

# TUBERCULOSIS PROCUREMENT AND MARKET-SHAPING ACTION TEAM (TPMAT)

## SUMMARY MEETING REPORT OF THE SIXTH GENERAL MEETING

19 February 2021  
Meeting Held Virtually

### Background and Introduction

**Content of Presentation: TPMAT Overview & Progress Update; Meeting Objectives and Agenda**

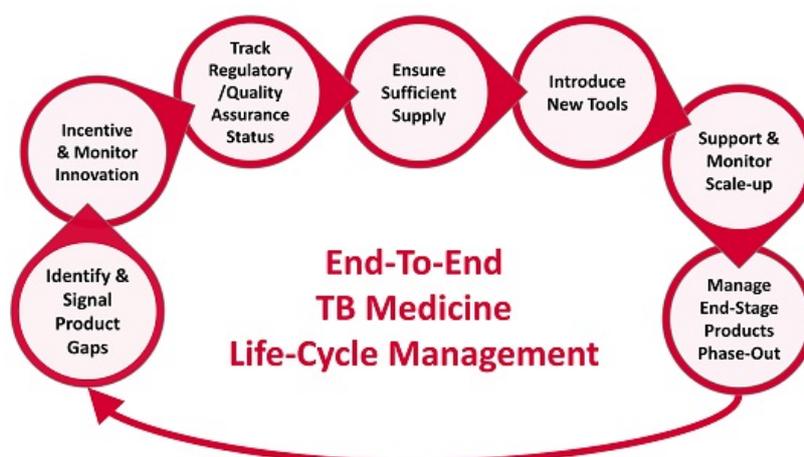
**1. TPMAT Overview & Progress Update** Presenter: Brenda Waning (GDF)

#### TPMAT Overview

The Global Drug Facility (GDF) opened the meeting by providing an overview of TPMAT and summarizing recent TPMAT progress. The TB Procurement and Market-Shaping Action Team (TPMAT) – established in July 2016- is the key global forum that brings together stakeholders to address common market-shaping and procurement challenges related to ultra-fragile TB commodity markets. It serves as an umbrella for all TB stakeholders to align on issues and coordinate activities towards common goals of expediting and optimizing access to quality-assured TB products for people living with TB, irrespective of procurement modalities or funding source. The TPMAT is comprised of procurers, donors, implementers, international organizations, non-governmental organizations, regulators, WHO, civil society, and National TB Programs. Its current members can be found in [Annex 2](#).

TPMAT works end-to-end across the entire TB product life cycle (Figure 1). In the upstream, TPMAT ensures appropriate, adapted products are developed and available in a timely manner and in sufficient supply, in the downstream to accelerate introduction and scale-up, and at the end of the lifecycle to manage product phase-out.

**Figure 1: TPMAT's End-To-End Product Life-Cycle Approach**



### TPMAT Progress Update

TPMAT progress updates focused on coordination as well as upstream and downstream activities. Numerous updates and changes to the [TB Medicines Dashboard](#) – TPMAT’s roadmap for product prioritization and organizational harmonization – were presented.

To date, TPMAT coordinated stakeholder alignment and input to five rounds of the Global Fund Expert Review Panel (ERP) Expression of Interest (EOI). More than 35 updates/changes were made to the GF ERP EOI to ensure EOI alignment with WHO treatment guidelines and market evolution. Five priority TB medicine formulations have been shepherded through the GF ERP ad-hoc/priority review process, thereby decreasing the time to market for these formulations. Similarly, TPMAT partners have contributed to two comprehensive reviews of the WHO Model Essential Medicines List (EML) making more than 40 changes; and TPMAT partners made 20, 28, and 27 changes to the WHO Prequalification (PQ) EOI, the Global Fund List of Health Products, and the GDF catalogue, respectively, to improve harmonization across these partners’ lists of products.

Key upstream progress updates included: a) introducing new paediatric products, such as the 20mg bedaquiline formulation at a negotiated price of \$200 per 6-month treatment course for 6–12-year-olds; b) achieving a 32% price reduction for adult bedaquiline; c) providing procurement support for research projects which can struggle with procurement due to the small volume of products required for research purposes and gaps in researchers’ experience with procuring medicines.

Key downstream progress updates included: a) expediting the introduction of new, all-oral adult and paediatric DR-TB regimens; b) supporting mitigation of access issues related to countries’ transition to domestic procurement; c) working on establishing a Task Force on Domestic Procurement; d) engaging with the Vatican High Level Dialogue on Paediatric HIV to include paediatric HIV-TB coinfection and organizing over 200 commitments from partners.

### TPMAT Meetings- Looking Forward

TPMAT will be transitioning from two-day, biannual, in-person meetings to shorter, more frequent video conference meetings focused on discrete topics.

### Objective and Overview of this Meeting

TPMAT’s 19 February 2021 meeting was focused on two topics:

- 1) Nitrosamine impurities identified in rifapentine (RPT) and rifampicin (RIF) products
- 2) Current status of formulations for paediatric TB and alignment of coordination platforms for paediatric TB medicines access

The meeting objectives were to:

- Summarize issues associated with nitrosamine impurities in rifapentine and rifampicin products; review actions taken and timeline for future actions;
- Identify nitrosamine-related risks to TB medicine markets (both prevention and treatment), along with potential mitigation actions and lead organizations to implement the mitigation actions.
- Describe actions taken and progress made on development and introduction of child-friendly TB medicines;
- Identify unmet needs/ gaps in research and access to pediatric TB formulations and discuss what can be done to address these gaps.

The meeting agenda can be found in [Annex 1](#).

## Meeting Wrap Up and Closure

The meeting was attended by 44 people representing all members of TPMAT. The list of participants can be found in [Annex 3](#).

### Action Points

- Based on a request from Stop TB Partnership’s Coordinating Board, establish a Task Force on Domestic Procurement comprised of key procurers as well as both global and national civil society organizations (CSOs)

## Session 1: Nitrosamine Impurities in rifapentine and rifampicin

### Content of Presentations: Nitrosamine Impurities

#### **1. Overview of WHO Prequalification Approach to Risk Assessment of Nitrosamine Impurities in Rifapentine and Rifampicin** - Presenter: Isabel Ortega, with Deus Mubangizi and Wondiyfraw Zeleke Worku (all WHO PQT)

The WHO Prequalification Team (PQT) discussed the challenges for both manufacturers and regulators related to testing for nitrosamine impurities and establishing guidelines and regulations around safe intake levels and mitigation measures. PQT emphasized that the potential consequences of these decisions include batch recalls and medicine shortages, so it is important to carefully weigh the risk and benefit of medicine recall versus that of nitrosamine exposure.

PQT has a general strategy in place for manufacturers (including of active pharmaceutical ingredients (API) to assess risk and mitigate nitrosamine levels over time ([Annex 4](#)). With respect to nitrosamines in TB products specifically, rifapentine and rifampicin products have been found to have nitrosamines present (CPNP and MeNP respectively).<sup>1</sup> Manufacturers have been requested by PQT to measure and mitigate these impurities, clarifying that higher interim limits can be accepted on a temporary basis while manufacturers begin putting in place mitigation measures.

For rifapentine, the manufacturer has been regularly updating PQT on steps it is taking for mitigation, and this information—in combination with decisions by U.S. Food and Drug Administration (FDA) and other stringent regulatory authority (SRA) mechanisms—feeds into PQT recommendations and guidance on rifapentine. With respect to rifampicin, PQT has requested all manufacturers (including of API) to test nitrosamine impurities in a representative number of batches. Results are expected in 2021. Risk analyses will then be conducted on a case-by-case basis. No interruption of rifampicin supply will take place until more evidence becomes available.

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<sup>1</sup> Key nitrosamines discussed in this report are 1-cyclopentyl-4-nitrosopiperazine (CPNP) and 1-methyl-4-nitrosopiperazine (MeNP) found in rifapentine and rifampicin respectively.

**2. Updates on Impurity Messaging to Civil Society** - Presenter: Mike Frick (TAG), Thokozile Nkhoma (FACT Malawi), Edna Tembo (Coalition of Women Living with HIV and AIDS Malawi)

TAG and its CSO partners discussed the issue of nitrosamine impurities in the context of a) the growing CSO movement to scale up rifapentine-based TB preventative treatment (TPT) in light of the difficulties patients are encountering with isoniazid preventative treatment (IPT); b) the increasing evidence (e.g. the Study 31 trial on HPZM<sup>2</sup>) for short-course regimens for drug-sensitive TB. CSOs are concerned with how governments make risk-benefit decisions about the continuation of regimens when impurities are found to be present and how manufacturers work to remediate impurity issues in a time-bound, transparent way.

TAG and partners have taken a number of actions to ensure confidence in TPT and rifamycin-based products, including the dissemination of information on nitrosamines, manufacturer remediation plans, and steps by both governments and advocates to ensure TPT safety. Other actions include a) providing support for partners encountering TB medicines with nitrosamine levels over interim limits; b) anticipating the impact on supply chain, pricing and quality assurance of both nitrosamine impurities and remediation steps. Materials have been created to show how calculations on risk-benefit have been made and how progress on reducing nitrosamine concentrations is being tracked. Further information on nitrosamine concentrations in rifampicin and rifapentine, benchmarks for interim and less-than-lifetime limits of nitrosamine concentrations and support for people on TB regimens or TPT can be found at: <https://www.treatmentactiongroup.org/publication/nitrosamines-and-tb-medicines-information-note-and-patient-faqs/>

**Text Box 1: Civil Society Perspectives**

CSO partners described how the issue of nitrosamine impurities has been dealt with in Malawi following a Global Fund communication in October 2020 that resulted in a 3HP batch recall.<sup>3</sup> CSOs had already spent a lot of time advocating and mobilizing demand for 3HP. Following the recall, CSOs and local IMPAACT4TB partners strategized on key messaging and how to engage and mobilize government, treatment beneficiaries, communities, and media. CSOs also worked with stakeholders to ensure that TPT programme was not interrupted. The key message to communities was that, when any drug is introduced, safety monitoring has to take place and 3HP is no different. The key message to providers was that beneficiaries who have started treatment can continue, a message supported by providers already dispensing the 3-month course on a monthly basis, making it easier to monitor clients. A toll-free number was also provided to monitor side effects. CSOs asked partners to support the logistics, storage, monitoring and distribution of 3HP, and help improve buy-in by government as, initially, the Ministry of Health thought about returning to INH as testing on 3HP could not be done in-country or regionally. CSOs and partners argued that the high resistance to/low uptake of isoniazid (INH) was leading to stocks reaching expiry date. CSOs remain in close conversation with the Government of Malawi as it decides how to go forward with scaling 3HP from 5 to 28 districts.

**Key Points Discussed: Nitrosamine Impurities**

*WHO PQT Action on Nitrosamine Impurities*

<sup>2</sup> HPZM is a new four-month TB drug regimen involving rifapentine, isoniazid, pyrazinamide, and moxifloxacin administered for two months, followed by another two months of rifapentine, isoniazid, and moxifloxacin.

<sup>3</sup> 3HP is a short-course TPT regimen that combines two antibiotics active against TB, isoniazid (INH) and rifapentine (RPT). 3HP is taken once a week for 12 weeks (12 doses in 3 months).

- WHO PQT has not recommended any specific limits on impurities.
- WHO PQT has asked manufacturers to risk assess nitrosamine levels. The results of the manufacturer risk assessments of different products have not resulted in any urgent actions by WHO PQT or the manufacturers (e.g., no recalls or withdrawals). There are no plans to publish results of risk assessment reports by manufacturers.
- WHO PQT is working with manufacturers to support them with risk assessment and mitigation measures. None have asked specifically for technical assistance on mitigation measures.
- WHO PQT will consult with the WHO Pharmacovigilance Team to determine if there are any registries or plans for registries for people receiving rifamycin-based products.

#### Monitoring of Impurities

- Several questions were raised about the monitoring of nitrosamine impurities, how this will take place, and who should be responsible for it.
- Information provided by manufacturers so far has not been enough to feed into country decision-making. KNCV gave an example of a manufacturer providing information to a Ministry of Health that there is a relationship between temperature and impurity concentration with rifapentine. However, without information from the manufacturer on the exact relationship (e.g., is it the extent of the temperature excursion, the duration of the temperature excursion or a combination of both) it is not possible to implement appropriate mitigation measures.
- Evidence for decision-making is in demand by national programmes. An activity to support the collection and dissemination of evidence for decision-making across the supply chain on nitrosamine impurities might be more helpful and cost-effective than, for example, support for countries doing their own spot-testing of products.
- Regarding the benefits of active tuberculosis drug safety monitoring (aDSM) among people receiving rifamycin-based products for nitrosamine-related adverse events: many participants felt that the presence of existing background exposure apart from treatment, along with the gap between exposure and potential adverse effects, would limit the benefits of aDSM for this particular adverse event. KNCV, however, noted that other research (such as registries on other classes of medicine) might serve as useful comparators.

#### Assessing Risk-Benefits

- WHO Global TB Program (GTBP) is working with TAG and KNCV to create illustrative examples of what one would expect from nitrosamine impurities in rifamycin-based products compared to exposures from environmental contamination so as to enable countries and partners to better understand and create messages around degree of risk.
- TAG also noted that calculations done on exposure were a) based on NDMA<sup>4</sup> exposures, so applying these findings to MeNP/CPNP may not be accurate and exposures may be less; b) established based on “worst case scenarios” in relation to current levels of impurities, but as manufacturers put in place mitigation measures, these exposures will necessarily decrease.
- TAG raised the issue of exposure from HPZM versus standard regimens, noting that there is a clear disparity between the 8 years of equivalent exposure as per HPZM (as was used in Study 31) and HRZE<sup>5</sup> which equates to only a few months.

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<sup>4</sup> NDMA refers to N-Nitrosodimethylamine, another type of nitrosamine.

<sup>5</sup> HRZE is the standard six-month TB treatment regimen involving rifampicin, isoniazid, pyrazinamide, and ethambutol administered daily for two months, followed by another six months of daily rifampicin and isoniazid.

- Calculations done on background versus rifampicin/rifapentine exposure will also feed into considerations around the Study 31 regimen which will be reviewed by WHO this year and will feed into further guideline development around mitigation.

#### Messaging From Civil Society

- There is resilience in communities when thinking about risk-benefit of nitrosamine exposure, as communities already understand tradeoffs associated with different regimens of HIV medicines.
- Messaging on risk – benefit should also target regulatory authorities, because without clear and detailed information on nitrosamine contamination and exposure, procurement and registration of products can be held up.

#### Impact of Mitigation Measures on Price

- There are several concerns about the impact of mitigation measures on price, especially with respect to rifampicin-based products.
- Both TAG and KNCV noted that, for rifampicin manufacturers, where margins are very small, remedial actions (e.g., the upgrading of packaging or the inclusion of temperature monitoring on shipments) may lead, in the best-case scenario, to less of a likelihood of further price reductions and, in the worst, to significant price increases. Countries are also worried about price increases.
- There is a negotiated price with the supplier of rifapentine 150mg tablets that ended in 2020; however, pricing for new procurements of rifapentine 150mg tablets remains unclear. UNITAID prioritized development of one generic rifapentine-isoniazid fixed-dose combination product with a negotiated price that expires at the end of 2021.
- More information needs to be made available with respect to associated costs of mitigation to plan for and potentially prevent significant price increases.

#### **Action Points: Nitrosamine Impurities and Mitigation**

- Implementing partners to explore what additional information may be needed to support country decision making on using these products.
- WHO GTBP, WHO PQ, and GDF to discuss how best to monitor suppliers to reduce impurity levels and minimize any barriers to access to these product for treatment of TB.

## Session 2: Paediatric DR-TB

### Content of Presentations: Paediatric TB

#### 1. *Update on introduction and scale-up of TB formulations in children and stakeholder coordination*

- Presenter: Brian Kaiser (GDF)

GDF described progress since 2018 with respect to the pricing, introduction/uptake/scale-up, and stakeholder coordination of paediatric medicine for drug-resistant TB (DR-TB). It is estimated that only around 500 children less than 5 years of age (those most likely to benefit from child-friendly formulations) are treated each year globally. These low volumes and individualized regimens create numerous barriers to access and require pooled procurement because of the mismatch between batch size and order quantities as most countries treat no more than 10 – 20 children a year (some treating just 3 – 5 children) and many manufacturers have minimum order quantities. Nevertheless, since 2018, 13 DR-TB paediatric formulations have become available, as well as new paediatric formulations of bedaquiline (20mg) and delamanid (25mg, now under development). The bedaquiline price at launch means that an all-oral, bedaquiline-based regimen for a child is less than \$1000, while a 12-month all-oral regimen has been brought down to \$1900. Seventy-one countries had taken up these formulations by the end of 2020, with bedaquiline alone taken up by 18 countries in the first ix months it has been available.

Progress has also been made on stakeholder coordination. TPMAT facilitated more than 200 commitments from key stakeholders for paediatric TB, with many focused on product development, in advance of the Vatican 2020 High Level Dialogue.<sup>6</sup> TPMAT has been coordinating with GAP-f over the past year and half, showcasing the approaches and successes that TPMAT has already accomplished in paediatric TB medicines and stakeholder coordination while highlighting the key differences in paediatric TB medicines compared to HIV medicines (e.g., development pipeline, development funding landscape, implementation funding landscape, regulatory approaches, disease burden, etc.).

As GAP-f expands from HIV products into paediatric medicines for TB, HCV, NTDs, and NCDs, TPMAT wants to help ensure there is not duplication of efforts in diseases where there are already mechanisms working in this area (e.g., TPMAT and TB, see [Annex 5](#)) and the nuances of the different diseases are understood and accounted for in the GAP-f model.

#### 2. *Update from PADO TB* - Presenter: Tiziana Masini (WHO GTBP)

WHO GTBP described recent work by WHO's Paediatric Antituberculosis Drug Optimization (PADO-TB) group on optimization of paediatric TB drugs and how PADO-TB aligns to and complements TPMAT. PADO-TB focuses on the upstream research agenda (the "Prioritize and Evaluate" section of the GAP-f approach) while TPMAT focuses on near final formulation development, quality assurance and implementation (the "Develop" and "Deliver" sections of the GAP-f approach) (see Annex 5). PADO-TB's key activity is to create consensus-based lists providing clear signals to researchers and manufacturers as to which formulations should be prioritized for research and development (R&D). These recommendations could also be used as part of the update process for the PQ EOI. In February 2019, PADO-TB met to create a list of paediatric TB medicines to be prioritized in research and has since met again to review new developments and update the priority list. WHO is developing a guidance document to outline the general process by which this happens, which will also reflect how PADO-TB works.

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<sup>6</sup> For more information on the Paediatric HIV & TB Rome Action Plan, see <https://www.paediatrichivactionplan.org>

PADO TB has a number of priorities going forward. First, rifapentine remains a priority in the short-term, especially a 150mg scored rifapentine dispersible standalone formulation that can support different indications (e.g. 3HP and 1HP). PADO-TB agreed this should be a prioritized to be updated in the WHO PQ EOI, adding the scored tablet to the EOI and removing the child-focused rifapentine and fixed-dose combination (FDC) currently in the EOI. These two changes would bring the WHO PQ EOI in line with the TPMAT recommendations and priorities previously submitted for the GF ERP EOI. Delamanid formulation (25mg) has been flagged for potential prioritization because, as of now, it is only available for compassionate use. WHO and GDF collaborated on an application to include delamanid 25mg dispersible and to lower the age limit for the WHO Model Essential Medicines List for Children. Taste-masked moxifloxacin formulation has been flagged for prioritization. Bedaquiline has been flagged to be removed from the short-term list because now the 20mg dispersible tablet is available, but this decision will be reviewed further as it is unclear whether this is the best formulation across all age bands.

PADO-TB is also seeking to hold further discussions on what it means to remove a drug from its list of priorities, and how to develop clear messages around the factors that inform decision-making for removal. Besides the guidance document for PADO processes across diseases being produced by GAP-f, there is also documentation being developed by GTBP to support the changes to child-friendly rifapentine formulations in the WHO PQ EOI and an agenda and research questions for PADO TB activities in 2022.

### **3. Opportunities to increase the speed of paediatric TB research - Presenter: Lindsay McKenna (TAG)**

TAG described recent progress in paediatric TB medicine R&D, including clinical trials (e.g., the Odyssey and SHINE trials). Progress includes a) bedaquiline approval for children aged 5 – 12 years who are at least 15 kgs; b) European Medicines Agency's (EMA) positive opinion that delamanid could be used in adolescents and children over 30kgs. Additionally, there are ongoing and planned paediatric studies on how to extend benefits of new preventative therapies to children, how to expand access to certain regimens to children under the age of 5 years and how to optimize paediatric drug dosing, combinations, and treatment duration.

Many gaps remain. TB treatment research is primarily focused on optimization of medicines for adults (e.g., how to optimize dosing to balance efficacy, toxicity and treatment duration). Paediatric research is often done in reaction to these adult findings, to determine the corresponding paediatric dosing and safety. In reaction to ongoing dose optimization work in adults, paediatric TB medicine research is also often iterative, with findings frequently revisited in a way that does not happen with, for example, paediatric medicines for HIV. Paediatric TB treatment R&D also begins well after adult formulations are approved, takes a long time to complete once started and sometimes involves suboptimal design elements such as age de-escalation (i.e., R&D starts with older children, then goes down by age band). This means that the adult – paediatric R&D gap is anywhere from 6 to 13 years or more. At Phase IIa of ongoing trials, product manufacturers should already have begun planning for paediatric investigations. However, for many of the newer TB compounds under development in the phase II stage of clinical research, TAG is not currently aware of any paediatric investigation plans having been developed.

TAG proposed a number of steps to accelerate R&D for paediatric treatment, including increasing investment in R&D, supporting new TB drug sponsors to begin their paediatric investigation plans (PIPs) earlier and design them in a way that can help expedite their completion (especially for the youngest age groups) and expanding clinical trial sites conducting paediatric TB research. There should also be advocacy towards ensuring that work on paediatric formulations begins much earlier in the drug development pathway. Data gaps should also be addressed earlier, in particular those highlighted by optimization of adult dosing studies and those related to younger age groups. Children living with HIV should be included in paediatric TB studies, and vice versa. Finally, flexible paediatric formulations

that can be used across indications should be prioritized, as should applications to extend the indication of these formulations and their use across age groups.

TAG proposes the creation of a platform trial such as those created in response to COVID-19 therapeutics development. A platform trial could use a master protocol focused on cutting edge approaches to expedite paediatric studies, which then could be amended to include investigations of novel drugs as they move through the pipeline and are ready for paediatric investigation (after phase IIa). The proposed name for such a trial is *Chasing Expedited and Equitable Treatment Access (CHEETA) for Children*.

**4. Communities of practice for paediatric drug resistant tuberculosis: essential partners for scaling up access to child – friendly products** - **Presenters:** Jennifer Furin (The Sentinel Project/Harvard University), Ivy Apolisi (The Sentinel Project/MSF Khayelitsha, South Africa) and Nirupa Misra (King Dinuzulu Hospital, South Africa)

The Sentinel Project described its role in creating communities of practice for the paediatric DR-TB space. The paediatric DR-TB space is small and, in the past, researchers often left children out of studies because they were less likely to transmit. Practitioners often feel isolated and unable to leverage resources or experiences to improve practice. Scientific literature on paediatric TB is comparatively little, and practical and logistical guidance has not been readily available in the past, so practitioners in the paediatric DR-TB space often miss out on innovations and benefits. The Sentinel Project was founded in 2011 to create a community of practice focused on the prevention and treatment of paediatric DR TB. It is made up of over 1,000 people in 73 countries and focuses on creating support and practical tools for practitioners in the field, enabling joint advocacy, and sharing of experience.

Sentinel works closely with GDF on the question: once drugs are available, how can countries, programmes, and organizations be supported to use them? Since 2018, Sentinel has helped 16 countries starting on new paediatric DR-TB formulations, bringing together various groups to pool procurement in the context of small orders. Sentinel has supported a further 46 countries on tools for these formulations and provides advice to practitioners on clinical management and monitoring. Smaller groups have especially benefitted from participating in Sentinel: if a group is too small to apply for a grant independently, Sentinel can bring groups together to apply and can help disperse funds to the grassroots and the frontline. Sentinel also provides training and support for field guides and serves as a forum where frontline people can have their work shared widely.

#### **Text Box 2: Practitioner Perspectives**

Sentinel Project community members from Khayelitsha and King Dinuzulu Hospitals in South Africa noted how beneficial new dispersible paediatric formulations have been in treating children living with DR-TB, as it is no longer necessary to put human resources toward manipulating adult formulations by cutting down and crushing up pills, nor do non-literate parents have to struggle with reading directions and measuring. Previously, they were using levofloxacin (Lfx), ethambutol (E), and pyrazinamide (Z) tablets, but changes to guidelines in 2019 reduced the usage of E and Z and now Lfx oral formulation is used, with caregivers and health workers very happy with this formulation. At King Dinuzulu hospital, health workers have been taste-testing Lfx, as children found the Lfx dispersible had a bad taste. Taste-testing adult formulations revealed that adult formulations also had a bad taste and that the dispersible was actually markedly better. The hospital is taking steps to deal with the taste issue by using masking agents and bringing in youth facilitators to carry out an acceptability study to understand how clients are finding child-friendly formulations in taste.

## **Key Points Discussed: Paediatric TB**

### Clarification of Roles with Respect to Research versus Prioritization and Evaluation

- There is a good understanding of PADO-TB's upstream work and TPMAT's roles in signalling product development, implementation and scale-up. There is cross-representation of members across both groups and the work of both organizations is ultimately guided by the TB Medicines Dashboard.
- Researchers noted that identifying and addressing research gaps involves additional steps and stakeholders (e.g., funders) that WHO/PADO may wish to include in their guidance document to ensure alignment on research priorities and in particular on funding priorities to address identified gaps.

### Alignment of TPMAT, PADO, and GAP-f

- WHO explained as background that the WHA put forth a resolution in 2016 for WHO to address the delays in paediatric formulation availability across all disease categories which often come 7 – 10 years after adult formulations. The WHO HIV team had lots of experience in paediatric drug optimization. It started inviting the TB team to meetings and requested TB to bring its existing optimization work under the umbrella of GAP-f.
- WHO clarified that GAP-f is a WHO-wide network under its science division that serves to encourage all areas of WHO to support and advocate for the development of paediatric formulations. Some disease control programmes—like TB—already have long-established organizations that do this work, so GAP-f exists to help where there are gaps via three main working groups: clinical research, product development and regulatory affairs, and product access and treatment delivery. It is not meant to duplicate effort.
- There was robust discussion amongst participants on approaches to sharing lessons learned and collaboration with PADO-TB and GAP-f to maximize effectiveness and minimize duplication of efforts. Internal notes and action points of that discussion will be followed up on by the respective TPMAT partners.

### Platform Trial on Paediatric TB Medicines

- There was consensus that *Chasing Expedited and Equitable Treatment Access for Children* (CHEETA) should be pushed forward.

## **Action Points: Paediatric TB**

- GDF and WHO GTB to discuss how best to share lessons learned with GAP-f and identify opportunities for collaboration without duplication.
- TAG to solicit further inputs on their proposal to accelerate TB research in children via a platform trial with relevant partners, including GAP-f.

## Annex 1: Final Meeting Agenda

<b>February 19, 2021</b> 8:00-11:00am New York / 2:00–5:00pm Geneva		
Chair: Brenda Waning		
14:00–14:05	Opening, Welcome, and Participant Introductions	
14:05–14:30	TPMAT Overview and Progress Updates Meeting objectives:  Session 1 <ul style="list-style-type: none"> <li>Summarize issues associated with nitrosamine impurities in rifapentine and rifampicin products; review actions taken to date as well as timeline for future actions.</li> <li>Identify nitrosamine-related risks to the TB medicine markets (both prevention and treatment), along with potential mitigation actions and lead organizations to implement the mitigation actions.</li> </ul> Session 2 <ul style="list-style-type: none"> <li>Describe actions taken and progress made on development and introduction of child-friendly TB medicines.</li> <li>Identify unmet needs/gaps in research and access to paediatric TB formulations and discuss what can be done to address these gaps.</li> </ul>	Brenda Waning (GDF)
Session 1. Nitrosamine Impurities		
14:30–14:45	Overview of WHO Prequalification approach to risk assessment of nitrosamine impurities in rifapentine and rifampicin	WHO PQ (TBC)
15:45–15:00	Updates on impurity messaging to Civil Society	TAG (Mike Frick) FACT (Thokozile Nkhoma) COWLHA (Edna Tembo)
15:00–15:40	<u>Facilitated Discussion</u> <ul style="list-style-type: none"> <li>What are the key identifiable risks to programmes? Supply?</li> <li>How can these risks be mitigated? Who can lead the mitigation actions?</li> <li>Agreed next steps and timelines</li> </ul>	GDF (Brian Kaiser)
Session 2. Paediatric TB		

15:40–15:50	Update on introduction and scale-up of TB formulations in children and stakeholder coordination	GDF (Brian Kaiser)
15:50–16:00	Update from PADO TB	WHO GTB (Tiziana Masini)
16:00-16:10	Opportunities to increase the speed of paediatric TB research	TAG (Lindsay McKenna)
16:10-16:20	Communities of practice for paediatric drug resistant tuberculosis: essential partners for scaling up access to child friendly products	The Sentinal Project (Jen Furin)
16:20-16:55	Facilitated Discussion <ul style="list-style-type: none"> <li>• How best to align with other stakeholders in the paediatric space?</li> <li>• Key action points and which partners will take those points forward</li> </ul>	TAG (Lindsay McKenna)
16:55-17:00	Meeting Wrap Up & Closure	GDF (Brenda Waning)

**Annex 2: Current Members of TPMAT (in alphabetical order)**

- Elizabeth Glaser Paediatric AIDS Foundation (EGPAF)
- Global Drug Facility (Stop TB Partnership)
- Global Fund
- KNCV Tuberculosis Foundation
- Médecins sans Frontières, Access Campaign
- Medicines Patent Pool
- Pan American Health Organization (PAHO)
- Partners in Health (PIH)
- Representatives of Country TB Programmes
- Results UK
- TB Civil Society Organizations
- TB Clinical Experts and Researchers
- The International Union Against TB and Lung Diseases (The Union)
- The Sentinel Project
- Treatment Action Group (TAG)
- UNICEF
- Unitaid
- United Nations Development Programme (UNDP)
- United States Agency for International Development (USAID)
- WHO Essential Medicines Programme (EMP)
- WHO Global TB Programme (GTBP)
- WHO Prequalification Team (PQT)

## Annex 3: List of Participants

### List of Participants

1. **Brenda Waning (Chair)**  
GDF Chief – Stop TB Partnership  
Geneva, Switzerland
2. **Cheri Vincent**  
Chief Infectious Diseases Division - USAID  
Washington DC, USA
3. **Thomas Chiang**  
Senior TB Technical Advisor - USAID  
Washington DC, USA
4. **Amy Piatek**  
Senior TB Technical Advisor - USAID  
Washington DC, USA
5. **Mukadi YaDiul**  
Medical Officer - USAID  
Washington DC, USA
6. **Charlotte Colvin**  
Senior TB Technical Advisor – USAID  
Washington DC, USA
7. **Brian Kaiser**  
Technical Officer, GDF – Stop TB  
Partnership  
Geneva, Switzerland
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#### Annex 4: Timeline of WHO Prequalification Unit - Medicines Assessment Team (PQT/MED) Strategy for Nitrosamine Impurities

April 2020	The WHO Prequalification Unit - Medicines Assessment Team (PQT/MED) put in place nitrosamine process in April last for manufacturers of API and medicines
December 31, 2020	<p>Risk evaluations should be carried out within 6 months of acceptance of PQ applications for all applications submitted <u>before</u> December 31, 2020</p> <p>For all submissions <u>after</u> December 31, 2020, risk evaluation should be carried out prior to submission</p> <p>If risk identified, confirmatory testing is to be carried out and PQT contacted regardless of the amount found</p> <p>If nitrosamine is detected, submissions of variations and mitigation plans should be submitted to PQT.</p>
April 2023	All of the above steps should be finalized

**From TPMAT Meeting Presentation:** *Overview of WHO Prequalification Approach to Risk Assessment of Nitrosamine Impurities in Rifapentine and Rifampicin (Ortega, Mubangizi and Zeleke)*

### Annex 5: Current Alignment of PADO, TPMAT, and GAP-F Activities across the Product Development Pipeline for Paediatric Formulations

From TPMAT Meeting Presentation: *Update from PADO TB (Masini)*

