Meeting Report: A Silent Crisis: Tuberculosis Drug Shortages in the United States

January 18, 2013, PATH Offices, Washington, D.C.

Introduction

On January 18, 2013, Treatment Action Group (TAG) convened a community consultation in Washington, D.C., on the U.S. and global tuberculosis (TB) drug shortage crisis. Cosponsors of the consultation included the American Thoracic Society, RESULTS, the Center for Global Health Policy, and PATH. The community consultation provided an opportunity to increase multi-stakeholder awareness and action on TB drug shortage issues. Additionally, participants sought to identify areas for further collaboration, investigation, and advocacy.

Meeting participants included over 60 advocates; TB control program managers; researchers; representatives from the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO) Global Drug Facility (GDF); supply-chain managers and pharmaceutical representatives; TB survivors; and members of the press. Meeting presenters included Captain Jouhayna Saliba of the Center for Drug Evaluation and Research Drug Shortages Program, FDA; Dr. Sundari Mase, team lead for medical affairs at the Field Services and Evaluation Branch in the Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, CDC; Dr. Ann Cronin, associate director for policy and issues management in the Division of TB Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, CDC; Ms. Liliana Torres, a multidrug-resistant TB (MDR-TB) survivor from Texas; Dr. Maunank Shah, medical director at the Baltimore City Health Department TB Program and assistant professor in the Division of Infectious Diseases, the Johns Hopkins University; Dr. Jon Warkentin, president of the National Tuberculosis Controllers Association and state TB control officer and medical director of the TB Elimination Program, Tennessee Department of Health; and Dr. Joël Keravec, GDF manager ad int. at the Stop TB Partnership, WHO.

Presentations took place in the morning session, and the afternoon session was reserved for break-out group conversations and a facilitated full-group discussion. Outcomes of the consultation include the development of an initial set of recommendations and an overall agreement among participants to continue collaborating to address specific action items and issues associated with TB drug shortages. Additionally, TAG identified a number of policy recommendations that are outlined in the last section of this report.

Summary of Problem

The majority of TB programs across the United States have experienced difficulty accessing first- and second-line drugs to treat TB, because of a nationwide shortage or intermittent access issues, or because needed drugs were too expensive to purchase. This multifaceted problem has also affected the global supply chain of second-line TB drugs. Inadequate or interrupted treatment with TB drugs has not only burdened domestic TB control programs but, at times, led to suboptimal treatment regimens for patients. Further, stressed state and local TB control managers spend inordinate amounts of time and resources dealing with the challenges posed by persistent drug shortage issues. Since 2005, there have been shortages of the following first- and second-line TB medications: isoniazid, rifampin, cycloserine, ethionamide, rifabutin, amikacin, capreomycin, kanamycin, aminoglycosides, and streptomycin. The primary reasons reported for these shortages are usually related to manufacturing difficulties, delays in manufacturing or shipping, active pharmaceutical ingredient (API) shortages, and manufacturing-business decisions resulting from perceived low demand.

Summary of Presentations

Capt. Jouhayna Saliba – Center for Drug Evaluation and Research Drug Shortage Program, FDA

Captain Saliba gave an overview of the history of the FDA's drug shortage program and detailed what the FDA can and cannot require of a manufacturer. She noted that one of the first critical drug shortages in the United States occurred in the 1990s with an isoniazid injectable—that shortage actually prompted the creation of the FDA's drug

shortage program. Captain Saliba explained that the new FDA Safety Initiative Act requires drug shortage reporting from the manufacturing industry to the FDA. She also claimed that drug manufacturers have been largely compliant with FDA shortage-reporting requirements—however, she admitted that there are no enforcement mechanisms in place if manufacturers flout the drug shortage–reporting rules. According to Captain Saliba, the main reasons for most drugs shortages include too few manufacturing lines, complex manufacturing processes, quality issues, supply disruptions, discontinuations and delays, manufacturing changes, and questions of profit.

Captain Saliba explained that the FDA does not have the authority to mandate a manufacturer to produce drugs. Additionally, the FDA cannot require that a manufacturer continue to produce older products, even those that are medically necessary or of great public health significance. She went on to define a drug "shortage" as occurring when manufacturers experience issues or delays, and/or when market-share data demonstrate that production is not meeting total demand. However, at times there are also spot shortages of drugs, where certain areas of the country are experiencing shortages while others are not. Captain Saliba stated that the majority of drug shortages occur with generic drugs and older products, and that shortages are rare for products under patent. The FDA is working on finding ways to incentivize manufacturers to produce drugs. Lastly, she indicated that the FDA is working on the current pressing issue of isoniazid oral tablet shortages and plans to allocate available isoniazid based on need. The FDA's drug shortage index site is accessible at http://www.fda.gov/drugs/drugsafety/drugshortages/ucm050792.htm.

Dr. Ann Cronin – Associate Director for Policy and Issues Management, Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, CDC

Dr. Sundari Mase – Team Lead for Medical Affairs, Field Services and Evaluation Branch, Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, CDC

Dr. Cronin spoke about the CDC's role in monitoring the TB drug shortage crisis and about the importance of assuring uninterrupted treatment regimens for patients, as drug resistance can spread as a consequence of treatment lapse. She also spoke about the impact that budget cuts have had on domestic TB control programs, exacerbating the drug shortage crisis.

Dr. Mase gave some additional background information about her work on TB drug shortages at the CDC. She mentioned that she is primarily responsible for tracking shortages and adverse events; she also actively consults with TB programs nationwide to provide evidence of the impact of drug shortages and drug costs and collaborates with a key contact at the FDA.

Dr. Mase also spoke about the two *Morbidity and Mortality Weekly Report* (*MMWR*) articles recently released by the CDC on the isoniazid shortage and about second-line drug shortages generally. She provided the audience with some epidemiological data on current domestic TB surveillance. She mentioned that between 2005 and 2010, TB drug shortages have tripled—owing mostly to the difficulty in manufacturing sterile injectable agents. Expiration of medications and increased costs also affect the ability of programs to treat patients effectively.

Dr. Mase has taken the lead in responding to the isoniazid shortage. She has conducted a needs assessment of programs in the United States, and, of the 54 of 68 jurisdictions contacted, 42 are experiencing a shortage of isoniazid at the 300-mg dosage. Program managers have begun switching patients from 300 mg to 100 mg, but the pill burden is drastically higher, especially for patients receiving 900-mg treatments. She also mentioned that some jurisdictions have begun to share medications. Dr. Mase would like to work with advocates to collaborate more effectively with the GDF to get an uninterrupted supply of drugs through their mechanism, as she is currently trying to get capreomycin from global drug manufacturers.

Also as reported in the *MMWR* article, Dr. Mase spoke about the National TB Controllers Association survey conducted in 2010, wherein 33 domestic TB control programs responded and 26 reported MDR-TB cases between

2005 and 2010. Of the 26 programs that reported MDR-TB cases, 21 reported difficulties in obtaining medications to treat their patients. The programs reported myriad causes for these difficulties, including nationwide shortages, shipping delays, and expenses, and as a result of these shortages delays in treatment initiation, treatment lapses or interruptions (which is how resistance develops), inadequate regimens, and substantial staff time being used to obtain medications for patients. Additionally, Dr. Mase spoke about the exorbitant cost of treating a patient with MDR-TB in the United States—$150,000 to $200,000 per patient depending on the individual level of resistance.

Ms. Liliana Torres – MDR-TB survivor from Texas

Liliana Torres, a young woman from Texas, was diagnosed with MDR-TB in 2009; she does not know how she contracted the disease, but in 1998, when she was in high school, she was treated for latent TB after having a positive TB skin test. In October 2008, right before her wedding, Ms. Torres began experiencing a cough, which her doctor thought was bronchitis. Her doctor prescribed an inhaler, and she experienced a short reprieve from her cough. But during her honeymoon, her cough returned and was much worse. Ms. Torres sought out the care of specialists and was eventually diagnosed with MDR-TB after getting a chest X-ray and sputum samples taken.

Upon hearing of her diagnosis, her employers sent out a companywide e-mail, and everyone was given TB skin tests (fortunately, no one else came up positive). Ms. Torres had to leave her job and was not given any short-term disability benefits. Three weeks after Ms. Torres began treatment, her doctors determined that she was resistant to most of the medications she was taking and had to put her on a new regimen. She experienced mixed emotions about what was happening to her, including denial and anger, but she was thankful to have the support of her husband.

Ms. Torres spent two months in a hospital a couple of hours away from her home. She experienced muscle aches, fatigue, diarrhea, nausea, and a metallic scent in her nose during treatment and had to endure painful daily injections until she was eventually given a peripherally inserted central catheter (PICC) line. The only reprieve from her treatment regimen and her isolation was that she was allowed to go outside of the hospital daily and walk around outdoors. After she was released from the hospital, she returned to work and was treated at home. The total duration of her treatment was a little over a year and a half. Ms. Torres expressed gratitude for her successful treatment and said that she could not imagine what the experience would have been like if she had not been able to get access to the medications she needed to survive.

Dr. Maunank Shah – Medical Director, Baltimore City Health Department TB Program and Assistant Professor, Division of Infectious Diseases, the Johns Hopkins University

Dr. Shah gave a historical overview of TB in Baltimore, including how Baltimore evolved from a city with one of the highest TB burdens in the United States to a city with a comprehensive approach to fighting TB to, now, a city with a resource-strapped TB program. Currently, about 40 percent of foreign-born Baltimoreans have latent TB, and about 10,000 of these individuals have no access to care. Managing all latent and active TB infections falls on the shoulders of very few clinicians and other staff, meaning that when shortages occur, clinicians spend their limited time resolving the shortages rather than attending to patients. For example, in Baltimore City there is currently no full-time staff to coordinate a response to drug shortages; instead, this task falls to part-time clinicians, which detracts from time spent caring for patients, and there are 20–30 patients at a time on directly observed therapy (DOT) being cared for by one DOT worker.

The system is broken in terms of caring for patients with MDR-TB and providing necessary ancillary services such as pain management, antiemetics, audiology monitoring, PICC lines, and food support. Dr. Shah has tried to coordinate with the private sector to take up latent TB care, but the private sector often lacks the interest and expertise necessary to deal with TB. These problems raise major questions about patient rights and other ethical issues

involved in TB care and prevention. Additionally, a lack of resources means that programs cannot effectively intervene to stem the epidemic.

Dr. Jon Warkentin – President, National Tuberculosis Controllers Association, and State TB Control Officer and Medical Director of the TB Elimination Program, Tennessee Department of Health

Dr. Warkentin gave an overview of what TB is and of the difference between latent and active TB, highlighting that TB is treatable, curable, and preventable. He highlighted the need for isoniazid, which underpins the treatments for both latent and active TB. Dr. Warkentin also noted that the available TB programs and resources vary greatly between jurisdictions. There are shortages of the first-line drugs ethambutol and isoniazid, and these shortages affect many jurisdictions in the United States. The domestic isoniazid shortage is widespread and urgent (about 60% of jurisdictions have no isoniazid or will be out of it within one month). This could mean delaying treatment or that treatment will be less effective, more expensive, and more costly. Sandoz is releasing an emergency supply of 300-mg tablets. There is also an uncertain supply of Tubersol, a component of the tuberculin skin test.

Dr. Warkentin explained that 50 percent of TB cases in the United States are within five states (Texas, California, Florida, New York, and Illinois). He lamented that the CDC has the authority to purchase drugs but has chosen to limit the capacity of cooperative agreements to pay for the salaries of TB control staff in the states.

Dr. Joël Keravec – GDF Manager ad int., Stop TB Partnership, WHO

Dr. Keravec touched on the difficulty of organizing an effective supply chain when the demand for TB drugs is small, and also described his surprise at the differences in price between drugs purchased in the United States versus globally. The GDF is a Stop TB Partnership initiative, and its main donor is the U.S. Agency for International Development. The GDF offers one-year agreements to bridge gaps in procurement of first- and second-line drugs to countries, federal governments, and civil-society organizations.

The GDF has ten years of experience with drug shortages and is working on developing ways to prevent them. Historical GDF delays have resulted from issues with the financial mechanisms that are in place—disbursement of GDF grants, response times or communication challenges with TB programs, issues on the receiving end—and Dr. Keravec does not believe these would be issues if the GDF worked with the United States on domestic drug shortages. He noted that the pace of the GDF response is limited by the capacity of countries to implement their TB programs. Additionally, the GDF has been able to bring down prices through pooled procurement and expanding the number of suppliers.

The WHO prequalification program works on assuring the quality of drugs being supplied to countries, donor and financing mechanism issues, and monitoring the quality chain from APIs to finished products. Countries decide on the quality level of the drugs they will use in their programs, but the GDF does not compromise international standards for the quality of drugs they supply. Strategic interventions that the GDF supports include early-warning systems for stock-outs, forecasting tools for manufacturers, and regional placement of personnel to work with national TB programs in countries to provide some technical assistance.

The GDF plans to work with partners to develop global stockpiles and to mitigate financial issues that delay the procurement process. Prices of second-line drugs have decreased by 30 percent over the years through the pooled-procurement methods of the GDF.

<u>Break-Out Group Discussion Notes</u>

During the afternoon session of the consultation, participants broke out into three working groups for an hour and identified questions for further discussion and analysis.

Addressing the problem of too few API suppliers	FDA drug approval is a long and onerous process that can take years. Some participants lamented that the FDA's stringent policy and procedures for API manufacturers might be even more stringent than the European Medicines Agency's processes. Questions posed for further discussion included: What can be done to fast track the FDA's specification process for TB drugs? How can the approval process for new APIs be shortened and streamlined?
Interagency communication	The Fukushima nuclear power plant disaster happened in the spring of 2011, knocking out one of the main manufacturers that produce the API for isoniazid. The United States started experiencing the early warning signs of the impending shortage in the late spring of 2012, when the National Institute of Allergy and Infectious Diseases at the National Institutes of Health (NIH) got word that an AIDS Clinical Trial Group study site had had trouble accessing the drug. However, because of poor notification and interagency communication, the CDC was not notified until mid-November 2012 of the isoniazid shortage. There currently is no effective system in place to track TB drug shortage issues; there are constant interagency delays in notification and no clear pathway for communications or evaluation among manufacturers, the CDC, the NIH, the FDA, and others.
Supply-chain management	The potential for hoarding and price gouging was described as a significant ongoing concern related to TB drug shortages. A domino effect occurs when there is a shortage or interruption of a particular drug—for instance, now that there is a 300-mg isoniazid shortage, clinicians might switch to rifampin or 100-mg isoniazid; thus, we need to be thinking immediately about forecasting for a potential shortage of 100-mg isoniazid and rifampin.
Risk management	Can we create a safety net or repository to stockpile TB drugs? Where would this program be housed? How would it work, and how would it be managed? Can we use the public health emergency preparedness programs to do some of the surveillance and response?
Surveillance and tracking	How do we define what is an adequate supply and what is a shortage? When should shortages be reported? How can we encourage TB programs to track inventory and share medications more effectively? Some of the interesting ideas brought up during the meeting were about changing the directionality of early notification. Currently, manufacturers are supposed to communicate to the FDA and then to TB programs (anyone can go to the FDA website to see what is posted; however this is a reactive method and will not help us prevent shortages and address TB control program supply-and-demand needs in the future). Participants suggested that TB control programs should become more proactive and develop forecasting methods to track their drug-stock needs based on surveillance, epidemiological, and previous-year data.
Redefine "latent TB"	Can and should we de-emphasize "latency" in favor of communicating about a spectrum of TB? Treatment is prevention: by treating people who are infected with TB, we can prevent active cases, which will stop primary and secondary infections, especially in hot-spot areas.
Funding issues	How can federal and state TB advocates push for more funding for TB programs in this resource-scarce environment? Answer: we need to push for specific drug shortage language and a funding stream in the 2014 reauthorization of the Comprehensive Tuberculosis Elimination Act. Some participants also wanted to see bill language requiring the FDA to report to Congress about drug stock-outs and shortages. There may be an opportunity to push for funding in a future immigration bill, if one ever comes to the floor, to reach those who will continue to be uninsurable under the Affordable Care Act, who account for a large percentage of the active TB cases among the foreign-born

	population in the United States. One proposal was to have the FDA establish a toll-free number to report drug stock-outs anonymously. Finally, participants spoke about the need to keep expanding the network of people working on TB, for example, those working in diabetes and HIV; in corrections societies; and on issues facing seniors and people who are homeless.

Recommendations and Action Steps

Proactively addressing first- and second-line TB drug shortage problems in the United States will require immediate attention, multilevel approaches, and collaboration among advocates, drug manufacturers, health care professionals, TB control managers, members of Congress, and other relevant federal agency partners. The following recommendations developed by TAG reflect specific policies for immediate application that will improve our ability to prepare for and address TB drug shortage issues in the future.

Regulatory barriers that impede the FDA's authority to address drug shortage issues must be overcome. The FDA must investigate and propose effective mechanisms to expand its authority to better monitor manufacturing production and quality and quantity metrics. These could include the requirement of additional reporting from manufacturers to facilitate better communication and forecasting of potential drug shortage problems. For instance, manufacturers should inform the FDA of any and all product withdrawals long before their market exit. Similarly, the FDA should require notification when there is a single API or manufacturing source, especially if that source may be threatened in any capacity, since the interruption of raw-material supplies can be easily forecast and alternative avenues pursued. As Captain Saliba noted during the consultation, the FDA drug shortage–reporting process is not enforceable. The FDA should create mechanisms to enforce these reporting requirements.

The FDA should consider mechanisms to expand its authority and oversight of drug shortages to include the promulgation of economic or other manufacturing and reporting incentives to ensure the ongoing production of injectable and other older, off-patent drugs that are of vital public health significance. The FDA has a long history of providing innovative incentive solutions to encourage the development of orphan and other drugs through grant mechanisms and expedited-review and reduced-cost investigational new drug applications. These and other incentive-based programs should be pursued to better leverage the authority of the FDA to monitor and address critical drug shortage problems.

The task force should develop strong recommendations that mandate increased cross- and interagency collaboration, with the promulgation of disease-specific task forces whenever there are confirmed reports of drug shortages. Eliminating the problem of TB drug shortages in the United States will require the ongoing communication of multiple agencies and departments and stronger communication with the GDF. In instances where there are drug shortages that result from regional misdistribution of a drug, the FDA, with the guidance provided by the Centers for Medicare and Medicaid Services, the NIH, and the Department of Health and Human Services, should be empowered to assist with the planning and execution of distribution channels to ensure efficient and equitable access to needed drugs by programs where supply is low. TAG proposes the creation of a standing high-level and cross-agency strategic drug shortage task force composed of representatives from the FDA, the CDC, the NIH, the Health Resources and Services Administration, and the Department of Health and Human Services; members of Congress; product manufacturers; researchers; clinicians; and community representatives. The task force will enhance meaningful and transparent collaboration and ongoing communication among agencies, affected communities, providers, and the FDA toward developing workable solutions to some of the most vexing drug shortage problems.

The FDA should adapt the tentative approval process it has used over the past decade to approve anti-HIV medications for purchase by the President's Emergency Plan for AIDS Relief (http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm) to enable the review and approval of high-quality medical products made in foreign countries and, working with

other federal agencies, develop mechanisms to allow the purchase and domestic use of products when domestic shortages or stock-outs occur. In addition, it should create mechanisms to ensure that at least two or, if possible, three manufacturers are able, at all times, to provide a medical product for use in the United States in cases where there have been frequent or severe shortages or stock-outs.

Improved cross-agency collaboration on TB drug shortages is long overdue. The FDA should consult with the CDC; the U.S. Office of the Global AIDS Coordinator, its; the U.S. Agency for International Development; the Global Fund to Fight AIDS, Tuberculosis and Malaria; the GDF, currently housed in the Stop TB Partnership Secretariat of the WHO; and the Joint United Nations Programme on HIV/AIDS, as well as with other organizations with relevant expertise such as the Clinton Health Access Initiative and others, to develop integrated, rigorous, and robust structures that can effectively forecast demand and assure a continuous global and domestic supply of high-quality medical products for the diagnosis, prevention, and treatment of TB and other serious and life-threatening diseases.

The Obama administration and members of Congress must expand investment in TB control and elimination at the CDC. The domestic TB control and prevention infrastructure in the United States is crumbling. The perceived low prevalence coupled with a lack of political vigilance and declining federal and state resources for TB control and elimination have set the stage for a dangerous and costly resurgence of TB. This pattern of complacency, financial divestment, and infection- and disease resurgence is all too familiar in the United States. The recurrent, ongoing, and severe shortages of both first- and second-line TB drugs in the United States reveal a lack of political commitment, an effective TB drug supply and management system, and a reliable system of procurement and distribution of anti-TB drugs. Adjusting for inflation, TB control programs have been coping with deleterious budget cuts for the last decade. Frequently, state TB programs are unable to pay for needed drugs to treat individuals with active and drug-sensitive TB with the preferred regimen. To put the United States back on the path to zero TB deaths, infections, and suffering, the CDC's domestic TB program must be fully funded by Congress at its $243 million authorization level set by the Comprehensive Tuberculosis Elimination Act (P.L. 110-392) of 2008. Additionally, NIH funding must continue to be increased to address current gaps in TB research, including the development of more tolerable, shorter-treatment regimens, a point-of-care diagnostic test, and a TB vaccine. Finally, members of the TB congressional caucus should conduct a hearing to examine the causes of TB drug shortages and issue recommendations on how to prevent or alleviate drug shortages in the future, including but not limited to proposals to create a centralized stockpile of TB medications.

Press from the Consultation

- Barton A. CDC report on U.S. TB drug shortage reflects local and global challenges. 2013 January 17. Available at: http://sciencespeaksblog.org/2013/01/17/cdc-report-on-u-s-tb-drug-shortage-reflects-local-and-global-challenges/#ixzz2KK6T7XLp. (Accessed 2013 March 23)

Appendix

- **Food and Drug Administration Drug Shortages Task Force and Strategic Plan – Treatment Action Group's Public Comment**
- **List of Consultation Participants**
- **Handouts from the Consultation**

Centers for Disease Control and Prevention (CDC). Notes from the field: national shortage of isoniazid 300 mg tablets. MMWR Morb Mortal Wkly Rep. 2012 Dec 21;61(50):1029. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6150a4.htm. (Accessed 2013 March 23)

Centers for Disease Control and Prevention (CDC). Interruptions in supplies of second-line antituberculosis drugs--United States, 2005-2012. MMWR Morb Mortal Wkly Rep. 2013 Jan 18;62(2):23–6. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6202a2.htm. (Accessed 2013 March 23)

McKay B. TB's global resurgence amplifies U.S. risk. Wall Street Journal [Internet]. 18 December 2012 [cited 2013 March 23]. Available at http://online.wsj.com/article/SB10001424127887324296604578178314246581852.html.