TAG
Treatment Action Group

January 11, 2019

The Honorable Alex M. Azar II
Secretary, Department of Health and Human Services (HHS)

The Honorable Scott Gottlieb
Commissioner, Food and Drug Administration (FDA)

Department of Health and Human Services
200 Independence Avenue, SW
Washington D.C., 20201

Re: Docket No. FDA-2018-N-3272, Identifying the Root Causes of Drug Shortages and Finding Enduring Solutions; Request for Comments

Dear Secretary Azar and Commissioner Gottlieb:

As an organization dedicated to ensuring uninterrupted access to affordable treatment for HIV, tuberculosis (TB), and hepatitis C virus (HCV), Treatment Action Group (TAG) thanks the FDA and the Agency Drug Shortages Task Force for its attention and commitment to addressing ongoing pharmaceutical drug supply shortages and issues in the United States. Undoubtedly, strengthening and finding solutions to the overall U.S. pharmaceutical drug supply is imperative. However, we caution that blanket market-based policy solutions provide limited benefit to address domestic drug supply issues for diseases that are considered 'market failures' - diseases which receive little to no attention by private investment, such as TB. We submit this comment to call your attention to acute concerns facing our nation's supply for pharmaceutical drugs to treat and prevent TB, and the need for unique public policy strategies and solutions to mitigate against future stock-outs of these essential public health tools.

TB is an airborne disease and has become the world's leading infectious killer, surpassing HIV. Dangerous drug-resistant forms especially constitute a public health concern for the U.S., and require costly and complex treatment regimens comprised of multiple drugs to successfully disrupt transmission and cure patients. However, a history of acute TB drug shortages in the U.S. due to unstable market conditions have had severe public health consequences and have limited efforts to address outbreaks. The drugs used for treatment regimens are often prone to shortages and in the event of interruptions in our nation's TB drug supply, persons with TB disease may lapse and TB can spread. Treatment interruptions, or regimens that contains too few drugs, can foster drug-resistance. Additionally, treatment costs for patients with TB disease increases as drug resistance escalates. Direct treatment costs in the U.S. average $19,000 to treat a single case of drug-susceptible TB (DS-TB), $164,000 for multidrug resistant TB (MDR-TB) and upwards

of $526,000 to treat extensively drug-resistant TB (XDR-TB). Much of these resources come at the expense of already strained TB program budgets.[1]

Lack of adequate TB drug supply is directly linked to fragile market conditions in the U.S. for these vital public health products. The current fragile, fragmented TB market is inadequate to support multiple suppliers. A varying number of purchasers nationally – such as state programs, clinics, hospitals, etc. – make up a patchwork of individual procurers of TB treatments, but the volumes purchased for these products are low and demand is difficult to predict. The U.S. only sees just under 10,000 new cases of active TB a year nationally, but individual states can see unexpected variation in new cases which leads to stress on public health budgets to quickly and affordably procure proper treatments and other products. For example, some states in 2017 saw double the number of active TB cases, while in others, the number of cases decreased as much as 50%.[2] Even for TB infection, which affects many more people in the U.S. – an estimated 13 million individuals – the market is far smaller than the need, given inadequate funding for public health programs to systematically test and treat for TB infection.[3]

Our nation overall lacks a centralized procurement model, and even at the state-level to smoothen demand to generate a predictable market for suppliers. Less than a handful of states utilize a centralized procurement model to pool demand for TB products across individual purchasers and TB care providers. As a result, with too many purchasers and too few volumes purchased, the market for the TB products in the U.S. remains unstable, which leads to too few manufacturers of these products interested in the domestic market and overcoming regulatory hurdles to sell in the U.S. The limited number of suppliers leaves our TB drug supply extremely vulnerable when manufacturing challenges arise, or suppliers decide to exit the market.

In recent years, there have been several documented shortages of core drugs to treat patients with TB in the U.S. These include isoniazid and rifampin, two drugs used in combination that are important to treat both active TB disease, as well as TB infection, which affects millions of people in the U.S., and can activate to infectious TB disease at any time if untreated. Shortages of these critical public health drugs were well documented when in 2012 three pharmaceutical manufacturers – Teva, Sandoz, and VersaPharm – all reported low inventory of isoniazid due to an insecure supply of the active pharmaceutical ingredient (API), leading to treatment interruptions for patients with TB.[4] Since then however, in May 2018, Sandoz unexpectedly discontinued manufacturing isoniazid, citing reasons as a "business decision" made by the company, further putting access and supply to this important drug at risk.[5]

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[1] U.S. Centers for Disease Control and Prevention. The Costly Burden of Drug-Resistant TB in the U.S.. https://www.cdc.gov/nchhstp/newsroom/docs/factsheets/costly-burden-dr-tb-508.pdf

[2] U.S. Centers for Disease Control and Prevention. Mortality and Morbidity Weekly Report: Tuberculosis - United States. 2017. https://www.cdc.gov/mmwr/volumes/67/wr/mm6711a2.htm?s_cid=mm6711a2_w

[3] U.S. Centers for Disease Control and Prevention. TB in the United States: A Snapshot. https://www.cdc.gov/nchhstp/newsroom/docs/factsheets/tb-in-the-us-a-snapshot.pdf

4 U.S. Centers for Disease Control and Prevention. Impact of a Shortage of First-Line Antituberculosis Medication on Tuberculosis Control — United States, 2012–2013. https://www.cdc.gov/MMWr/preview/mmwrhtml/mm6220a2.htm

[5] U.S. Food and Drug Administration. FDA Drug Shortages – Current and Resolved Drug Shortages and Discontinuations Reported to the FDA: Isoniazid Oral Tablets. https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Isoniazid+Oral+Tablets+&st=d&tab=tabs-2

Indeed, TB drugs having sole suppliers in the U.S. is frequent; at least three of the five core drugs used in the treatment of drug-resistant TB have single manufacturers: clofazimine, cycloserine, and bedaquiline. This reliance on single manufacturers makes treatment very vulnerable to shortages, prone to unexpected price spikes, or difficult to procure by domestic TB programs. For example, manufacturer Purdue GMP has reported an acute shortage of cycloserine since mid-December 2018.[6] Clofazimine, produced by Novartis, is only available through filing a rigorous investigational new drug (IND) application. Bedaquiline, one of only two new MDR-TB treatments in nearly 40 years that are FDA approved, has seen slow uptake and implementation due to prohibitive pricing placed upon public health programs. Navigating distinct procurement processes for each drug, and their fragile supply impose on understaffed public health programs long lead times, additional administrative work, and difficult decisions about designing regimens with limited and unavailable drugs for patients with TB. Importantly, a disjointed TB drug supply makes it difficult for U.S. public health practitioners to align with an impending update to national treatment guidelines for drug-resistant TB, if core drugs are in chronic shortage or difficult to procure.

Given the fragility of the market for these products and to provide enduring solutions to mitigate the unique challenges and stabilize the TB drug supply for U.S. patients with TB, we strongly recommend the Task Force consider the following tranche of policy strategies:

- *Allowing U.S. TB program procurement through the Global Drug Facility (GDF):* Recognizing unstable and fragmented global market dynamics that are detrimentally unique to TB products, the GDF was established at the Stop TB Partnership with a mission to centralize access and procurement to quality-assured TB medicines at low prices with short lead times. This program, supported by funding through the U.S. Agency for International Development (USAID), uses a pooled procurement model to counteract instability in the market for TB drugs by facilitating procurement, maintaining supply, and managing demand for products that meet rigorous quality assurance standards at a low cost for all countries to address their localized TB epidemic. Domestic TB programs are already welcome to purchase through GDF as an alternative mechanism to procure drugs that are often in short supply, and are less costly with GDF pricing. However, specific directive and endorsement from appropriate HHS leadership for U.S. TB programs is needed to build awareness amongst public health on the opportunity to purchase through GDF. Furthermore, to allow for domestic use of internationally qualified TB products available through GDF that are not FDA approved, the FDA must also issue importation waivers to allow unencumbered procurement and use of these products by U.S. programs *(see recommendation on importation waivers below)*.

- *Emulate the GDF procurement model for U.S. TB programs:* Given the success of the GDF model globally that was built through U.S. taxpayer support and technical assistance, an efficient centralized/pooled procurement model could be similarly implemented stateside to mitigate shortfalls in the domestic supply for TB products. In

[6] U.S. Food and Drug Administration. FDA Drug Shortages – Current and Resolved Drug Shortages and Discontinuations Reported to the FDA: Cycloserine Capsules, USP. https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Cycloserine%20Capsules,%20USP&st=c&tab=tabs-1

fact, with a relatively nominal investment, the HHS Supply Service Center at Perry Point, Maryland, which currently administers a small stockpile of TB drugs and serves domestic TB programs by filling gaps in the supply could be transitioned with modest changes to its existing infrastructure. Additional resources would allow for Perry Point to transition from its current static stockpile model to a rotating reserve in order to meet the demand. Resources would also be needed for TB programs nationwide to sensitize and build capacity on this process and transition them from their normal procurement flow. Alternatively, the FDA could explore and pilot ways to collaborate with GDF and Perry Point to facilitate and procure drugs at GDF pricing, such as bedaquiline.

- *Provision of temporary importation waivers for TB drugs in shortage:* When critical TB drugs are in short supply domestically, the FDA should issue temporary importation waivers to allow for the emergency importation of these needed drugs that are available on the global market. At the same time, since TB suppliers have little market incentive to register their products with the FDA, the FDA could also use its authority to expedite or subsidize product registration, or waive the annual facility inspection fees, for quality assured TB drugs that have been already approved via WHO prequalification, Global Fund Expert Review Panel, the European Medicines Agency, or other stringent regulatory authorities such as Canada or Japan.

- *Establish a U.S. essential medicines list for diseases of public health concern, including TB:* Such a list would be useful to direct and prioritize procurement of medicines that are vital to the health of U.S. citizens, and are important tools for public health programs to execute their mandate in prevention and control of disease outbreaks. Such a list should be reviewed and modified annually to reflect changing treatment guidelines, and as new treatments and other interventions come online. Furthermore, the list could be based upon and reflect the WHO Essential Medicines List, allowing for the FDA to facilitate rapid acceptance of globally quality assured TB products approved through the aforementioned stringent regulators.

- *Extend the expiration dates for TB drugs at risk for shortage, where scientifically justified:* With low and infrequent volumes associated to TB products, the FDA extending the expiration dates of TB drugs where scientifically justified would benefit TB drug supply, especially as new therapeutics are slowly introduced. Furthermore, extending expiration dates could support the shelf life of the current static inventory of TB products at Perry Point, until it has the necessary resources to transition to a rotating stockpile. Currently several options are available to the FDA in exercising its authority to extend the expiration of stockpiled TB products. This could be done by encouraging manufacturers to submit more long-term stability data, qualify important TB public health products for the Shelf Life Extension Program (SLEP), or issue an Emergency Use Authorization (EUA) to extend stockpiled TB products in shortage that are nearing expiration and needed by domestic TB programs to control concurrent outbreaks.

- *Bolster resources for the domestic TB program at CDC:* Even as these recommendations strengthen the TB drug supply, flat-funded TB programs nationally will require increased federal support to take on additional capacity to expand testing, procurement and

implementation of appropriate treatment, particularly for the millions of individuals in the U.S. with TB infection. The U.S. government should increase resources for the Centers for Disease Control and Prevention's (CDC) Division of TB Elimination (DTBE) from $142.2 million to $195.7 million in fiscal year 2020, in order to begin dually addressing TB drug supply infrastructure, and fund a robust national TB elimination program that has the capacity to scale-up the implementation of these important public health interventions among communities that are hardest-hit by TB.

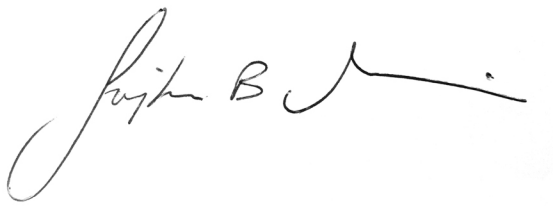
- *Fund research and support the FDA to enhance access to future TB treatments and vaccines:* While TB is preventable, treatable, and curable, the treatment regimens themselves are lengthy with often harmful and debilitating side-effects. Thus, increasing research investment is needed to ensure that newer, safer treatments and vaccines can be advanced through our publicly funded research institutions. The U.S. government is currently the leading funder of TB research and development (R&D) globally at $313.5 million through eight agencies, many under the auspices of HHS. Boosting this federal investment by $131 million to $444.5 million across these agencies to meet a target of dedicating just 0.1% of total U.S. government outlays on research overall (gross domestic expenditure on R&D) towards TB R&D, could catalyze ongoing and prospective research at these U.S. agencies, including eventual approval and registration through the FDA.[7] The FDA would play a vital role in ensuring that these promising new products are made accessible, and similarly do not suffer the same fate as the current slate of TB therapeutics.

The preceding recommendations ultimately require an increased government role, intervention, and investment in shaping and stabilizing the domestic market for public health to procure important therapeutics for TB, and for other health conditions that are similarly prone to market fragility. Without specificity in policy solutions and subsequent increased government investment, public health threats like TB will continue to see supply challenges, even as market-based solutions are implemented through this Task Force. As the threat of TB grows globally and in the U.S., American patients with TB and domestic programs should not have to wait for lifesaving treatments.

We commend the efforts of the FDA and Agency Drug Shortages Task Force to find and implement solutions to prevent national drug shortages, and hope you commit to further action to ensure diseases like TB that have their own unique set of drug supply challenges are not left behind. Please do not hesitate to contact Suraj Madoori at suraj.madoori@treatmentactiongroup.org for further questions or concerns.

Respectfully submitted,

[7] Treatment Action Group. Tuberculosis Research Funding Trends, 2005–2017. New York: December 2018. http://www.treatmentactiongroup.org/sites/default/files/tb_funding_2018_final.pdf



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