March 14, 2013

To: Food and Drug Administration Drug Shortages Task Force and Strategic Plan – Public Comment

From: Mark Harrington and Coco Jervis, Treatment Action Group

Re: Urgent Recommendations to Address and Resolve Ongoing Shortages of Tuberculosis Drugs in the United States

We welcome this opportunity (https://www.federalregister.gov/articles/2013/02/12/2013-03198/food-and-drug-administration-drug-shortages-task-force-and-strategic-plan-request-for-comments) to provide recommendations for the FDA Drug Shortages Task Force's strategic plan, in development, per the requirements of the Food and Drug Administration Safety and Innovation Act of 2012. This strategic planning process provides us with a critical window of opportunity to further the development of better procedures and enforcement mechanisms to mitigate the effects of drug shortages as well as provide for increased interagency collaboration and greater efficiencies to advance the standard of care for all Americans with TB and other life-threatening infectious diseases.

Treatment Action Group (TAG) is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS and its two major coinfections, hepatitis C virus (HCV) and tuberculosis (TB). TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information. We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions. TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end AIDS, HCV, and TB. TAG supports a policy program that includes advocacy for domestic and international treatment access, science-based treatment and prevention policies, universal access to care and treatment for people with HIV, TB, and viral hepatitis, and stronger global and domestic health systems.

According to the World Health Organization's Stop TB Strategy, political will to reduce and ultimately eliminate tuberculosis is the first pillar of the Stop TB Strategy, which includes "an effective drug supply and management system" and "an uninterrupted and sustained supply of anti-TB drugs" along with a "reliable system of procurement and distribution of anti-TB drugs" (Ann Cronin and Sundari Mase, U.S. CDC, personal communication, January 18, 2013).

The recurrent, ongoing, and severe shortages of both first- and second-line TB drugs in the United States reveal 1) a lack of political commitment, 2) the lack of an effective TB drug supply and management system, and 3) a lack of a reliable system of procurement and distribution of anti-TB drugs. Together these developments imperil the progress which has been made against tuberculosis in the decades since the New York City outbreak of multidrug-resistant TB in the late 1980s and the federal government's 1989 commitment to work toward the elimination of TB in the United States (http://www.nytimes.com/1989/04/22/us/secretary-of-health-backs-a-plan-to-end-tuberculosis-in-us.html).

Adding insult to injury, the shrinking supply of second-line TB drugs has led to unacceptable price-gouging by the limited number of manufacturers left, who are taking advantage of the ongoing shortages to increase prices by up to thirtyfold—as Akorn did when it took over manufacturing capreomycin from Eli Lilly (in 2007, the price was $11.71 for a one-gram vial; in 2011 it was around $300 for the same vial) (Cronin/Mase, op. cit.). Meanwhile, states and localities are experiencing severe budget cuts for TB control (Dr. John Warkentin, President, National TB Controllers Association, personal communication, January 18, 2013).

Ongoing first- and second-line TB drug stock-outs and shortages continue to threaten the public health, compromise patient care and safety, and burden providers and TB control programs throughout the U.S. Proactively addressing these problems will require immediate attention, multilevel approaches, and the collaborative efforts of advocates, drug manufacturers, health care professionals, TB control managers, members of Congress, and other relevant federal agency partners. Below are TAG's recommendations to significantly improve the FDA's ability to prepare for and address TB drug shortage issues to ensure uninterrupted access to TB medications and other essential drugs of public health significance.

Following the Fukushima Daiichi nuclear disaster in March of 2011, a leading manufacturer of the active pharmaceutical ingredient (API) for isoniazid (INH) was compromised. Isoniazid is the preferred drug for treatment of latent tuberculosis infection (LTBI) and one of the key drugs in first-line treatment of TB. Over the past two years, access to INH has been interrupted in the U.S and recently one of the three INH manufacturers in the U.S. ceased production, severely disrupting the market and causing drug stock-outs in many areas. Currently, according to U.S. Centers for Disease Control and Prevention (CDC), 42 of 54 reporting jurisdictions are experiencing a shortage of 300 mg INH, requiring a massive pill burden (nine individual pills) among patients requiring 900 mg/day of treatment (Dr. Sundari

Mase, Division of TB Elimination, CDC). The events leading up to the INH shortage could have been avoided if FDA had policies and procedures in place to mandate the timely reporting from manufactures when and if an API is threatened.

Recurrent stock-outs and shortages of second-line drug to treat TB, particularly the injectables amikacin, capreomycin, and kanamycin, have been reported on the FDA drug shortages web page for the past few years. Currently one of the two manufacturers "expects to continue to allocate [i.e., ration] the product through at least the end of March 2013," while the other "has 500mg/2ml and 1gm/4ml available in limited quantities. Once this supply is depleted, the next estimated release dates are unknown."
(http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm314739.htm - amikacin, last updated 3/13/13)

1. Regulatory barriers that impede the FDA's authority to address drug shortage issues must be overcome. The Task Force must investigate and propose effective mechanisms to expand the FDA's authority to better monitor manufacturing production, quality, and quantity metrics. This could include the requirement of additional reporting from manufacturers to facilitate better communication and forecasting of potential drug shortage problems. For instance, manufactures should inform the FDA of any and all product withdrawals significantly prior to 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. Currently, the FDA drug shortage reporting process is not enforceable (Capt. Jouhaya Saliba, PharmD, CDER Drug Shortage Program, FDA, personal communication, January 18, 2013). FDA should create and enforce mechanisms to enforce these reporting requirements.

2. The Task Force should consider mechanisms to expand FDA 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 better to leverage the authority of the FDA to monitor and address critical drug shortage problems.

3. 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 U.S. will require the ongoing communication of multiple agencies and departments and stronger communication with the Global Drug Facility of the World Health Organization (WHO). In instances where there are drug shortages that result from regional misdistribution of a drug, FDA, with the guidance provided by CMS, NIH, and HHS, should be empowered to assist with the planning and execution of distribution channels to ensure efficient and equitable access of needed drugs to programs that are in short supply. We propose the creation of a standing high-level and cross-agency strategic drug shortage task force compromised of representatives from the FDA, CDC, NIH, HRSA, HHS, members of Congress, product manufacturers, researchers, clinicians, and community representatives. The Task Force will enhance meaningful and transparent collaboration and ongoing communication between agencies, affected communities, providers, and the FDA toward developing workable solutions to some of the most vexing drug shortage problems.

4. 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 (PEPFAR) (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, there should be mechanisms to assure at all times that at least two and if possible three manufacturers at any time are able to provide a medical product for use in the United States in cases where there have been frequent or severe shortages or stock-outs.

5. The FDA should consult with the Centers for Disease Control and Prevention (CDC), the U.S. Office of the Global AIDS Coordinator (OGAC), its Supply Chain Management System (SCMS), USAID, and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the Global Drug Facility (GDF) currently housed at the Stop TB Partnership in the World Health Organization (WHO), UNAID, and with organizations with relevant expertise

such as the Clinton Health Access Initiative (CHAI) 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. We have seen over the past decade how U.S. TB drug shortages have tripled (Dr. Sundari Mase, Division of TB Elimination, CDC, personal communication, January 18, 2013).

The current FDA consultation and Task Force provide an urgently needed bridge to the next step of bringing together all stakeholders to work together to achieve the solutions for the ongoing shortages of first- and second-line TB drugs vital to public health and individual patient safety.

Yours truly,

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