TBCAB
GLOBAL TB COMMUNITY ADVISORY BOARD

Meeting Report
11th Semi-annual Global TB Community Advisory Board Meeting

23–24 October 2016
Liverpool, United Kingdom

TB CAB Meeting in Liverpool
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Global Drug Facility *(Brenda Waning, Chief, GDF)*
Dr. Brenda Waning, chief of the Global Drug Facility (GDF) presented to the Global TB Community Advisory Board (TB CAB) and guests about the history and function of the GDF since its' founding in 2011. Dr. Waning explained the importance of pooling procurement for tuberculosis (TB) products, the types of support the GDF provides to countries, and how this work has helped to bring down TB drug prices and increase the number of prequalified products three-fold.

Dr. Waning discussed progress made and issues experienced rolling out bedaquiline, delamanid, the shortened regimen for multidrug-resistant TB (MDR-TB), and the new pediatric fixed-dose combinations (FDCs). Cancelled orders due to inaccurate and, in some cases, overly ambitious forecasting have also become a serious challenge for the GDF and its suppliers. In an effort to address some of these issues and to better coordinate the TB market and its many stakeholders, in July 2016, the GDF launched the TB Procurement and Market Shaping Action Team (TPMAT)– both TAG and the TB CAB will have representation on the group.

The discussion of issues related to new tools then dovetailed into a discussion around GF transition and its potential to adversely impact the stability of the TB medicines market. Dr. Waning explained that as countries transition out of GF and begin issuing their own drug tenders for second-line medications, the GDF's purchasing power will decrease potentially destabilizing the availability and price of quality assured TB products. Dr. Waning expressed her concern that without a transition plan, the TB market could return to the state it was in in 2000, when countries procured local products of variable quality and at high prices.

Dr. Waning closed her session by summarizing gains made in TB in recent years and urging the TB CAB to get involved in GF transition conversations. Underscoring the importance of an organized market and funding for bringing new TB tools to fruition and to the patients who need them, the TB CAB discussed (1) what we want a post-GF transition world to look like and (2) what we need to do to get there.

Regulatory training *(Christophe Perrin and Sandrine Cloez MSF)*
Christophe and Sandrine, a Pharmaceutical Coordinator and Pharmacist with Médecins Sans Frontières (MSF), conducted a ninety-minute regulatory training covering the respective roles and responsibilities of regulatory authorities and developers, and existing and proposed regulatory mechanisms with potential to expedite access to new tools without compromising stringency.

Christophe opened the training with a review of the history of drug laws and regulatory authorities, explaining that while drug laws and regulators are designed to protect people, in the absence of adequate resources to develop regulatory capacity and enforce regulations, regulatory authorities can sometimes delay access to new tools. Regulatory

harmonization is often proposed as a way to remedy the challenges presented by under developed or under resourced regulatory mechanisms, and to simplify and expedite market entry for new products. Christophe provided an overview of efforts to harmonize regulatory requirements across countries, highlighting how National Medicines Regulatory Authorities (NMRAs) gather every two years at the International Conference of Drug Regulatory Authorities (ICDRA), where they exchange perspectives with ministries of health and drug developers and sponsors. While harmonization is attractive for companies and regulators alike, Christophe noted that sovereignty and country discomfort with surrendering the responsibility of registration to another remain a challenge.

Christophe then covered early access mechanisms, highlighting their importance, but also their tendency to shift risk and responsibility from sponsors to countries, providers, and patients. He also discussed how many countries lack mechanisms for early access and only register new drugs once phase III data is available– out of 26 countries surveyed by MSF, just 15 had early access mechanisms in place. Regulatory flexibilities (import waivers) can be used to expedite access while country programs are waiting on the additional data required for registration, but these still require the approval of country health authorities (i.e. political will). The regulatory training session closed with a facilitated discussion of ways to address some of the access barriers presented earlier in the session.

GeneDrive (formerly Epistem) *(David Budd, CEO and Gino Miele R&D Director)*
David Budd, who started at GeneDrive in March 2016, met with the TB CAB in Liverpool following a series of correspondences and a teleconference regarding GeneDrive's TB test and its plans to launch in India. David explained that GeneDrive's goal is to produce a diagnostic test that can detect TB and drug resistance and at affordable price. He provided an overview of the company and described the GeneDrive platform and its capabilities.

David shared GeneDrive's perspective– the Indian regulator approved GeneDrive based on studies conducted within its target market and they therefore feel they are commercializing under the appropriate legal permissions. The company noted it collected additional internal post-market surveillance data, which aligned to the DCGI approved claims. The TB CAB maintained its original position, reiterating that the data upon which the test's regulatory approval was based were not peer-reviewed for journal publication, and the findings not replicated in another independent, peer-reviewed study, and that data in that study indicates it is not a suitable replacement for sputum smear microscopy. The TB CAB encouraged Genedrive to continue R&D to develop an evidence-based, sensitive point-of-care test.

Sanofi (*Felix Lee, New Product Planning, South East Asia*)
Felix updated the TB CAB on Sanofi's progress registering rifapentine and its future access plans for the uptake of the 3-month, once-weekly regimen of rifapentine and isoniazid (3HP) for the treatment of latent TB infection (LTBI), including registration plans, manufacturing capacity, and affordability.

TB Alliance (*Willo Brock, Senior VP External Affairs; Dan Everitt, Vice President and Senior Medical Officer; Christo van Niekerk*, Senior Director, Clinical Development; *Sarah Mdebah*

and Maureen Morenga from Kenya and community representatives to the TB Alliance's Stakeholder Association)
The TB Alliance presented early results from its Nix-TB study (designed to evaluate 6–9 months of bedaquiline, pretomanid, and linezolid for XDR-TB) and discussed how these findings have influenced its future development plans. Given encouraging though very preliminary findings, the TB Alliance is planning NC007, a phase III study of the NiX-TB regimen that will include sites in South Africa and Eastern Europe and is expected to open in Q3 of 2017. NC007 will explore how to optimize the duration and dose of linezolid. The TB Alliance also updated the TB CAB on progress advancing other candidates from the oxazolidinones class, including tedizolid and sutezolid, one or both of which they hope will prove to be a more tolerable alternative to linezolid.

The TB Alliance mentioned ongoing discussions with regulatory authorities about how much data would be required for a provisional approval of pretomanid for use within the context of the NiX-TB regimen (for XDR- or failing MDR-TB). The TB Alliance assured the TB CAB that they are simultaneously continuing to seek support to initiate a compassionate use program for pretomanid, pointing to the lack of precedent for a non-profit to introduce such an access mechanism and the need for community support for such initiatives and the funding required to support them.

The TB Alliance then updated the TB CAB on the status of its phase III STAND trial, designed to evaluate 3–4 months of pretomanid, moxifloxacin, and pyrazinamide (PaMZ) for DS- and some forms of DR-TB (requires pyrazinamide susceptibility) that was placed on hold following three participant deaths. The TB Alliance also presented promising findings from its phase IIb NC005 study, which evaluated the treatment-shortening potential of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (BPaMZ) highlighting its ability to cure more strains of DR-TB than the PaMZ regimen given that that the addition of bedaquiline ensures three active drugs including in patients with either pyrazinamide or moxifloxacin resistance.

The TB Alliance closed its presentation with an update on the status of its pediatric program for pretomanid, explaining that additional studies in adults and juvenile animals are required before studies in children can advance.

Medicines Patent Pool (*Esteban Burrone, Head of Policy; Chan Park, General Counsel; Erika Dueñas, Advocacy Officer; Grania Brigden, 3P/ the Union)*
Representatives of the Medicines Patent Pool (MPP) who previously consulted members of the TB CAB regarding whether and how stewardship might be incorporated into MPP licenses granted under its new mandate in TB, closed the loop by presenting an overview of the main findings submitted to UNITAID in the MPP's recent stewardship report. Chan then gave the TB CAB an update on progress made in negotiations with Johns Hopkins University (JHU) and the TB Alliance regarding the rights to develop sutezolid in combination for TB.

Mobilizing community and civil society responses to TB

The TB CAB attended a half-day meeting sponsored by the Stop TB Partnership, organized by Lynette Mabote (ARASA), and facilitated by Kenyon Farrow (TAG). The meeting provided an opportunity for civil society and community groups working at the global level to share their respective advocacy priorities and to develop a shared advocacy agenda, and, where feasible, a unified community message/voice.

Otsuka *(Marc Destito, Communications Director & Director of Access Programs for India and South Africa; Rajesh Gupta, Senior TB Project Director)*
Otsuka provided an update on its efforts to expand access to delamanid, including progress made with in-country registrations and its compassionate use program. Otsuka acknowledged the difficulty it has faced in advancing access to delamanid, attributing its challenges to fact that Otsuka is a mid-sized pharmaceutical company with no previous experience in the global health space.

Otsuka disagreed with the TB CAB's suggested approach to expand access globally by allowing all countries to purchase delamanid via the GDF as opposed to just those that are Global Fund eligible. Otsuka informed the TB CAB that it is in the process of finalizing negotiations with two partners that have a broader presence globally, including in high TB burden countries.

In terms of in-country registrations, delamanid was approved in Hong Kong in 2016. In the last year, Otsuka has filed in China, Indonesia, Turkey, and the Philippines and is currently preparing submissions in Peru, Vietnam, Russia, India, and South Africa. In the process, Otsuka identified barriers to filing in some countries, including in Russia where a local study is required, and in South Africa, where a sponsor must be an official legal entity to register a new product. Otsuka also updated the TB CAB regarding its plans to advance access to delamanid in India through a pilot program similar to the one that is currently in place for bedaquiline, but with less-restrictive criteria.

Otsuka updated the TB CAB on its research initiatives, including its phase III and pediatric studies of delamanid, and two additional technologies– a new TB compound and a treatment-monitoring tool. The session closed with Otsuka's perspective on where the activist community can help facilitate broader access to delamanid, including by pushing regulatory authority review timelines, encouraging in-country stakeholders focused on bedaquiline about the need for both new drugs, raising awareness of delamanid's availability via the GDF, encouraging Global Fund-funded countries to include the new drugs in their proposals, and supporting global AMR initiatives.