines for malaria through the commercial private sector, NGOs, and the public sector, AMFm combines a global buyer subsidy with support for implementation at the country level. He was formerly Coordinator of Public Health Programs at World Bank, where he led a number of initiatives on global public health policies, strategies, and analyses of the integration of health systems and health interventions. Dr. Adeyi has extensive experience in policies, strategies, and programs for health systems, service delivery, and disease control at the global, regional, and country levels in Africa, Eastern Europe, and Central Asia. He has had responsibilities with the Federal Ministry of Health in Nigeria, WHO, UNAIDS (Joint United Nations Programme on HIV and AIDS), and the Harvard School of Public Health. He has authored research papers and books on service delivery, quality of care, maternal health, health financing, HIV/AIDS, TB, malaria, and chronic noncommunicable diseases. Dr. Adeyi specializes in global health policies, strategies, and financing. He speaks English, Yoruba, and French (working knowledge).

Vincent Ahonkhai, M.D., FAAP, is the Senior Regulatory Affairs Officer for Global Health at BMGF. His role is to provide strategic regulatory oversight for on-time development and registration of foundation health technologies, including vaccines, drugs, diagnostics, and public health pesticide products. His background is in biopharmaceutical global health R&D, including Clinical Development, Medical Affairs, Regulatory Affairs, and Product Safety and Pharmacovigilance. His specialty is Infectious Disease medicine.

Rifat Atun, M.B.B.S., M.B.A., FRCGP, FFPH, FRCP, is Professor of International Health Management at the Business School and the Faculty of Medicine at Imperial College London. He is Head of The Health Management Group at Imperial College Business School. His research focuses on health systems reform, innovation in the life sciences, and diffusion of innovations in health systems. He has published widely in these areas. Between 2008 and 2012, he was a member of the Executive Management Team of the Global Fund in Switzerland as the Director of the Strategy, Performance, and Evaluation Cluster. He is Chair of the Stop TB Partnership Coordinating Board. Dr. Atun has worked at the UK Department for International Development Health Systems Resource Centre and has acted as a consultant for World Bank, WHO, and a number of international agencies on the design, implementation, and evaluation of health systems reforms. Dr. Atun has served as a member of the Advisory Committee for the WHO Research Centre for Health Development in Japan. He is a member of the PEPFAR Scientific Advisory Board and the UK Medical Research Council's Global Health Group. He is also a member of the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries. Dr. Atun studied medicine at the University of London as a Commonwealth Scholar and subsequently completed his postgraduate medical studies and M.B.A. at the University of London and Imperial College London. He is a Fellow of the Faculty of Public Health of the Royal College of Physicians (UK), a Fellow of the Royal College of General Practitioners (UK), and a Fellow of the Royal College of Physicians (UK).

Jim Barrington, M.B.A., is the Global Program Director of "SMS for Life," Novartis, a public–private partnership and a Roll Back Malaria Partnership Initiative, directly aimed at making sure every child contracting malaria has access to malaria medicines, when and where they need it. Previously, Mr. Barrington was the Corporate CIO of Novartis, where he was accountable for all Novartis information systems, IT, and infrastructure worldwide, with an annual IT budget of $1.6 billion. Prior to joining Novartis, he worked with ABB in Zurich, Switzerland, where he was Senior Vice President and Group CIO. Before this, he spent 5 years in Italy as Vice President of IT with the Whirlpool Corporation with accountability for all IT in Europe, the Middle East, Africa, Asia Pacific, India, and China. He also worked with Gillette for 10 years in the United Kingdom and Germany, and spent 4 years with Eli Lilly in Ireland. Mr. Barrington was born in Ireland and holds an M.B.A. from Kingston University.

Amy S. Bloom, M.D., graduated from Smith College with a major in American Studies/Government-Labor History and received her M.D. from Albany Medical College of Union University. After completing her residency

in medicine at the University of Rochester, she worked at the University as an intensivist and Emergency Department attending. After several years in practice, she joined CDC as an Epidemic Intelligence Service (EIS) officer assigned to the Virginia Department of Health, continuing as a Preventive Medicine Resident in the Respiratory and Childhood Diseases Branch, Division of Bacterial and Mycotic Diseases. Following her training, she served as a medical epidemiologist in the HIV section of the Women's Health and Fertility Branch, Division of Reproductive Health, where she worked on HIV shedding and mucosal immunity as well as the development of HIV preventive technologies. She also participated in CDC's response to the Ebola outbreak in Kikwit, Democratic Republic of the Congo, heading the epidemiology team. The following year she became an American Association for the Advancement of Science, Science, Engineering, and Diplomacy Fellow assigned to USAID. Since that time she has worked for CDC and USAID on a broad range of HIV and TB care issues in more than 20 countries and provided technical assistance to many international, national, and local agencies, governments, and NGOs. She is currently serving as Acting Chief, Division of Infectious Diseases, USAID, covering TB, malaria, and Neglected Tropical Diseases (NTDs).

Peter Cegielski, M.D., M.P.H., received his B.A. in Biochemistry from Harvard University in 1978 and his M.D. from the University of California, San Diego in 1984. He completed a residency in Internal Medicine in 1987 and a fellowship in Infectious Diseases and International Health in 1990, both at Duke University Medical Center. After his fellowship, he joined Duke's faculty, simultaneously earning an M.P.H. in Epidemiology from the University of North Carolina at Chapel Hill. After Duke, he held faculty positions at Muhimbili University Medical Center, Dar es Salaam, Tanzania; the University of Texas Health Sciences Center in Tyler; and Johns Hopkins School of Public Health, including 2 years as Field Director of Hopkins' HIV/AIDS research unit at Chiang Mai University, Thailand. In 1998, he joined the Division of TB Elimination at CDC, becoming the Team Leader for DR TB in 2001. Dr. Cegielski was a founding member of the Stop TB "Green Light Committee" (GLC) in 2000 and its chair from 2004–2006. He was the first person to recognize the global emergence of XDR TB and led the team that first defined, documented, and described it.

Gordon Comstock, M.B.A., serves as the Director, Global Supply Chain, for the Partnership for Supply Chain Management, Inc. He directs the global supply chain activities supporting both the PEPFAR/USAID SCMS project and the Global Fund's Voluntary Pooled Procurement initiative. He also serves as a Principal Program Associate in the Center for Pharmaceutical Management of MSH. Previously, he was Director of Intellectual

Property for the College of Medicine, University of Illinois. Mr. Comstock served as a managing partner for LifeScience Partners, developing business models and strategies for start-up companies, and was a senior consultant with Deloitte & Touche and Opinion Research Corporation. As vice president of MAP International, his managerial experience includes leading international health education and pharmaceutical distribution programs with operations in the United States, Europe, Africa, Caribbean, and South America. Mr. Comstock earned his M.B.A. at Northwestern University, Kellogg Graduate School of Management.

Lucica Ditiu, M.D., has been appointed Executive Secretary of the Stop TB Partnership, WHO. A native of Romania, Dr. Ditiu is a physician and researcher who has devoted her career to improving the lives of people living in communities heavily burdened by TB. Dr. Ditiu began a career with WHO in 2000 as a medical officer for TB in Albania, Kosovo, and Macedonia within the disaster and preparedness unit of the WHO European Regional Office. In this role she worked with all institutions involved in TB care, including ministers of health and justice. She also directly supported civil society and communities, funding their efforts through a grant from the European Commission for Humanitarian Assistance. In 2006, she was selected to be a medical officer in the TB unit of the European Regional Office in Copenhagen. In 2010, Dr. Ditiu joined the Stop TB Partnership Secretariat in Geneva to lead the TB REACH initiative, whose goal is to improve access to TB treatment. The program awards grants of up to $1 million USD to applicants demonstrating that their organizations can reach poor and vulnerable populations and provide them with TB care. A 1992 graduate of the University of Medicine and Pharmacy in Bucharest, Dr. Ditiu completed specialty training in pulmonology through a joint program with the Romanian National Institute of Lung Diseases (Marius Nasta). In 1999, she received a certificate in International Public Health from the George Washington University in Washington, DC, which she completed as a Fellow in epidemiology of lung diseases, TB control, program management, and evaluation. In 2004, she received the National Order of Merit medal for medicine in recognition of her fundraising efforts on behalf of the Romanian TB Control Program and Ministry of Health.

David Ferreira, M.Sc., M.A., is Managing Director for Innovative Finance, and Head of the Washington, DC, Office, GAVI Alliance. Mr. Ferreira joined GAVI in 2010, following his tenure as founding Investment Manager of Soul City Broad-Based Empowerment Company, an investment firm owned by a health communications nonprofit in South Africa. He continues to serve as a non-executive director there. Mr. Ferreira has also served as a non-executive director at the listed education company ADvTECH and,

through appointment by the government of President Nelson Mandela, at the MIIU Company, which assisted South African municipalities in creating public–private partnerships. Mr. Ferreira, whose career has focused on finance and on public–private partnerships, was a founding shareholder and director of Praxis Capital, a private equity firm that invested in South Africa's health care and education sectors. He also established and managed the Private Sector Investments Unit of the Development Bank of Southern Africa. At World Bank, he helped design financial instruments for governments in Asia and Latin America to attract private financing to infrastructure projects. Mr. Ferreira began his career as a human rights and labor lawyer in South Africa and later practiced at the U.S. law firm Davis Polk & Wardwell. He is a Rhodes Scholar, with an M.Sc. from the London School of Economics, an M.A. from Oxford University, and B.A. and L.L.B. degrees from the University of the Witwatersrand in Johannesburg.

Hamish Fraser, M.B.Ch.B., is an Assistant Professor of Medicine at Harvard Medical School, a Research Associate at Brigham and Women's Hospital, and Former Director of Informatics and Telemedicine, Partners In Health. He trained in General Medicine, Cardiology, and Knowledge Based Systems in the United Kingdom and completed a fellowship in Clinical Decision Making and Cardiology at the Massachusetts Institute of Technology (MIT) and the New England Medical Center. His work has led to the migration of medical informatics tools and expertise from developed countries to some of the most challenging environments in the developing world. For 11 years Dr. Fraser has been the Director of Informatics and Telemedicine at Partners In Health, where he leads the development of Web-based medical record systems, data analysis tools, and pharmacy systems. These systems support the treatment of DR TB and HIV, primary care, and heart disease in Haiti, Malawi, Peru, the Philippines, and Rwanda. Along with colleagues from the Regenstrief Institute at the University of Indiana and the South African Medical Research Council, Dr. Fraser is a co-founder of the OpenMRS collaborative, a broad international collaboration to develop a flexible, open-source medical record system platform for use in developing countries. He also cofounded a training program in Rwanda to train local computer scientists to build medical information systems like OpenMRS, and co-leads a course at Harvard and MIT on the role of information systems in improving quality of care in developing countries. Dr. Fraser has a strong interest in the evaluation of medical information systems in developing countries and is currently working with WHO to develop a framework for such evaluation worldwide.

Anne Goldfeld, M.D., is a Professor of Medicine at Harvard Medical School, Professor of Immunology and Infectious Diseases at the Harvard

School of Public Health, Senior Investigator at the Immune Disease Institute and Program in Cellular and Molecular Biology at Children's Hospital, Boston, and a Physician at Brigham and Women's Hospital in the Department of Medicine and the Infectious Disease Division. She is also the co-founder and President of the Cambodian and Global Health Committees. A major focus of her laboratory is the understanding of the mechanisms of transcriptional activation of the tumor necrosis factor (TNF) gene and of HIV-1. Through studies of TNF gene expression in a range of cell types, including T cells, B cells, macrophages, and fibroblasts, the laboratory developed the paradigm of cell type- and stimulus-specific inducible eukaryotic gene regulation through the formation of distinct enhanceosomes and higher-order chromatin structure. The characterization of the molecular mechanisms of the regulation of transcription and replication of HIV by *M.tb.* is another main research focus in the Goldfeld laboratory in model systems of HIV and TB co-infection. A third area of focus of the Goldfeld laboratory is the study of host susceptibility and resistance genes and their variants that influence the pathogenesis of TB and AIDS, including the first identification and description of a gene linked to TB susceptibility and the discovery of IL-10-producing T regulatory cells in TB and an infectious disease in general. In parallel work she has developed delivery-of-care networks and access to treatment for TB and HIV in Cambodia and treatment of MDR TB in Ethiopia. The Cambodian and Global Health Committees, respectively, have initiated and are scaling up MDR care in partnership with the Ministry of Health of each country. Recently, Dr. Goldfeld was the senior Principal Investigator of a trial to determine optimal timing of ARV therapy in immunosuppressed TB patients with HIV. This trial, the CAMELIA (CAMbodian Early vs. Late Introduction of Antiretrovirals), has resulted in improved timing of drug regimens that could reduce mortality globally from co-infection and provides a model for HIV/TB care that will be transferred and adapted to resource-poor settings elsewhere in Asia and Africa. By nesting scientific studies within this clinical trial, the laboratory is elucidating immunological mechanisms and genetic associations with different disease outcomes in TB, AIDS, and TB/HIV co-infection.

Jose Gomez-Marquez is Director, and Principal Medical Device Designer, Little Devices Lab, MIT, and creator of MIT's first course on affordable medical device hardware, D-Lab Health. He is co-inventor of the MEDIKit platform, a series of design building blocks that empower doctors and nurses in developing countries to invent their own medical technologies. The lab's work in TB includes the Adhere.IO platform of interactive diagnostics to enhance medication adherence. Other research projects include crowd-sourced diagnostics, paper microfluidics, and affordable diagnostics for extreme environments. Mr. Gomez-Marquez serves on the European

Union's Science Against Poverty Taskforce and has participated as an expert advisor on the President's Council of Advisors on Science and Technology. In 2009, Mr. Gomez-Marquez was selected to *Technology Review*'s T35, which also named him Humanitarian of the Year. In 2011, he was named a TED (Technology, Entertainment, Design) Fellow and is a co-founder of LDTC+Labs.

Andrew L. Gray, M.Sc. (Pharm.), FPS, is a pharmacist whose research interests include policy analysis (in particular, the development and implementation of National Drug Policies), rational medicines use, and the application of Highly Active Antiretroviral Therapy in resource-constrained settings. He is a Senior Lecturer in the Discipline of Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa. He is also a consultant pharmacist for the Centre for the AIDS Programme of Research in South Africa (CAPRISA) and non-executive chair of JEMBI Health Systems, a nonprofit company focused on developing computer/information technology-based health care solutions for the developing world. Mr. Gray is a Fellow and Honorary Life Member of the Pharmaceutical Society of South Africa, a past President of the South African Association of Hospital and Institutional Pharmacists, a past President of the Hospital Pharmacy Section, and currently Chair of the Board of Pharmaceutical Practice of the International Pharmaceutical Federation. He is a member of WHO's Expert Panel on Drug Policies and Management and has served on the Expert Committee on the Selection and Use of Essential Medicines. He also serves on the WHO Guideline Review Committee.

Lisa Hedman, M.S., is with the Essential Medicines and Health Products unit at WHO headquarters in Geneva, Switzerland. She manages a broad ranges of issues with a view of promoting access to medicines, especially essential medicines that may not be sufficiently available to people who need them. Ms. Hedman first joined WHO as project manager for the WHO Pandemic Influenza A (H1N1) Vaccine Deployment Initiative. Prior to joining WHO, she held several positions with the Program for Appropriate Technology in Health and supported other NGOs. She was the team leader for capacity development in procurement and supply chain with the Program for Appropriate Technology in Health, developing strategies for international donors and working onsite in low- and middle-income countries to implement activities related to access and quality of medicines.

Myriam Henkens, M.D., M.P.H., is the International Medical Coordinator for MSF. For more than 6 years, Dr. Henkens worked in field positions with MSF in several countries in Africa and Asia. After completing an M.P.H. at the Johns Hopkins University, she became the director of the medical

department at MSF in Brussels and is now in charge of MSF's international medical coordination. Besides coordinating the medical departments of all MSF sections, Dr. Henkens continues to be involved in several medical topics, such as drug and medical devices QA, TB, meningitis, cholera, vaccination, etc. Dr. Henkens represents MSF at several interagency platforms, such as the International Coordination Group for meningitis and yellow fever, among others. She participated in GLC. She has also been invited as an expert to several platforms on cholera vaccines, the WHO Essential Medicines List, etc.

Brad Herbert, M.B.A., is founder and Managing Director of Brad Herbert Associates. Mr. Herbert has more than 30 years of experience in international development, with a focus in the social sectors, including health and education. For 27 years, Mr. Herbert was with World Bank, where he spent the majority of his tenure based in developing countries. In 2002, he left World Bank to join and help establish the Global Fund. At the Global Fund, he was the Chief of Operations, with the equivalent rank of Assistant Secretary General at WHO, and was responsible for their multibillion-dollar grant program in over 130 countries. As a result of years of development experience and leadership roles, Mr. Herbert brings a practical, results-oriented approach to program policy, development, and accelerated implementation of health and education projects. He holds a B.A. in Business Administration from the University of Maryland and an M.B.A. from the George Washington University. He is currently a board member of Mothers 2 Mothers, an international NGO based in Cape Town, South Africa. He is working on the prevention of HIV transmission from mother to child. He is also a member of the Dalberg Global Development Advisor's Technical Advisory Committee and a member of a Technical Committee at the Global Fund for pricing options under AMFm.

Joël Keravec, D.V.M., Ph.D., M.B.A., is the Brazil Country Program Director for MSH. Dr. Keravec has 20 years of experience as a public health consultant and project manager in Latin America, Africa, and Europe for the United Nations Development Programme; United Nations Educational, Scientific and Cultural Organization; MSH; French Ministry of Foreign Affairs; Pan American Health Organization; and Brazilian Ministry of Health. As MSH Senior Technical Advisor/Country Director for Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program activities in Brazil, he managed an 8-year technical assistance and capacity building program for strengthening DOTS implementation and MDR TB control, for which the e-TB Manager system (www.etbmanager.org) was developed. He also provides technical assistance to the NTPs in Europe, Asia, and Africa to strengthen MDR TB Programs, SLD management, and

information systems. He has been appointed by WHO Geneva as a GDF Technical Review Committee member and Global GLC member. From 1999 until 2004, Dr. Keravec served as Deputy Director of Brazil's National Institute of Quality Control in Health (Brazil NRA Lab), where he managed reorganization of all aspects of the national drug reference laboratory. His areas of technical expertise include pharmaceutical management of product QA and international quality standards for medicine quality testing laboratories, selection of essential medicines for standardized TB treatment, improved policy and regulatory environment for essential medicines, and improved product management information systems.

Salmaan Keshavjee, M.D., Ph.D., Sc.M., is the Director of the Program in Infectious Disease and Social Change at the Department of Global Health and Social Medicine at Harvard Medical School. Trained as a physician and social anthropologist, Dr. Keshavjee is an Assistant Professor of Medicine and Social Medicine at Harvard Medical School and in the Division of Global Health Equity at Brigham and Women's Hospital. He is also an attending in Internal Medicine at Brigham and Women's Hospital. Dr. Keshavjee completed his thesis work in Harvard's Department of Anthropology and Center for Middle Eastern Studies on health policies in post-Soviet Tajikistan. His clinical research has focused on the implementation of DR TB treatment projects run by Partners In Health and associated treatment outcomes. He has worked extensively with Partners In Health's DR TB program in Russia since 2000. From 2006 to 2008, he was Deputy Country Director for the Partners In Health Lesotho Initiative, launching one of the first community-based treatment programs for MDR TB/HIV co-infection in sub-Saharan Africa. Since 2008 he has led Partners In Health's Russia research initiative, coordinating a multidisciplinary team studying treatment outcomes in DR TB. This work is informing efforts to treat DR TB in the region, including Central Asia, and has resulted in several manuscripts of global clinical and policy significance. Starting in 2005, Dr. Keshavjee represented Partners In Health/Harvard on GLC for MDR TB, the principal global mechanism for MDR TB treatment expansion, housed at the Stop TB Partnership and WHO. From 2007 until September 2010, he served as the Committee's Chair. Through his roles at Harvard, Partners In Health, and GLC, he has advised numerous national programs on the clinical and programmatic management of MDR-TB.

Michael Kimerling, M.D., M.P.H., is a Senior Program Officer on the Tuberculosis Global Health Program, BMGF. Dr. Kimerling joined BMGF in 2008 from the University of Alabama at Birmingham (UAB), where he was a tenured Professor of Medicine. Trained as an internist, he started

his medical career working with NGOs in refugee medicine and rebuilding primary health care services in chronic conflict zones, including several years with Doctors Without Borders in Cambodia and as a consultant to MSF on TB in Russia. He also worked as a TB consultant to WHO in Myanmar. At UAB, Dr. Kimerling was funded by USAID for more than 10 years to do capacity building and operations research on various aspects of TB control, building programs in multiple settings within Asia, Africa, Latin America, and the former Soviet Union. At BMGF, he works closely with established grantees (CREATE and FIND) and new country partners (Brazil and South Africa) on translational and operational research and on delivery issues relevant to the uptake of existing and new technologies. He has been a member of the Technical Review Panel of the Global Fund for 3 years and also serves on the coordinating board of the Stop TB Partnership. Besides his M.D., Dr. Kimerling has an M.P.H. in Epidemiology and an undergraduate degree in Medical Anthropology (with highest honors).

Patrick Lukulay, Ph.D., is currently the Vice President of Global Health Impact Programs for the U.S. Pharmacopeial Convention (USP), overseeing all grant-funded programs that provide technical assistance to developing countries. He is also Director of the Promoting the Quality of Medicines program, a 5-year, $35 million cooperative agreement supported by USAID and implemented by USP. In that capacity, Dr. Lukulay oversees the work of about 20 staff, providing technical assistance to 35 countries to help strengthen their QA and quality systems for pharmaceuticals. Dr. Lukulay holds a Ph.D. in Analytical Chemistry from Michigan State University and worked in the pharmaceutical industry for Wyeth and Pfizer for a combined 12 years as Senior Principal Scientist. He has authored several articles in separation science, spectroscopy, and medicines quality. He serves on the IOM committee on counterfeit drugs and frequently speaks at national and international conferences.

Sana Mostaghim works for CHAI as the MDR TB Drug Access Project Manager. He is based in New Delhi and focuses on CHAI's work to improve access to second-line anti-TB medicines in the global public market. Prior to this, he worked on a project to support the Indian government develop its scale-up strategy for MDR TB treatment. Before CHAI, he worked for 3 years in management consulting in Canada, where he focused on the utilities and retail industries. His role as a researcher for UNDP's "Growing Inclusive Business Models" initiative in 2007 fostered his overarching passion for the alignment of private-sector and human development interests. Mr. Mostaghim holds a B.A. with Distinction from the Richard Ivey School of Business in Canada.

Norbert Ndjeka, M.D., is a Specialist Family Physician with interests in TB and HIV. Dr. Ndjeka is the Director of MDR TB, TB and HIV, Department of Health, South Africa. He served as WHO Temporary MDR TB Advisor. He is a member of the TB TEAM Experts Roster as an Experienced Expert in M/XDR TB under the STOP TB Department of WHO, and a member of the Board of Directors for Bela Bela HIV/AIDS Prevention Group. Dr. Ndjeka previously worked as Clinical Head, Limpopo MDR TB Unit; Senior Specialist and Senior Lecturer in Family Medicine, University of Limpopo; MDR TB and Infection Control Advisor, University Research Corporation; Senior Medical Superintendent, Warmbaths Hospital, Limpopo Province; Medical Superintendent, St. Rita's Hospital, Limpopo Province; and Medical Officer at Botlokwa, Kgapane, and St. Rita's Hospital. Dr. Ndjeka's qualifications include an M.D. from the University of Kinshasa, Democratic Republic of the Congo; a Diploma in Health Service Management from the University of Witswatersrand; a Diploma in HIV Management from the College of Medicine of South Africa; and a Master of Medicine from Medunsa.

Meg O'Brien, Ph.D., is the Director of the Global Access to Pain Relief Initiative, a program of the Union for International Cancer Control and the American Cancer Society to improve access to essential pain medicines. Previously, Dr. O'Brien was the research director of the Center for Strategic HIV Operations Research at CHAI and worked on the establishment of HIV treatment clinics for the U.S. government's PEPFAR program in Tanzania as a Postdoctoral Fellow at the Harvard School of Public Health. She also worked as the Chief Epidemiologist of the HIV Outpatient Clinic in New Orleans while completing her Doctorate in Epidemiology at the Tulane School of Public Health and Tropical Medicine. Dr. O'Brien started her career as a biostatistician at Statistics Collaborative, Inc., while earning a master's degree in International Health from the George Washington University School of Public Health and Health Services. She also has a degree in Biology and a certificate in African Studies from Georgetown University.

Christophe Perrin, M.Sc., is a French QA pharmacist with The Union. Mr. Perrin earned an M.Sc. in Public Health at the Institute of Tropical Medicine in Antwerp. He worked in clinical research for oncology and diabetes medicines before doing several missions for humanitarian organizations. Since 2005, his activities have been concentrated on challenges affecting supply of QA medicines in low-resource countries, as well as access to treatment and innovation for neglected infectious diseases such as TB. Since joining The Union, his activities have also involved non-communicable diseases, such as asthma and diabetes.

Iain Richardson, M.S., is currently Senior Director of Global Supply Chain and Logistics for Eli Lilly and Company, responsible for global demand management, supply chain planning, risk management programs, and logistics. He is also responsible for Eli Lilly's Legacy Product portfolio and Transfer of Technology as part of Eli Lilly's philanthropic MDR TB program. Mr. Richardson has been involved in the MDR TB program since its beginning in 2003. He has a bachelor's degree in Chemical Engineering from the University of Edinburgh and a master's in Biochemical Engineering from University College London. He has been with Eli Lilly for 25 years since joining the company's Liverpool facility as a Technical Services Associate. Prior to his current role, he was Director of Contract Manufacturing for Eli Lilly's external manufacturing operations in Europe, Asia, and North America.

David H. Ripin, Ph.D., is the Executive Vice President of Access Programs and Chief Scientific Officer at CHAI, where he oversees CHAI's work on increasing access to medicines and diagnostics for HIV, malaria, and TB through the use of sustainable market interventions. CHAI's Access Programs have successfully implemented agreements with pharmaceutical companies to lower the price of key drugs and diagnostics for HIV/AIDS, malaria, and TB by up to 80 percent, among other achievements. 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 manufacture of drug candidates. Dr. Ripin received a B.S. in Chemistry and Asian Studies from Washington University in St. Louis and obtained his Ph.D. in Chemistry at Harvard University.

Owen Robinson, M.P.P., is a Program Manager at Partners In Health. Mr. Robinson has been at Partners In Health since 2010, where he has been involved in managing the development of a new national teaching and referral hospital in Haiti, and is now in a cross-site management role. Previously, he worked at CHAI addressing market-related challenges that prevent patient access to key health commodities, including medicines to treat MDR TB. Earlier, he advised clients in the health care sector as a consultant and project manager at The Boston Consulting Group.

Nina Schwalbe, M.P.H., is Managing Director of Policy and Performance at GAVI Alliance. Prior to joining GAVI in 2008, Ms. Schwalbe directed the policy department at the Global Alliance for TB Drug Development, a product development partnership focused on the development of medicines for TB. In this capacity, she led the TB Alliances efforts to promote adoption and introduction of new TB drugs, co-chaired the Stop TB Partnership's task force on retooling, and was a member of the Center for Global Development's working group on demand forecasting. She has spent more than 20 years in international health. For 7 years she directed the Soros Foundations' global public health program, which focused on a range of critical issues including strengthening health systems, TB, HIV/AIDS, and programs aimed at vulnerable populations. She also worked in maternal/child health, first with the Population Council and then with AVSC International (now Engender Health), focusing on the introduction of new programs and technologies. Ms. Schwalbe holds degrees from Harvard and Columbia Universities and is a member of the Council on Foreign Relations and of the faculty of the Department of Population and Family Health at Columbia's Mailman School of Public Health. She has served on the program committees for Doctors of the World USA, Treatment Action Groups' TB/HIV project, and the Open Society Institute's Public Health Watch program, as well as on the boards of the Stop TB Partnership, European Observatory for Health Care Reform, AIDS Foundation East/West, Open Health Institute in Moscow, and International Gay and Lesbian Human Rights Commission.

Robert Sebbag, M.D., is currently Vice President, Access to Medicines at Sanofi. In his role, Dr. Sebbag participates in the company's access to medicines strategy development for the Southern hemisphere. Prior to joining Sanofi, Dr. Sebbag worked in Brussels for the European Federation of Pharmaceutical Industries and Associations on creating a communications platform for the pharmaceutical companies operating in Europe. In his prior role, he was Senior Vice President of Communications for the vaccine company, Aventis Pasteur (today known as Sanofi Pasteur). In addition to his activities within the pharmaceutical industry, Dr. Sebbag is also teaching public health courses within the Paris hospital system, focusing on tropical parasitic diseases. He is active within the French Red Cross and has participated in numerous health missions in the Southern hemisphere. Dr. Sebbag is an M.D. with a specialty in tropical parasitic diseases and training in psychiatry.

Andreas Seiter, M.D., is a Senior Health Specialist and Expert for Pharmaceutical Policy and Management at the World Bank's Health, Nutrition, and Population Anchor. He joined World Bank in 2004 and is responsible for analytical and advisory work in all areas of pharmaceutical policy, such

as regulation, governance, QA, financing, purchasing, supply chain, and rational use. He has been working with World Bank teams, policy makers, and experts on the client side in several countries in Africa, Eastern Europe, the Middle East, Latin America, and South Asia. In 2010, he published the book *A Practical Approach to Pharmaceutical Policy*. Dr. Seiter, a German national, is a physician by training and practiced medicine before joining the pharmaceutical private sector in 1984. He held various positions in medical operations, product management, communications, and stakeholder relations in the industry prior to joining World Bank.

Tracy J. Sims is Vice President, Eli Lilly & Co. Foundation. Mr. Sims is responsible for leading strategy development and tactical implementation of Eli Lilly's global corporate responsibility programs. Eli Lilly's corporate responsibility vision for global health programs is to "catalyze sustainable access to improved health care outcomes for underserved populations." Mr. Sims oversees staff who are deployed globally in support of the global health strategy. Mr. Sims joined Eli Lilly in 1995 and has since held several sales, marketing, corporate affairs, and strategy leadership roles. Prior to joining Eli Lilly, Mr. Sims held positions with the American Diabetes Association as Regional Director and with a U.S. Senator as Assistant Director. Mr. Sims had also been responsible for leading the U.S. Public Policy Planning and Development team with a focus on both state and federal issues. He has acted as spokesperson for Eli Lilly with major media, international and domestic officials, trade, and advocacy organizations on a range of complex issues, including business administration, access to health care, and corporate responsibility. Mr. Sims holds a B.A. in Communications and History from Whitworth University in Washington State, where he graduated with honors.

Trish Stroman, M.S.P.H., M.B.A., is a Principal in the Washington, DC, office of The Boston Consulting Group (BCG). She is a core member of BCG's Health Care practice with a focus in Global Health. The majority of Ms. Stroman's work has been in HIV, malaria, and TB with clients including BMGF, WHO, and several of the product development partnerships. She received an M.B.A. and M.S. in Public Health from The University of North Carolina at Chapel Hill, as well as a bachelor's in Human Biology from Stanford University.

Cheri Vincent, M.S.P.H., is TB Team Leader, USAID, Global Health Bureau. Ms. Vincent is the TB Team Leader with USAID's infectious disease division, focusing on TB prevention and care. She provides the policy, strategic direction, and oversight for USAID's TB program. She also is a member of the Stop TB Partnership Coordinating Board as well as the core technical

groups on TB Infection Control and TB Public Private Mix. She is a member of the U.S. government's delegation on the Global Fund Board. She has more than 16 years of experience in international public health and has worked in the field and in Washington, DC, with USAID for 14 years. She has experience working in Eastern Europe, Asia, and Africa, living 6 years in the Central Asian Republics. Ms. Vincent received an M.P.H. with a concentration in Environmental Sciences from Tulane University and an undergraduate degree in Biochemistry.

Brenda Waning, Ph.D., M.P.H., serves as Coordinator of Market Dynamics at UNITAID, a WHO partnership based in Geneva. She leads UNITAID's technical team responsible for monitoring trends in HIV/AIDS, TB, and malaria markets; identifying strategic opportunities to intervene in these markets; and assessing the public health and market impact of UNITAID's interventions. Prior to joining UNITAID, Dr. Waning served as Director of Pharmaceutical Policy at Boston University School of Medicine, where she authored numerous peer-reviewed studies on pharmaceutical policy at local, national, and global levels. Dr. Waning serves on many expert advisory groups, including the Market Dynamics Advisory Group of the Global Fund and the Access and Delivery Advisory Committee of the Medicines for Malaria Venture.

Prashant Yadav, Ph.D., M.B.A., B.Chem.Eng., is Director of the Healthcare Research Initiative at the William Davidson Institute at the University of Michigan. He also holds faculty appointments at the Ross School of Business and the School of Public Health at the University of Michigan. A leading expert on pharmaceutical and health care supply chains in developing countries, Dr. Yadav's research explores the functioning of health care supply chains using a combination of empirical, analytical, and qualitative approaches. He currently serves as Chair of the Market Dynamics Advisory Group of the Global Fund.

Andre Zagorski, M.A., is Principal Technical Advisor for TB for the MSH Systems for Improved Access to Pharmaceuticals and Services Program based in Arlington, Virginia. He has more than 18 years of global TB and essential medicines project management experience in regions including Europe, Asia, and Africa. He oversees the SIAPS core TB portfolio of activities, including collaborative efforts with WHO, the Global Fund, GDF, GLC, Stop TB partners, and field programs aimed at strengthening pharmaceutical management systems for TB control programs. His technical areas of expertise include project management, implementation, and evaluation; health systems strengthening and policy; SCM; development

of pharmaceutical management tools and use of tools developed by MSH; management information systems; monitoring and evaluation; and development of training courses and capacity building programs. He holds a master's degree in Training and has completed Fellowships in Psychology.

Appendix C

Registered Workshop Attendees

Olusoji Adeyi
Sector Manager
World Bank

Vincent Ahonkhai
Senior Regulatory Affairs Officer
Gates Foundation

Sarah Alphs
Research Associate
The William Davidson Institute at the University of Michigan

Rifat Atun
Professor of International Health Management
Imperial College London

Jim Barrington
Global Progam Director
Novartis

Amy Bloom
Acting Chief, Infectious Diseases Division
USAID

Barry Bloom
Harvard University Distinguished Service Professor and Joan L. and Julius H. Jacobson Professor of Public Health
Harvard School of Public Health

Anthony Boni
Pharmaceutical Specialist
USAID

Gail Cassell
Visiting Professor
Harvard Medical School

Peter Cegielski
Team Leader for Drug-Resistant TB
U.S. Centers for Disease Control and Prevention

Rajni Chandrasekhar
Consultant
FSG Social Impact Consultants

Gordon Comstock
Director, Global Supply Chain
Partnership for Supply Chain Management

Henk den Besten
Senior Supply Chain Advisor
Partnership for Supply Chain Management

Lucica Ditiu
Executive Secretary
World Health Organization, Stop TB Partnership

Suzanne Essama-Bibi
TB Technical Advisor
FHI 360

David Ferreira
Managing Director for Innovative Finance
GAVI Alliance

Gary Filerman
President
Atlas Health Foundation

Hamish Fraser
Assistant Professor of Medicine
Director of Informatics and Telemedicine
Partners In Health
Harvard Medical School

Anne Goldfeld
Professor of Medicine
Global Health Committee
Harvard Medical School

Jose Gomez-Marquez
Director
MIT Little Devices Lab

Andrew Gray
Senior Lecturer, Pharmaceutical Sciences
School of Health Sciences
University of KwaZulu-Natal

Carol Hamilton
Senior Scientist
FHI 360

Debra Hanna
Associate Director, CPTR
Critical Path Institute

Lisa Hedman
Project Manager
World Health Organization

Myriam Henkens
International Medical Coordinator
Médecins Sans Frontières

Brad Herbert
Managing Director
Brad Herbert Associates

Julia Hipps
Senior Director
Eli Lilly and Company

Maria Insua
Senior Technical Advisor
University Research Co., LLC

Douglas Keene
Vice President
Center for Pharmaceutical Management
Management Sciences for Health

Joël Keravec
Brazil Country Program Director
Management Sciences for Health

Salmaan Keshavjee
Director, Program in Infectious Disease and Social Change
Harvard Medical School

Michael Kimerling
Senior Program Officer, Tuberculosis Global Health Program
Bill & Melinda Gates Foundation

Jenna Kohnke
Program Manager
American Cancer Society

Paul Lalvani
Director and Dean
Empower School of Health

Patrick Lukulay
Vice President
Global Health Impact Programs
USP

Robert Matiru
TB Portfolio Manager
UNITAID
World Health Organization

Montserrat Meiro-Lorenzo
Senior Public Health Specialist
World Bank

Thomas Moore
World Health Organization, Stop TB Partnership

Sana Mostaghim
MDR TB Drug Access Project Manager
Clinton Health Access Initiative

Betsy Myers
Program Director for Medical Research
Doris Duke Charitable Foundation

Norbert Ndjeka
MDR TB Director
Department of Health, South Africa

Meg O'Brien
Director, Global Access to Pain Relief Initiative
American Cancer Society

Christophe Perrin
QA Pharmacist
International Union Against Tuberculosis and Lung Disease

Claire Queresi
Senior Program Officer
Results for Development Institute (R4D)

Iain Richardson
Senior Director, Global Supply Chain and Logistics
Eli Lilly and Company

David Ripin
Executive Vice President of Access Programs and Chief Scientific Officer
Clinton Health Access Initiative

Owen Robinson
Program Manager
Partners In Health

Paul Ryu
Regional Manager of Western Europe
Dong-A Pharmaceutical Co., Ltd.

Nina Schwalbe
Managing Director, Policy and Performance
GAVI Alliance

Robert Sebbag
Vice President, Access to Medicines
Sanofi

Andreas Seiter
Senior Health Specialist
World Bank

Pooja Shaw
Program Officer
Results for Development Institute (R4D)

Tracy Sims
Vice President
Eli Lilly & Co. Foundation

Robert Stanley
Manager
Partnership for Supply Chain Management

Trish Stroman
Principal
The Boston Consulting Group

Jami Taylor
Senior Director, Global Access Policy
Janssen, The Pharmaceutical Companies of Johnson & Johnson

Cheri Vincent
TB Team Leader
USAID

Brenda Waning
Coordinator, Market Dynamics
UNITAID
World Health Organization

Prashant Yadav
Director, Healthcare Research Initiative
University of Michigan

Andre Zagorski
Principal Technical Advisor for TB, Center for Pharmaceutical Management
Management Sciences for Health