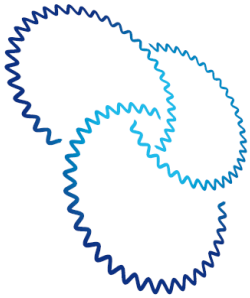

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The Medicines Patent Pool Foundation

TB Stewardship Report

November 28, 2016

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List of Abbreviations

AMR	Antimicrobial resistance
API	Active pharmaceutical ingredient
BDQ	Bedaquiline
BMS	Bristol-Myers Squibb
CAB	Community Advisory Board
DLM	Delamanid
CHAI	Clinton Health Access Initiative
DNDi	Drugs for Neglected Diseases initiative
EECA	Eastern Europe and Central Asia
EoI	Expression of Interest
ERP	Expert Review Panel
FDC	Fixed-dose combination
GARDP	Global Antibiotic Research and Development Partnership
GDF	Global Drug Facility
GMP	Good Manufacturing Practice
GNP+	Global Network for People Living with HIV
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICRC	International Committee of the Red Cross
IP	Intellectual property
LMICs	Low- and middle-income countries
MDR-TB	Multi-drug-resistant tuberculosis
MPP	Medicines Patent Pool
NTP	National treatment programme
PDP	Product Development Partnership
PEPFAR	President's Emergency Plan For AIDS Relief
PPM	Public-Private Mix
PQ	Prequalification
R&D	Research and development
SRA	Stringent Regulatory Authority
SSRN	Social Science Research Network
TB	Tuberculosis

UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
ViiV	ViiV Healthcare
WHA	World Health Assembly
WHO	World Health Organization

1. Executive Summary

Launched by UNITAID in 2010, the Medicines Patent Pool (MPP) is the only patent pool focused on the licensing of intellectual property (IP) to increase access to medicines in developing countries. Over the past several years, MPP has served as key implementer of UNITAID's pro-public health approach to the management of IP.[1] The MPP and its funder share a common mission of engaging in targeted market interventions to create positive health outcomes for low- and middle-income countries (LMICs). To date, the MPP has been successful in negotiating socially-responsible voluntary licences for 12 World Health Organization-recommended antiretrovirals and one new hepatitis C (HCV) antiviral. The terms and conditions of these non-exclusive, non-restrictive licences seek to ensure that the broadest number of countries can benefit from the delivery of quality, low-cost medicines.

In 2016, the MPP and UNITAID signed a Memorandum of Understanding to support the MPP's role in increasing access to HIV, HCV and TB treatments in developing countries. As part of this agreement, the MPP was asked to undertake the following study on the stewardship of new drugs for tuberculosis, specifically for multi-drug resistant TB (MDR-TB). This report acknowledges the importance of tackling three main public health challenges in combatting MDR-TB: improving the standard of care through the development of simpler, more affordable TB treatments and ensuring the availability of new and existing therapies while promoting the proper use of new TB medicines to prevent further development of resistance.

The MPP's stewardship report is based on extensive deskside research of the relevant literature surrounding the development and stewardship challenges facing antimicrobial resistance generally, and in TB specifically, as well as interviews with leading TB experts,

[1] UNITAID Strategy 2013-2016, April 2013; p. 28.

private sector leaders, intergovernmental organisations, product developers and academics. It seeks to provide an overview of key stewardship issues in TB, identifies ways in which the MPP could address these issues through public health licensing, and outlines potential terms and conditions that might be appropriate for TB licences. Importantly, the study summarises stewardship challenges that are beyond the MPP's purview and are best left to other public health actors. Interview questions focused on specific areas of manufacturing, regulatory oversight, control and distribution of new medicines, and patient use.

A summary of specific findings follows:

- The MPP should distinguish between stewardship-related mechanisms that are directly addressable in MPP licences (eg, quality standards, private vs public sector provision) and those that are not (eg, strengthening regulatory frameworks in developing countries, expanding the availability of diagnostics) and focus on the former.

- To promote quality standards, the MPP should continue to require licensees to meet international standards (WHO prequalification, Stringent Regulatory Agency approval), which includes a Good Manufacturing Practice (GMP) component in TB licences to provide guidance on wastage.

- In its approaches to TB licensing, the MPP should retain flexibility to permit incorporation of new learnings from the evolving field of antimicrobial stewardship. The current introduction of the new TB medicines bedaquiline and delamanid is providing valuable experience and lessons that could be incorporated into future MPP licences.

- The MPP should avoid being unduly prescriptive in the specific details of stewardship requirements, and should request that potential licensees develop a stewardship plan to which they are willing to be bound as part of the application process.

- To monitor best practices in marketing and promotion, the MPP will, as part of its Expression of Interest (EoI) process, ask potential licensees to submit binding marketing plans in line with the WHO's Ethical Criteria for Medicinal Drug Promotion and with national laws, as applicable. Moreover, the MPP will require additional information to be submitted as part of its EoI process for potential TB licences, including timelines for national registration and pricing plans.

- Although regulatory oversight is outside the scope of MPP-negotiated licences, the MPP will continue to require its licensees to comply with all applicable national laws and regulations, including pharmacovigilance requirements. These requirements can be specifically tailored to other stewardship-related laws that are implemented at the national level.

- In the area of procurement, the MPP will seek to collaborate closely with the Global Drug Facility (GDF) to ensure that the GDF stewardship-related safeguards are adapted, as appropriate, for use in MPP licences.

- Finally, given the heavy reliance of some countries on the private sector for the provision of TB treatment, the MPP should make its licensed TB drugs available to the private sector but in close consultation with National Treatment Programmes (NTPs) on mechanisms to ensure appropriate use.

The findings of the stewardship report confirm that the MPP can play a valuable role in countering misuse of TB treatments through provisions in its licences. The majority of interview respondents were very supportive of the MPP's entry into the field of TB and believed that the organisation's experience in negotiating HIV and HCV licences with already-established stewardship terms and conditions lends itself well to success in voluntary licensing for TB.

However, study findings confirm that the overall responsibility for stewardship programmes should lie with National Treatment Programmes, governments and international organisations tasked with providing guidance, funding and technical support. While the MPP licences can complement much broader efforts, many respondents felt that the MPP should avoid appearing to serve as a norm-setting body with respect to what constitutes appropriate stewardship standards.

2. Introduction

In the 2016-2020 Project Plan that forms part of the Memorandum of Understanding between UNITAID and the Medicines Patent Pool (MPP), the MPP agreed, at UNITAID's behest, to undertake a study on how voluntary licensing could incorporate terms improving the stewardship of new drugs for the treatment of tuberculosis (TB). This project stemmed from a recognition that the challenge in TB, and in particular in multi-drug-resistant TB (MDR-TB), is three-fold: (1) there is a need to improve the standard of care to make TB treatment safer, simpler, shorter and more affordable, and (2) there is a need to ensure the availability of new and existing therapies; but at the same time, (3) there is a need to ensure proper stewardship of existing and new TB medicines to prevent further development of resistance.[2]

In accordance with the Project Plan, this Report aims to do the following:

- Provide an overview of the key stewardship issues in TB (what they are, why they are important and how they interrelate to enhancing innovation, access and public health);

- Outline how the MPP may be able to address these issues through its public health licences, and provide a preliminary indication on how this may be done and how these could interact with other licensing provisions that may need to be developed in TB; and

[2] Medicines Patent Pool Foundation Project Plan "Expanding Access to Quality, Appropriate, Affordable, Safe and Efficacious Medicines and Technologies in Low- and Middle-Income Countries," p. 12. Submitted to UNITAID 10 March 2016.

- Provide a clear indication of which stewardship issues the MPP would not be able to address and how these could be addressed elsewhere.[3]

As described in the Project Plan, this Report is intended to assist both the MPP and other TB stakeholders in reaching a common understanding concerning the stewardship goals that can be pursued by the MPP. It also seeks to clearly identify which challenges/issues could potentially be addressed through the MPP's licensing process and which are beyond the scope of MPP's mandate, to help manage expectations from all sides. In developing this Report, the MPP sought extensive and detailed feedback from a wide range of stakeholders on how the MPP might contribute to broader stewardship efforts.

3. What is Stewardship?

In order to reach such a "common understanding," it was first necessary to decide upon a working definition of "stewardship." While there is no internationally recognised definition, the World Health Organization (WHO), in a Background Paper for a consultation of Member States and relevant partners for establishing a global development and stewardship framework to combat antimicrobial resistance (the "Background Paper"), put forth the following definition:

> *Antimicrobial stewardship can be defined as the promotion of appropriate use of antimicrobials while reducing their inappropriate use; improving patient outcomes; reducing microbial resistance; and decreasing the spread of infections caused by multidrug-resistant organisms. The ultimate aim of such stewardship is*

[3] Medicines Patent Pool Foundation Project Plan "Expanding Access to Quality, Appropriate, Affordable, Safe and Efficacious Medicines and Technologies in Low- and Middle-Income Countries," Section 2.3.1, p. 36. Submitted to UNITAID 10 March 2016.

to conserve the effectiveness of antimicrobial medicines by delaying the formation of resistance as long as possible through appropriate use.[4,5]

The Background Paper recognises the potential tension between the goals of stewardship and the promotion of access to medicines: "While a more lenient framework will fail to yield the desired conservation goals, provisions that are too strict might impede access to medicines."[6] Indeed, as clarified by the WHO Secretariat in a presentation during the Consultation of Member States and relevant partners, the aims of stewardship are best seen as one leg of a "policy tripod,"[7] with the development of new drugs and broad access to those drugs as the other two legs (see Figure 1).

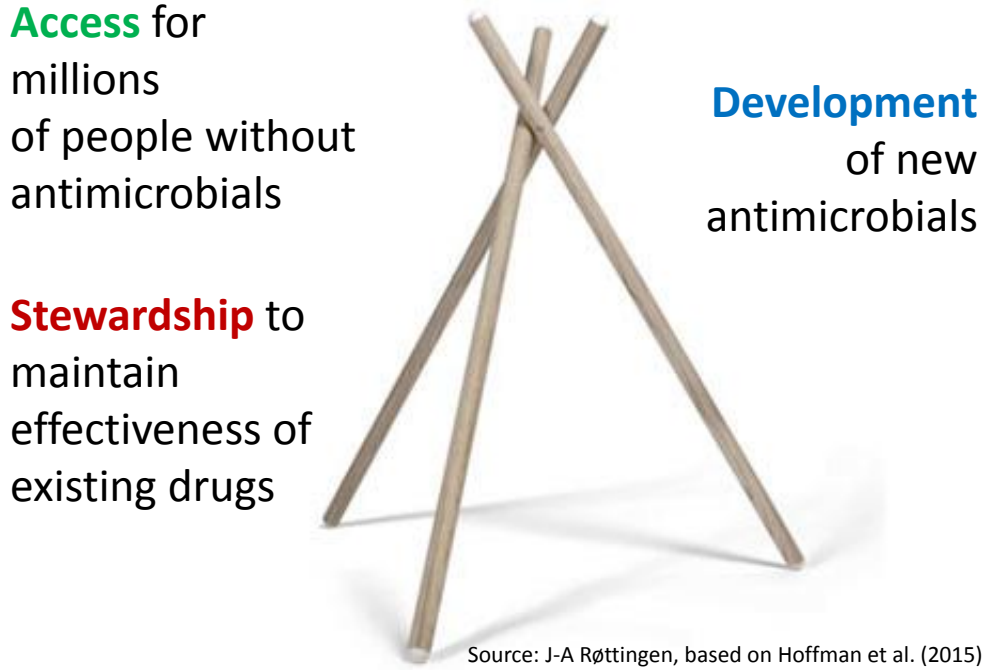
[4] Subsequent to the Consultation, the WHO prepared a report on this topic for the sixty-ninth World Health Assembly (WHA), which put forth a similar definition: "Stewardship describes the careful and responsible management of something entrusted to one's care. With respect to antimicrobials, careful management means their appropriate use to improve patient outcomes while minimizing the development and spread of resistance (Sixty-ninth World Health Assembly, Provisional Agenda Item 14.4; A69/24 Add. 1, 2016 May 13)."

[5] World Health Organization. Background Paper: "Consultation of Member States and relevant partners on options for establishing a global development and stewardship framework to combat antimicrobial resistance." Geneva, 29 February 2016 [cited 2016 Nov 14]. 9 p. Available from: http://www.who.int/phi/news/AMRbackground_document_consultation.pdf

[6] Ibid.

[7] Hoffman SJ and Outterson K. What Will It Take to Address the Global Threat of Antibiotic Resistance? Journal of Law, Medicine and Ethics Summer 2015 [cited 2016 Nov 24]; Boston Univ. School of Law, Public Law Research Paper No. 15-31. Available from SSRN: https://ssrn.com/abstract=2641060

Figure 1 – Policy Tripod



Source: J-A Røttingen, based on Hoffman et al. (2015)

Source of graphic: WHO antimicrobial resistance (AMR) consultation.[8]

In formulating the MPP's strategic approach to its intervention in TB, it is important to keep in mind all three legs of the policy tripod, recognising that there is inadequate research and development (R&D) activity for TB drugs – with just two new drugs (bedaquiline and delamanid) receiving approval within the past forty years – and that there are millions of people infected with TB who lack adequate access to the appropriate treatment.[9]

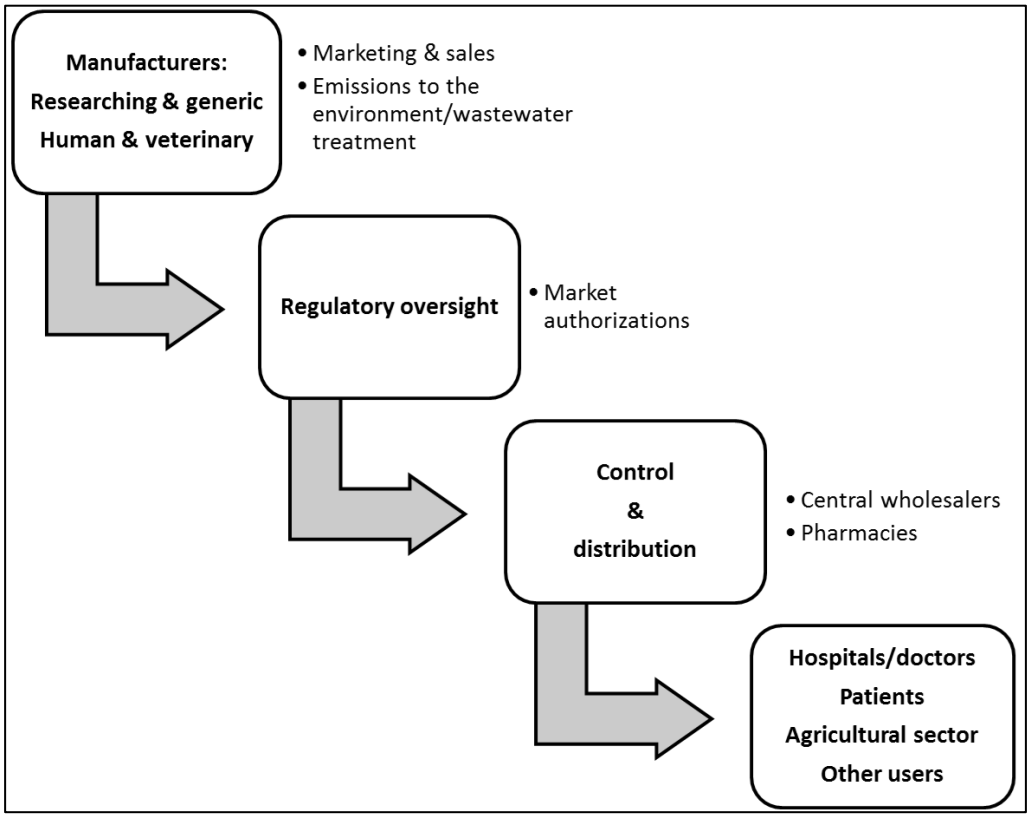
[8] Beyer P (WHO). Options for a global development and stewardship framework to combat AMR. Presented at WHO consultation of Member States and relevant partners. 2016 Feb 29 [cited 2016 Nov 16]; Geneva. Available from http://www.who.int/phi/news/amr_ppt_consultation2016-02-29.pdf?ua=1

[9] Frick M, Henry I and Lessem E. Falling Short of the Rights to Health and Scientific Progress: Inadequate TB Drug Research and Access. *Health and Human Rights Journal* 2016 [cited 2016 Nov 14];18(1). Available from https://www.hhrjournal.org/2016/06/falling-short-of-the-rights-to-health-and-scientific-progress-inadequate-tb-drug-research-and-access/

4. Stakeholder Interviews

In order to further explore how an MPP intervention in TB might contribute to broader efforts concerning stewardship of new TB drugs, the MPP interviewed a wide range of stakeholders, including governments, intergovernmental organisations, academics, originator and generic companies, representatives from civil society, and product development partnerships. A full list of the interviewees can be found in Annex I**.** In order to provide guidance and structure to the interviews, the MPP developed a questionnaire based on the four key points of intervention outlined in the Background Paper (see Figure 2). The central focus of the questionnaire was to obtain feedback and ideas on specific mechanisms/terms and conditions that the MPP might consider including in its licences for new TB drugs that could contribute to better stewardship. The questionnaire can be found in Annex II. To facilitate an open and frank discussion, respondents were assured that their responses would not be attributed. A summary of the feedback received is provided in Annex III.

Figure 2 – Four Key Points of Intervention



Source: WHO Background Paper.[10]

At each point of intervention, the MPP sought to obtain specific feedback from respondents about potential stewardship-related terms and conditions that might be incorporated into MPP licences. Further detail on the areas of inquiry can be found in Figure 3 below.

[10] World Health Organization, op. cit. (Background Paper).

Figure 3 – Stakeholder Consultations: Areas of Inquiry

Stakeholder Consultations – Areas of Inquiry			
Manufacturers	**Regulatory Oversight**	**Control and Distribution**	**End Users**
Quality requirements	Implication of national or regional bodies	Procurement (GDF)	Promoting rational use and adherence
Wastewater management	Potential incentives at the national level	Public vs private sector provision	Human vs animal use
Marketing and promotional practices			
Selection of licencees			

Finally, the MPP asked respondents to provide their feedback regarding the feasibility and wisdom of using intellectual property (IP) as a tool for the promotion of stewardship. A summary of the discussions, and of the MPP's initial thinking about how the feedback can be synthesised into an overall stewardship strategy, is presented in the following sections.

The MPP, in its current licences for HIV and HCV drugs, already includes certain obligations related to good stewardship that may be adopted or appropriately modified for use in TB licences. Examples of such provisions in existing MPP licences are provided in footnotes.[11]

5. Discussion

5.1 General observations

In addition to feedback on specific potential mechanisms to include in MPP licences for new TB drugs, several respondents provided general thoughts on how the MPP should approach its work on stewardship. Overall, respondents were very supportive of the MPP's entering into the field of TB, and felt that the MPP's approach of negotiating terms and conditions from a public-health perspective could play a positive role in both improving access and

[11] All of the MPP licence terms and conditions referenced herein can be accessed at http://www.medicinespatentpool.org/current-licences/.

promoting good stewardship. Some other common themes emerged from these discussions, which are detailed further below.

5.1.1 Distinguish between what MPP can and cannot do through its licences

In addition to the ongoing discussions at the World Health Assembly (WHA) regarding the possibility of establishing a Global Development and Stewardship Framework to combat antimicrobial resistance (AMR)[12,13], there is a large and growing body of literature[14,15,16,17] recognising the need to both urgently finance the development of new antimicrobials (including for TB) and implement mechanisms for their responsible stewardship.[18] Many of the most important mechanisms for promoting the appropriate use of antimicrobials, such as clear treatment guidelines, proper training for healthcare professionals and the availability of appropriate diagnostic tools,[19] are beyond the scope of the terms and conditions included in a manufacturing licence for a TB drug. Several respondents made this

[12] World Health Assembly Resolution WHA 67.25, 2014 May 24. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R25-en.pdf

[13] World Health Assembly Resolution WHA 68.7, 2015 May 26. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R7-en.pdf

[14] Balasageram M, Clift C, and Røttingen JA. The Global Innovation Model for Antibiotics needs Reinvention. J Law Med Ethics 2015 summer;43 Suppl 3:22-6. doi: 10.1111/jlme.12270.

[15] Clift C, Gopinathan U, Morel C, Outterson K, Røttingen JA and So A, editors. Towards a New Global Business Model for Antibiotics. Delinking Revenues from Sales. Report from the Chatham House Working Group on New Antibiotic Business Models. London: Chatham House; 2015 Oct [cited 2016 Nov 14]. 46 p. Available from: https://www.chathamhouse.org/publication/towards-new-global-business-model-antibiotics-delinking-revenues-sales

[16] Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al. Antibiotic resistance - the need for global solutions. *Lancet Infectious Diseases* 2013;13(12):1057–98. Epub 2013 Nov 21 [cited 2016 Nov 24]. doi: 10.1016/S1473-3099(13)70318-9 pmid:24252483.

[17] Outterson K, Gopinathan U, Clift C, So AD, Morel CM and Røttingen JA. Delinking Investment in Antibiotic Research and Development from Sales Revenues. The Challenges of Transforming a Promising Idea into Reality. *PLOS Med* 2016 Jun 14;13(6):e1002043. Available from: http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002043

[18] O'Neil J, editor. Tackling Drug Resistant Infections Globally: Final Report and Recommendations. London: The Review on Antimicrobial Resistance, May 2016 [cited 2016 Nov 14]. 84 p. Page 52. Available from: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

[19] Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al, op. cit.

observation, and stressed the need for the MPP to distinguish between stewardship-related mechanisms that are directly addressable in MPP licences (eg, quality standards, private vs public sector provision) and those that are not (eg, strengthening regulatory frameworks in developing countries, expanding the availability of diagnostics). While the MPP should not ignore the importance of these other mechanisms, these respondents advised that the MPP should focus on issues directly addressable in its licences.

5.1.2 Make reference to external standards and norms

Closely related to the point above, more than one respondent observed that the main responsibility for ensuring the proper stewardship of new TB drugs lies ultimately with national governments and the various international organisations tasked with providing guidance and support to them. While the MPP, through its licences, could play a complementary role to these efforts, these respondents felt that the MPP should avoid appearing to serve as a norm-setting body with respect to what constitutes appropriate stewardship standards. The MPP itself recognises that it lacks both the internal capacity and the global mandate to serve such a function, and already makes reference, whenever possible, to external norms with some global legitimacy when defining standards in its licences. For example, rather than making an assessment of whether its licensees are meeting acceptable quality standards, the MPP makes reference to WHO pre-qualification (PQ) or Stringent Regulatory Authority (SRA) standards, which enjoy broad acceptance within the international community as appropriate standards.[20] The MPP should seek to do the same with other stewardship-related criteria.

[20] UNITAID only funds products that have been prequalified by the WHO or by a stringent national regulatory authority. UNITAID's guideline for quality assurance of health products is available from: http://unitaid.org/images/events/UNITAID_grantee_forum-2014/UNITAID_QA.pdf

Implementers of programs for AIDS, TB or malaria who want to use Global Fund grants to purchase medicines must ensure that those pharmaceutical products meet the Global Fund's quality standards as set out in the

5.1.3 Retain flexibility to incorporate new learnings

As mentioned, there are several ongoing discussions and initiatives at the WHA and elsewhere concerning the development and stewardship of antimicrobials. The Final Report of the Review on Antimicrobial Resistance, for instance, proposes dramatic new financial incentives to fund the development of new antimicrobials, including for TB.[21] In exchange for the new funding for R&D for these drugs, stewardship and access conditions would be built-in.[22] The WHO and the Drugs for Neglected Diseases initiative (DND*i*) recently launched the Global Antibiotic Research and Development Partnership (GARDP), designed to address the AMR challenge through the development of new antibiotics.[23] As it prepares for its work, the GARDP is also engaging in an exercise of identifying what might constitute appropriate stewardship mechanisms. In short, the field of antimicrobial stewardship is a quickly developing one, and the MPP is likely to benefit from the future learnings of others (and vice versa). Similarly, the current introduction of the new TB medicines bedaquiline and delamanid is also providing valuable experience and lessons that could be incorporated into future MPP licences. Consequently, some respondents expressed the need for the MPP to avoid being overly prescriptive at this stage, and to retain some flexibility in its licences to incorporate future learnings. This could be done, for example, by incorporating periodic review provisions within the licences to give the parties an opportunity to take stock of new developments in TB drug stewardship.

Quality Assurance Policy for Pharmaceutical Products. These can be accessed at: http://www.theglobalfund.org/en/sourcing/qa/medicines/

[21] O'Neil J, editor. Op. cit., p. 52.
[22] Ibid.
[23] Press release: Global Antibiotic Research and Development Partnership garners key financial support for launch [internet]. Geneva: Drugs for Neglected Diseases initiative; 2016 May 24 [cited 2016 Nov 24]. Available from: http://www.dndi.org/2016/media-centre/press-releases/gard-garners-key-support-for-launch/

5.1.4 Licences need to be attractive for manufacturers

In addition to the previously-mentioned potential tension between stewardship and access considerations, several respondents also highlighted another area in which an appropriate balance should be sought: crafting licences that are responsive to stewardship concerns, but remain sufficiently attractive for potential manufacturers to consider. It would certainly be counterproductive in terms of both stewardship and access goals if a licence for manufacturing a new TB drug were so restrictive that no reputable generic pharmaceutical company would accept its terms. Given the national scope of patent protection (to be discussed further in 5.6, below), an overly restrictive licence on a new TB drug could place an MPP licensee at an undue competitive disadvantage vis-à-vis other manufacturers operating in a jurisdiction where the product might not be patented and thus not subject to similar stewardship obligations. In light of this, one respondent suggested that rather than spelling out all stewardship obligations in advance, it might be preferable to outline broad principles of stewardship and to ask potential licensees, through the MPP's Expression of Interest (EoI) process, to submit to the MPP a stewardship plan to which they would be willing to be bound. This would ensure that the obligations are those that licensees are willing to accept, while potentially harnessing the competitive nature of seeking an MPP licence to create a "race to the top" dynamic with regard to stewardship efforts.

5.1.5 Licences need to contribute to sustainable access

Bearing in mind the policy tripod in Figure 1, it is important to ensure that MPP licences, while helping to address certain stewardship concerns, remain a mechanism that enables affordable access to medicines to those in need. A number of respondents alluded to the use of overly restrictive mechanisms for MDR-TB treatments in the past (eg the former Green Light Committee in its previous role) that were felt to unduly limit access in a number of countries. Maintaining the right balance will be important to ensuring that MPP licences seek to contribute to all three pillars of the policy tripod.

Key Conclusions:

As the MPP develops its overall strategy and approach to stewardship, it will do the following:

- ***Distinguish between stewardship-related obligations that are directly addressable in MPP-negotiated licences and those that are not, and focus on the former;***
- ***When formulating stewardship-related obligations, make reference to external norms and standards that enjoy a wide degree of international legitimacy;***
- ***Retain flexibility in MPP licences in order to incorporate new developments in the field of antimicrobial stewardship and new lessons learnt in the introduction of the new TB products (eg, through periodic review provisions);***
- ***Avoid being unduly prescriptive in the specific details of stewardship requirements; require potential licensees to develop a stewardship plan to which they are willing to be bound as part of the application process for an MPP licence; and***
- ***Seek to ensure that MPP licences contribute to both good stewardship and sustainable access.***

5.2 Stewardship issues relating to manufacturers

The first point of intervention identified in the Background Paper – the manufacturing stage – represents the area in which the MPP could exert the most direct influence on drug manufacturers, and potentially on distributors, through its licences.[24] It also represents an

[24] It may be the case that for certain TB drugs with small volumes spread out over several countries, the identities of the manufacturers and distributors will be different: a drug company with geographical reach that is wider than that of a company specialised in TB drug manufacturing may take over distribution in certain areas. However, the distributors will also need to be responsible for certain stewardship provisions (eg, marketing plans, compliance with national regulations/treatment guidelines). This can be accomplished by having both the manufacturer and the distributor become MPP licensees, or through a mechanism in the manufacturer licence whereby the manufacturer will ensure that distributors are also bound by the terms of the licence. See, for example, the MPP-Gilead Form Sublicence Agreement, section 2.5(d)(ii): "If Licensee enters

area in which the MPP already includes obligations in its licences for HIV and HCV products that are relevant to stewardship.

5.2.1 Quality standards

Ensuring that a drug meets quality standards (ie, that it is safe and effective, contains the correct amount of active ingredient, has a stable shelf-life, and is manufactured in accordance with Good Manufacturing Practices (GMP)) is a central pillar of ensuring responsible stewardship.[25] In its licences for HIV and HCV products, the MPP requires that all licensees manufacture the product in a manner consistent with WHO pre-qualification (PQ) or Stringent Regulatory Authority (SRA) standards, or approval through an Expert Review Panel (ERP).[26] This is consistent with the standards used by the Global Fund to Fight HIV, Tuberculosis and Malaria (the Global Fund), UNITAID and the Global Drug Facility (GDF), and most respondents felt that it was appropriate to continue this requirement in the MPP's TB licences, given the importance of ensuring quality drugs in promoting good stewardship.

Several respondents did point out, however, that the global market share of TB products meeting these quality criteria would be smaller than that in the HIV market, as the share of TB drugs purchased with donor funding was smaller. This is because large middle-income

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into an agreement with any Third Party Reseller, then Licensee…shall certify that its arrangement with such Third Party Reseller is consistent with the terms and conditions of this Agreement."

[25] Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al. Op. cit.

[26] For instance, the quality provision in the MPP-ViiV Form Sublicense for dolutegravir, in section 4.2, provides as follows:

Licensee agrees that it will manufacture Raw Materials and Product in a manner consistent with (i) World Health Organization ("WHO") pre-qualification standards; or (ii) the standards of any Stringent Regulatory Authority ("SRA"), defined as regulatory authorities which are members, observers or associates of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, as may be updated from time to time. Where such approvals are not yet available, the Licensee will obtain temporary approval through a WHO Expert Review Panel, as appropriate and if applicable.

A similar provision can be included in MPP licences covering TB products.

countries such as Brazil, Russia and South Africa do not rely on donor funding for much of their TB drug needs, and thus do not require the products that they procure locally to meet these quality requirements. This, of course, does not necessarily mean that these products are of poor quality; some respondents opined that the Brazilian and South African regulatory requirements were just as stringent as WHO PQ or SRA standards.

Key conclusions:

- ***The MPP recognises the central importance of ensuring the provision of quality medicines for good stewardship, and will continue with its policy of requiring WHO PQ, SRA approval, or ERP certification (where appropriate).***

- ***The MPP will monitor for any developments that might expand the list of national regulatory authorities that may be considered as SRAs by international public health organisations such as UNITAID, the Global Fund and the Global Drug Facility.***

5.2.2 Release of active pharmaceutical ingredients into the environment

The Final Report of the Review on AMR observed that improper treatment of wastewater by manufacturers of antibacterial active pharmaceutical ingredients (APIs) and the resultant release of the APIs into the local environment can act as a "driver for the development of drug resistance, creating environmental reservoirs of antibiotic-resistant bacteria."[27] There was some disagreement among respondents about whether this was of specific concern in the TB context. Some downplayed the danger in TB, noting that the transmission of TB generally does not occur through consumption of contaminated groundwater. Others felt that the matter was nevertheless of some concern, as the consumption of groundwater containing trace amounts of a TB drug API may cause the host to develop resistance to that drug.

[27] O'Neil J, editor. Op. cit., p. 30.

Regardless of the magnitude of the risk in the TB context, many respondents felt that caution was warranted, that the MPP should seek to refer to an external norm governing API discharge into the environment. However, as the AMR Review Report observed, there are "no, or very few, standards for API discharge and limited systematic monitoring of discharge anywhere in the world."[28] The WHO GMP guidance document for API manufacturers does state that waste "should be disposed of in a safe, timely and sanitary manner."[29] Thus, MPP's current quality policy of requiring WHO PQ/SRA approval does include a GMP component that is relevant to wastewater management.

Key conclusions:

- ***The MPP's current quality policy does include a GMP component that provides guidance to licensees on disposal of waste products, and this policy will be maintained.***

- ***The MPP will continue to monitor the landscape for the development and agreement of more rigorous and/or detailed standards for acceptable levels of API discharge. Any such developments will be incorporated into MPP licence agreements, as appropriate, during the periodic reviews that are built into MPP licences for TB drugs.***

5.2.3 Marketing and promotional practices

The danger of overuse of an antibiotic arising from the aggressive sales promotion and over-marketing of a drug[30] is a concern that has been voiced in the broader AMR context. Respondents were asked to provide their feedback as to whether this was of specific

[28] O'Neil J, editor. Op. cit., p. 30.
[29] World Health Organization. WHO good manufacturing practices for active pharmaceutical ingredients. Geneva: World Health Organization; 2010 [cited 2016 Nov 16]. (WHO Technical Report Series, No 957) p. 142. Available from: http://www.who.int/medicines/areas/quality_safety/quality_assurance/GMPActivePharmaceuticalIngredientsTRS957Annex2.pdf?ua=1
[30] Clift C, Gopinathan U, Morel C, Outterson K, Røttingen JA and So A, editors. Op. cit.

concern in the TB context, and whether the MPP should consider placing some limitations on the types of marketing and promotional activities that are allowed in relation to products made under MPP licences. Respondents felt that over-marketing of TB drugs was less of a concern in countries where TB treatment is available predominantly or exclusively through the public sector, such as Brazil and South Africa. In these cases, the availability of clear treatment guidelines and national procurement would make inappropriate marketing less problematic. However, in countries such as India, where there is considerable private sector involvement in the provision of TB care, respondents did agree that aggressive marketing could be a concern. At a minimum, some respondents felt that the MPP should allow marketing only in accordance with the approved label and only in a manner consistent with national rules and regulations.

The Lancet Commission on Essential Medicines recently observed that the WHO's Ethical Criteria for Medicinal Drug Promotion remain the "gold standard" for controlling pharmaceutical manufacturers' promotional activities,[31] and the MPP could require compliance with such guidelines in its licences. One respondent also suggested that the MPP could ask potential licensees to develop a marketing plan as part of the application process for an MPP licence, as discussed above in more general terms in 5.1.4. Another respondent felt that it was particularly important to allow concerned third parties the ability to bring inappropriate marketing practices to the MPP's attention. This respondent suggested that the MPP incorporate a "whistleblower" mechanism into its licences, whereby any third party could bring suspected instances of inappropriate activity to the MPP's attention, which would trigger further investigation by the MPP and potential remedial action.

[31] Wirtz VJ, Hogerzeil HV, Gray AL, Bigdeli M, de Joncheere CP, Ewen MA et al. Essential Medicines for Universal Health Coverage. The Lancet Commissions. Lancet [internet]. 2016 November 07 [cited 2016 Nov 24]. Available from http://dx.doi.org/10.1016/S0140-6736(16)31599-9,

Key conclusions:

- ***The MPP will, as part of its Expression of Interest process, ask potential licensees to submit marketing plans in line with the recommendations set out in the WHO's Ethical Criteria for Medicinal Drug Promotion and with national laws and regulations;***

- ***These marketing plans will become binding obligations upon the licensees, along with a potential "whistleblower" mechanism that will allow concerned third parties to bring potential suspected violations to the attention of the MPP;***

- ***In the event that an investigation triggered by a whistleblower reveals improper conduct by the licensee, the MPP will take appropriate remedial action under the licence, up to and including termination of the licence.***

5.2.4 Selection of licensees

For its HIV and HCV licences, the MPP selects licensees through its Expression of Interest (EoI) system, which allows the MPP to assess the potential licensee's ability to promptly bring a quality-assured product to market at an affordable price in the countries included in the licence.[32] Respondents generally felt that the criteria that the MPP currently uses for evaluating licensees (eg, ability to obtain WHO PQ/SRA approval, ability to make fixed-dose combinations (FDCs), manufacturing capacity) were also fit for purpose in evaluating TB licensees. However, given the specific stewardship concerns in TB, some respondents felt that the EoI system could be leveraged to require interested licensees to submit additional information, such as timelines for submitting for national registration, marketing plans (as discussed above in 5.2.3), and information relating to the licensee's track record in promptly and affordably responding to orders.

Depending on the product, however, some respondents felt that the number of licensees that the MPP should select would generally have to be smaller than for some of MPP's HIV

[32] See http://www.medicinespatentpool.org/expressions-of-interest/.

product licensees (eg, for dolutegravir, the MPP currently has nine licensees), although there was wide agreement that the MPP should avoid situations of relying on a single supplier. The appropriate number would have to be based on realistic market projections, and in cases where the market is projected to be very small, some respondents felt that it might be appropriate for the MPP to consider including provisions to ensure affordability of the product.[33] However, one respondent made the important observation that it was by no means guaranteed that the market for new TB drugs would remain small, especially if and when a "pan-TB" regimen, effective against both drug-susceptible and drug-resistant TB, is developed. In its HIV licences, the MPP has not generally included specific guidance on the pricing of products, as the model relies on harnessing competition among manufacturers to achieve low prices. Depending on the underlying market projections for a particular product, and subject to the results of negotiations with the potential licensors, the MPP could consider continuing with this approach or including more concrete measures of affordability. Some respondents suggested that such measures could involve, for example, specifying what a maximum allowable price would be under the agreement, or adopting a "cost-plus" model, where the licensee is allowed to recoup the cost of goods and production plus a reasonable margin.

Key conclusions:

- ***The MPP will continue using its EoI system to evaluate and select licensees in TB, determining the precise number of licensees in accordance with market projections for a particular product developed in collaboration with WHO and other experts;***

- ***The MPP will require additional information to be submitted as part of the EoI process for potential TB licensees, including proposed timelines for national***

[33] The MPP currently includes broad language on affordability in some of its licences: for example, in the BMS licence for daclastavir, section 4(c) states: "In recognition of the humanitarian objectives of this Sublicense Agreement, the Sublicensee also will use all reasonable efforts to promote the affordable access to the Licensed Products in the Territory."

registration, marketing plans, and information relating to the licensee's track record in promptly and affordably responding to product orders;

- ***The MPP will make a case-by-case determination as to whether, in the event that only a few licensees are appropriate (or interested), to include provisions relating to affordability of the product.***

5.3 Regulatory issues

The Background Paper discusses the possibility of incorporating certain measures aimed at ensuring proper stewardship into national regulatory marketing authorisations, including:

- Limiting prescription of dispensing to certified institutions, trained providers, or specific healthcare settings;

- Requiring demonstration of need through clinical algorithm or diagnostic test findings; and

- Monitoring though a clinical registry of treated patients.[34]

Respondents generally agreed that such mechanisms, if implemented at the national level, could be helpful in promoting good stewardship. However, they generally also agreed that this was an area largely outside the MPP's direct control, as it would require action and implementation by the national authorities and not by the MPP or its licensees. Nevertheless, in the event that stewardship-related regulations are implemented at the national level, the MPP can, in line with its current practice, require its licensees to abide by all applicable national laws and regulations and to comply with all the conditions under

[34] World Health Organization, op. cit. (Background Paper)

which national marketing authorization was provided by the national regulatory authority.[35] Such a provision can be specifically adapted to any stewardship-related national laws, regulations, or product-specific approvals that may be introduced. For instance, a number of MPP licences – in particular those for recently-approved products – contain a specific reference to national pharmacovigilance requirements, and require that MPP licensees comply with any local requirements for the reporting of adverse reactions to the appropriate authorities.[36]

Key conclusions:

- ***Regulatory efforts at improving stewardship, while important, are largely outside the direct control of MPP-negotiated licences;***

- ***However, the MPP can, and does, require its licensees to comply with all applicable national laws and regulations, including pharmacovigilance requirements. These requirements can be specifically tailored to other stewardship-related laws that are implemented at the national level. In the event that licensees do not comply with such requirements, the MPP will take appropriate remedial action under the licence, up to and including termination of the licence.***

5.4 Control and distribution

5.4.1 Procurement

An important share of global TB drug procurement is conducted through the Global Drug Facility (GDF), which accounts for approximately 20% of public-sector market share for first-

[35] For example, in the MPP-ViiV Form Sublicence Agreement for dolutegravir, section 4.3 states: "The Licensee will obtain from the relevant authorities in the Territory and maintain in force, as appropriate, all health registrations, permissions, consents and regulatory authorisations relating to the importation, manufacture and sale of the Products…"

[36] See, for example, the MPP-BMS Form Sublicence Agreement for daclatasvir, section 6.1: "The Sublicensee will, in accordance with its standard protocols, maintain effective and reliable systems for receiving and tabulating any reports of adverse reactions to the Licensed Products and to report such information on a timely basis to the relevant regulatory authorities. The Sublicensee shall be responsible for fulfilling all required reporting responsibilities under applicable laws and regulations within the Territory."

line TB drugs and 36% of market share for second-line drugs.[37] Many of the services that the GDF provides are important for stewardship, including the provision of competitively-priced, quality-assured medicines, product standardisation, and technical assistance to national treatment programmes.[38] In addition, both Janssen and Otsuka have made their new TB drugs, bedaquiline and delamanid, available to eligible countries through the GDF[39]. As part of its implementation of the bedaquiline donation programme, the GDF requires the National TB Treatment Programme (NTP) requesting bedaquiline to sign a form certifying that it will adhere to the five key principles outlined by the WHO's Interim Policy Guidance on the appropriate use of bedaquiline.[40, 41]

Given the central role that the GDF plays in global TB drug procurement and the steps that it takes to ensure that quality-assured drugs are used responsibly, respondents were asked whether the MPP should consider, for example, requiring MPP licensees to supply only to GDF-mediated tenders. Although there was general agreement that the services provided through the GDF were important for both stewardship and access, many respondents observed that it was largely (although not exclusively) donor-funded TB programmes that were procuring their drugs through the GDF. Self-financing middle-income countries with

[37] Lunte, K (Global Drug Facility). Barriers in accessing and scaling up of anti-TB medicines in EECA Region. Presented at the Eastern Europe and Central Asia Regional Consultation on Expanding Access to Affordable and Quality-assured Antiretroviral and Antituberculosis Medicines. 2016 Nov 02; Minsk, Belarus. Presentation available on request from the author.

[38] Matiru R and Ryan T. The Global Drug Facility: a unique, holistic and pioneering approach to drug procurement and management. *Bulletin of the World Health Organization 2007*;85:348-53.

[39] Press release: Stop TB Partnership's Global Drug Facility jumpstarts access to new drugs for MDR-TB with innovative public-private partnerships [internet]. Geneva: Stop TB Partnership; 2016 Feb 24 [cited 2016 Nov 14]. Available from: http://www.stoptb.org/news/stories/2016/ns16_005.asp

[40] The five conditions are: (1) effective treatment and monitoring; (2) proper patient inclusion; (3) informed consent; (4) adherence to WHO recommendations; and (5) active pharmacovigilance and management of adverse events [cited 2016 Nov 14]. Available from: http://www.stoptb.org/assets/documents/gdf/drugsupply/Bedaquiline%20Donation%20%20Annex%201%20and%20SAE-ADR%20Form.doc

[41] World Health Organization. The use of bedaquiline in multidrug-resistant tuberculosis: Interim policy guidance. Geneva: World Health Organization; 2013 [cited 2016 Nov 14]. Available from: http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf?ua=1

large TB burdens generally procure directly rather than through the GDF, and thus these respondents felt that limiting availability through the GDF would result in an unacceptably high number of people not having access. However, respondents felt that it would be important for the MPP to work closely with the GDF to explore how some of the stewardship-related safeguards that the GDF implements in the procurement and distribution of new TB drugs could be adapted into standards in MPP licences. For example, specific reference could be made to WHO policy guidance documents for any new TB drug, or product standardisation requirements could be harmonised.

Key conclusions:

- ***The MPP will seek to collaborate closely with the GDF to ensure that the stewardship-related safeguards that the GDF implements are adapted, as appropriate, for use in MPP licences and harmonised;***

- ***Specifically, for any new TB drugs for which the WHO issues policy guidance, the MPP will explore requiring licensees to obtain from purchasers a commitment similar to that required by GDF for its bedaquiline donation programme.***

5.4.2 Public- vs private-sector provision

While some countries have strong NTPs that provide all or most TB care in that country, others rely to a greater or lesser extent on the private sector. Several respondents cited India as an instructive example of the latter. One study estimated that as many as 2.2 million TB patients in India were treated in the private sector in 2014, as compared to 1.42 million in the public sector.[42] Thus, for countries such as India with a heavy reliance on the private sector, there needs to be availability of TB drugs in both the public and private sectors.

[42] Arinaminpathy N, Batra D, Khaparde S, Vualnam T, Maheshwari N, Sharma L et al. The number of privately treated tuberculosis cases in India: an estimation from drug sales data. Lancet Infect Dis 2016;16(11):1255-60. Available from: http://dx.doi.org/10.1016/S1473-3099(16)30259-6

However, respondents voiced concern regarding the quality of care in many private health clinics. One study in Mumbai, India found that less than 6% of private clinicians were able to write a prescription for a correct TB regimen.[43]

Thus, while both the public and private sectors need to have access to the correct TB drugs and regimens, respondents felt that for the private sector some measure of control was needed to ensure that the drugs would be prescribed and used correctly.[44] Respondents pointed out the importance of the Public-Private Mix (PPM) initiative at the WHO, which fosters collaboration between NTPs and private sector care providers to ensure that proper guidance is provided and the right diagnostic tests are available.[45] One respondent suggested that in the interest of ensuring that private-sector care providers were in contact with the NTP under the PPM framework, the MPP should only authorise sales to entities that the NTP in each country identified as eligible. While this could be an interesting approach,

[43] Udwadia ZF, Pinto LM, Uplekar MW. Tuberculosis Management by Private Practitioners in Mumbai, India: Has Anything Changed in Two Decades? *Plos One* 2010 Aug 9;5(8):e12023. Available from: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0012023

[44] The MPP has introduced internal country segmentation between the public and private sectors in one of its licences for HIV, adopting a broad definition of the "public" sector to include not just the NTP, but also a variety of non-profit and humanitarian actors. The MPP-ViiV Form Sublicence Agreement for dolutegravir defines the "Public Market" in section 1.30 as:

"the following organisations to the extent that they are not for profit organisations: (i) Governments including without limitation government ministries and agencies, together with government-funded institutions and programs, such as state-run hospitals and prison services in those countries; (ii) NGOs including without limitation those recognized by the applicable local government ministry; (iii) UN-related organizations working for or in those countries, including but not limited to UNDP and UNICEF; (iv) Not-for-profit organizations including without limitation, Médecins Sans Frontières, Save the Children, OXFAM and the International Committee of the Red Cross (ICRC); (v) Funding mechanisms and programs funded by such mechanisms, including without limitation, UNITAID, PEPFAR, USAID, Global Fund, etc; and agencies based outside of an applicable country to the extent that they are supporting implementation locally in an applicable country, and (b) nominally for profit procurement organisations but only to the extent that such procurements are supporting not-for-profit treatment programmes as described in (a) of this Clause."

Such a provision could potentially be adapted for use in TB, in order to capture the types of private sector entities to whom MPP licensees may make their products available.

[45] More details on the Public-Private Mix initiative can be accessed at: http://www.who.int/tb/areas-of-work/engaging-care-providers/public-private-mix/about/en/

others have indicated the logistical difficulties for its implementation in countries with substantial private sector TB care, where national TB programs may have limited capacity to play that gate-keeping role. With the gradual and controlled introduction of the new TB medicines in such countries (eg, bedaquiline in India), practices will be evolving in this area, with active roles for both the NTPs and the regulatory authorities. The MPP will closely follow such developments, and will work closely with NTPs in ensuring that there is sufficient visibility as to which private-sector providers are procuring the new drugs.

Key conclusions:

- ***Given the heavy reliance on the private sector for the provision of TB treatment in some countries, it would not be appropriate for the MPP to fully restrict access to its licensed TB drugs to the public sector only;***
- ***The MPP will work closely with key NTPs to identify the best mechanisms by which to make the products available in the private sector;***
- ***The MPP will closely monitor any country-level developments regarding the introduction of new TB medicines, and will work to ensure that its licences are harmonised with such efforts.***

5.5 End users

5.5.1 Promoting rational use and better adherence

Respondents were asked whether the MPP should consider requirements concerning formulation or packaging that would contribute towards rational use and better adherence by the patient. As a general matter, respondents felt that fixed-dose combinations (FDCs) are useful in simplifying treatment and improving adherence. However, with the new TB drugs presently available – bedaquiline and delamanid – there are insufficient data concerning other potential components of co-formulations. The same is true for MDR-TB more generally. It seems unlikely that there will be sufficient data in the near future to be

able to determine which FDCs should be developed, and different people with different resistance patterns would in any case require different regimens. There are a number of studies ongoing that may provide greater clarity on this in the coming years,[46.47,48] and one respondent suggested that the MPP could build in a periodic review mechanism to incorporate new knowledge into the licence agreements.

Looking beyond bedaquiline and delamanid, one respondent stated that ideally, future TB treatments would be developed and approved as full regimens and not as single agents. In such cases, it would be important for the MPP to plan to license the full regimens (preferably as FDCs), without granting licensees the ability to market the individual components. This would be done in consultation with the WHO to ensure that licences are in line with WHO guidance for introduction and use of such new regimens. Respondents advised that whatever requirements the MPP might choose with respect to packaging and co-formulation be harmonised with the GDF's product standardisation efforts.[49]

Key conclusions:

- ***Although FDCs are generally preferable for TB treatment, there is limited knowledge regarding the ideal regimen for the new TB drugs currently on the***

[46] Leading medical organisations team up to bring treatments to those in need [internet]. Geneva: Médecins Sans Frontières; 2015 Mar 19 [cited 2016 Nov 14]. Available from: http://www.msf.org/en/article/leading-medical-organizations-team-bring-new-tb-treatments-those-need

[47] STREAM clinical trial to test first all-oral MDR-TB treatment regimen [internet]. Paris: International Union Against Tuberculosis and Lung Disease [cited 2016 Nov 14]. Available from: http://www.theunion.org/what-we-do/research/clinical-trials

[48] The TB Alliance initiated the Nix trial, which began in Q2 2014. Details of the trial can be found at https://www.tballiance.org/portfolio/trial/5089

[49] See GDF Products list, available at http://www.stoptb.org/gdf/drugsupply/drugs_available.asp: "GDF has adopted standards for blister design which specify the layout, materials, markings and color coding, where necessary that should be used. The blister packs offer similar shelf life as loose drugs at same or lower costs, help health workers identify the drugs needed, provide better protection for the tablets once the container is opened and can be used in all types of health facilities."

market. In the event that knowledge regarding optimal regimens becomes available in the coming years, the MPP will incorporate such knowledge into its agreements through a periodic review mechanism;

- ***In addition to seeking public health-oriented licences for single agent TB compounds that may become priorities for licensing, the MPP will aim, for future TB regimens that are developed and approved as regimens, to in- and out-license them as full regimens, in consultation with the WHO and in a manner consistent with WHO guidance for introduction of such new regimens;***

- ***Any product packaging and co-formulation requirements will be harmonised with standards defined by the GDF for product standardisation.***

5.5.2 Different indications/human vs animal use

Ensuring appropriate use of new antibiotics, including new TB drugs, is key to ensuring good stewardship.[50] A new TB drug could have other approved indications, potentially including veterinary use, and respondents were asked whether these alternative uses should be explicitly allowed or prohibited under MPP licences. Respondents generally agreed that new TB drugs should be reserved for human use only, but were more open to allowing the use of a TB drug for another approved indication in humans. Some respondents felt that as long as the drug in question had been proved to be safe and effective in another indication, use for that indication should always be allowed under MPP licences, as the additional volume could contribute towards economies of scale and price reductions. Others favoured a more case-by-case approach, considering factors such as whether other equally effective treatments were available for the other indication and the public health importance of the alternative indication. Of course, the precise indication (or "field of use" in licensing terms) that is permissible in a licence agreement is subject to negotiation with the patent holder, and the MPP will focus primarily on obtaining legal rights for the prevention and treatment of TB.

[50] World Health Organization, op. cit. (Background Paper).

Key conclusions:

- ***The MPP, in line with its mandate, will focus its negotiating efforts at obtaining licences with field of use covering the prevention and treatment of TB in humans;***

- ***In the event that a broader field of use is offered, the MPP will conduct a case-by-case analysis as to whether a broader field of human use is appropriate.***

5.6 Use of IP as a tool for stewardship

The Background Paper notes that "reliance on intellectual property rights is…not a realistic option for controlling distribution – at least of existing medicines – as it would only affect a small fraction of antimicrobial medicines on the market."[51] Even for new drugs that are still under patent, stewardship-related obligations included in a licence would, as a general rule, last only until the expiration of the underlying patents, and in any event they would not apply to non-licensees operating in a jurisdiction where the product might not be patented. Given the shortcomings of using IP licences as a tool for stewardship, respondents were asked to give their thoughts on the wisdom of including stewardship obligations in MPP-negotiated licences.

Respondents generally agreed that there were a number of imperfections in the use of IP to enforce stewardship obligations, but felt that to completely ignore such obligations when there was an opportunity to include them was not an ethically acceptable option. However, given the incompleteness of IP as a vehicle for stewardship, these respondents advised the MPP to not overburden its licensees with so many restrictions as to place them at a competitive disadvantage vis-à-vis non-licensees, and to keep in mind that the MPP's efforts would be a small but important contribution towards a much larger global effort to improve TB drug stewardship.

[51] World Health Organization, op. cit. (Background Paper).

If stewardship provisions are to be included in licences for TB drugs, the MPP may be uniquely positioned to implement and enforce such stewardship obligations. As demonstrated above, the MPP is *already* implementing, monitoring and enforcing stewardship-related obligations in its current licences with drug manufacturers. This includes the careful evaluation and selection of licensees through its EoI system, strict quality requirements, provisions for pharmacovigilance, and regular reporting requirements for product development, national registration, and sales and volume data, coupled with quarterly meetings with licensees to discuss performance. Through these binding requirements and close monitoring of licensees' compliance, the MPP has enjoyed success in getting its licensees to adhere to such obligations, and has sought remedies up to and including termination of licences for those who fail to perform. The existing licence management infrastructure within the MPP could readily be adapted to encompass a broader set of stewardship-related obligations along the lines set forth in this Report.

Key conclusions:

- ***Although IP licences are imperfect as a comprehensive stewardship tool, the ability to create binding obligations related to certain stewardship principles within the context of MPP licences is a goal worth pursuing;***

- ***As it crafts stewardship-related obligations in its TB licences, in negotiation with patent holders and generic manufacturers, the MPP will keep in mind the need to attract reputable licensees and to not place them at a competitive disadvantage vis-à-vis non-licensees;***

- ***The MPP will leverage its existing licence management and enforcement infrastructure to encompass additional stewardship-related obligations along the lines reflected in this Report.***

6. Conclusion

Promoting good stewardship of TB drugs is a complex and multifaceted challenge that requires action at every level, ranging from the establishment of international norms and guidance to improving patient adherence, and at every point in between. While there are many aspects that contribute to the proper stewardship of TB medicines that are beyond the scope of work of the MPP, and ultimate responsibility for stewardship remains in the hands of governments, the findings of this Report suggest that the MPP is perhaps uniquely placed to implement, monitor and enforce certain stewardship-related obligations for TB drug manufacturers through its public health-oriented licensing model that could contribute to a broader stewardship framework. This Report has sought to identify specific areas in which the MPP could seek to negotiate stewardship-related provisions in its licences for patented TB drugs, while bearing in mind the importance of maintaining a proper balance between the need for access, innovation and stewardship. As in any negotiation, the specifics of each type of provision will be subject to discussion and agreement with potential licensors and licensees, and will be worked out in consultation with leading experts in TB, in particular the WHO. However, it is hoped that this Report, and the extensive stakeholder input that was gathered in generating it, will provide useful guidance to both the MPP and other key stakeholders in helping to come to a "common understanding" on the stewardship goals to be pursued by the MPP.

Annex I List of Interiewees

Governments	
1	Government of South Africa – Anban Pillay
2	Government of Brazil – Denise Arakaki
Originator Companies	
3	Otsuka – Marc Destito
4	Merck Sharp and Dohme - Michael Wong
5	Eli Lilly – Evan Lee
Generic Companies	
6	Macleods - Vijay Agarwal, Niteesh Shrivastava
7	Lupin - Mukul Jerath, Shrikant Kulkarni
International Organisations	
8	World Health Organization – Peter Beyer, Christian Lienhardt
9	Stop TB Partnership - Suvanand Sahu
10	Global Drug Facility – Brenda Waning
11	UNITAID – Karin Timmermans & Draurio Barreira
12	Global Fund to Fight Aids, Malaria and Tuberculosis - Azizkhon Jafarov
13	The Bill and Melinda Gates Foundation – Jan Gheuens
Civil Society	
14	Global Network for People Living with HIV (GNP+) - Wim Vandevelde
15	Treatment Action Campaign - Marcus Low
16	Global TB Community Advisory Board (CAB) Members: Julia Kalancha, Ukraine Ketholelie Angami, India Wim Vandevelde, South Africa Blessina Kumar, India Giselle Israel, Brazil Lindsay McKenna, USA Erica Lessem, USA Zied Mhirsi, Tunisia Ezio Tavora, Brazil Patrick Agbassi, Côte d'Ivoire *In addition, following people also joined:* James Malar from APCASO Mike Frick, Suraj Madoori, and Kenyon Farrow from TAG Unubold Tsogt-Erdene from STREAM CAB in Mongolia Shailly Gupta & Leena Menghaney from MSF Access Campaign in India
17	Médecins Sans Frontières (Epicentre) - Maryline Bonnet

18	Médecins Sans Frontières Access Campaign - Christophe Perrin
Product Development Partnerships (PDPs)	
19	TB Alliance – Mel Spigelman & Robert Lorette
20	Global Antibiotic Research and Development Partnership (GARDP) - Manica Balasegaram
Academics	
21	Johns Hopkins University - Anthony D. So
22	Boston University – Kevin Outterson
23	Cape Western Reserve University - Jennifer Furin
Others	
24	Clinton Health Access Initiative (CHAI) - Regina Osih
25	JS Consulting – Andrew Jenner
26	International Union against Tuberculosis and Lung Disease – ID Rusen

Annex II Stewardship Questionnaire

1. What is "stewardship"? [*Note that these questions are purposely broad and open-ended, but the intention is to establish a common background for more specific questions in subsequent sections*]

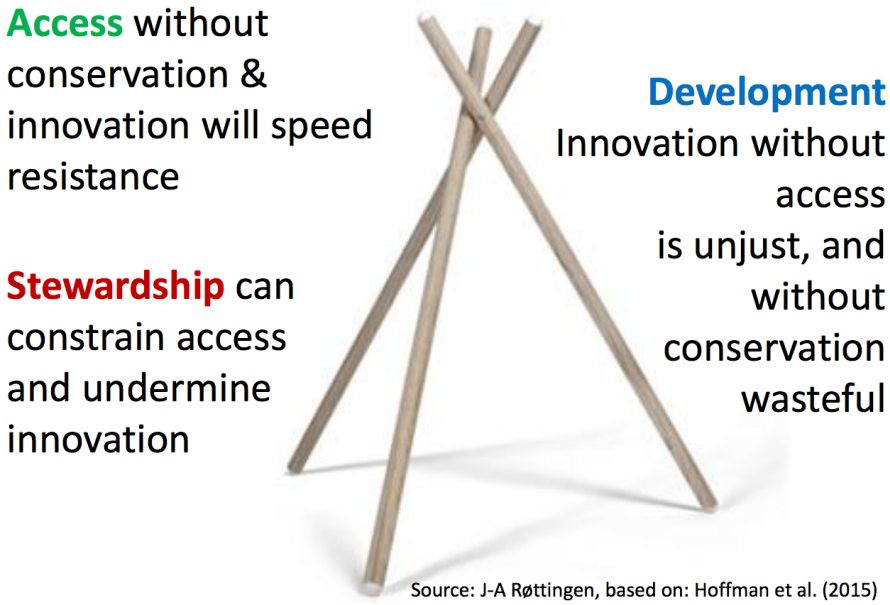
1.1 [*Refer to background material*] The WHO Discussion Paper defines stewardship as "the promotion of appropriate use of antimicrobials while reducing their inappropriate use; improving patient outcomes; reducing microbial resistance; and decreasing the spread of infections caused by multi-drug resistant organisms. The ultimate aim of such stewardship is to conserve the effectiveness of antimicrobial medicines by delaying the formation of resistance as long as possible through appropriate use." Are there other concepts that should be captured within the definition of stewardship?

1.2. [*Refer to background material*] Given the breadth of the definition of stewardship, there are a number of distinct areas that are relevant to proper stewardship, among them:

- *Quality assurance* – to ensure medicines of quality and efficacy are administered to patients;
- *Manufacturing practices* – to ensure that emissions to the environment during manufacturing do not contribute to fuelling resistance to medicines;
- *Marketing practices* – to ensure that marketing and promotional activities do not result in improper or over-use;
- *Regulatory oversight* – to impose certain measures by the drug regulator to ensure proper use;
- *Procurement* – to ensure that medicines are supplied to reputable purchasers, which are then distributed to the end-user through proper channels;
- *Supply chain management* – to ensure uninterrupted supply of medicines to prevent treatment interruptions;
- *Rational use* – to ensure that patients receive medicines appropriate to their needs in appropriate doses for an adequate period of time;
- *Monitoring adherence* – to ensure optimal patient outcomes and prevent resistance from developing

Are there other key areas that are relevant to stewardship? Are there specific areas in which the MPP, through the terms it negotiates into its licences, can play a greater or lesser role?

1.3. [*May not be appropriate for those less familiar with the subject-matter*] [*Refer to Figure 1 in Background Material*] The WHO Secretariat's presentation to the WHA posits stewardship as one pillar in a "policy tripod," with the others being access and innovation, with key areas of interplay among them:

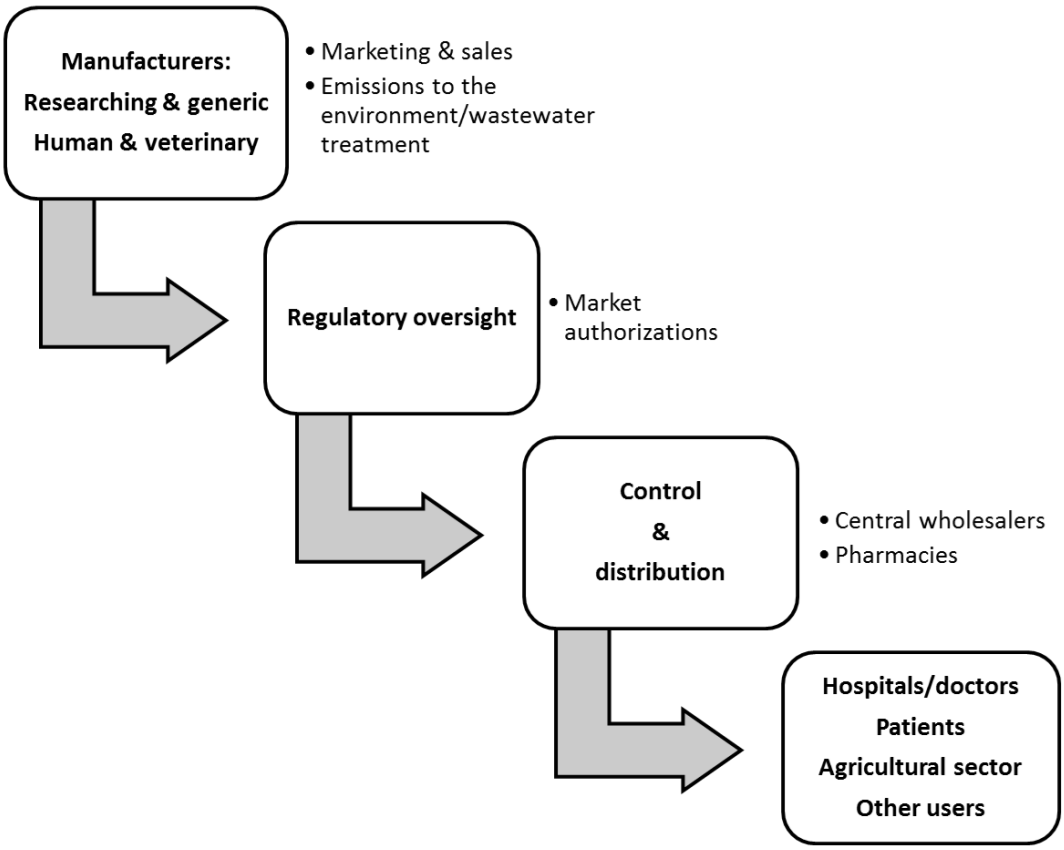


Source: J-A Røttingen, based on: Hoffman et al. (2015)

Do you think that the above model is a good representation of the situation in TB? Do you think there is a stewardship challenge in the field of TB that would need to be addressed?

2. What could be the MPP's potential role in stewardship?

[*Refer to Figure 2 in Background Materials*] The WHO Discussion Paper identifies four points at which various interventions for better stewardship might be considered, as follows:



The following questions will address potential mechanisms relevant to each of the four points of intervention:

2.1. Manufacturers – Researchers & Generic

2.1.1. ***Quality.*** MPP licences currently require all licensees to manufacture products consistent with WHO Prequalification/Stringent Regulatory Authority standards. The Global Drug Facility, which provides procurement services for many public-sector TB drug procurements, also requires this for any TB drugs that it procures on behalf of treatment programmes.

- To your knowledge, to what extent do TB drugs currently being supplied in low- and middle-income countries (LMICs) meet these standards? In which circumstances?

- Do you view the MPP's current quality requirements of WHO PQ/SRA as appropriate for its work in TB? Why/why not?

2.1.2. ***Manufacturing processes.*** The AMR Review Report, a recent study commissioned by the UK Prime Minister to recommend policy solutions to the growing problem of antimicrobial resistance, observed that some manufacturers of antibiotics API do not adequately treat waste products, thus causing the antibiotics API to be released into the local environment. This, the Report concluded, was a major potential driver of the creation of environmental "reservoirs" of drug-resistant bacteria.

- [*Primarily for manufacturers – originator and generic*] What mechanisms do (a) you, and (b) the pharmaceutical industry in countries where you manufacture currently have in place to ensure that waste products from the manufacturing process do not contribute to drug-resistant bacteria? Are you aware of key manufacturing countries where such mechanisms or practices are not in place, and if so which are those countries.

- [*Primarily for clinicians, scientists*] Is this of particular concern in the TB context, or is this less of a concern given how TB is generally transmitted?

- Are there any generally-accepted objective manufacturing standards for controlling the release of antibiotic API into the environment that the MPP could adopt as a standard in its licences? (The MPP lacks internal capacity and infrastructure to determine what might be appropriate manufacturing standards, so reference to an external objective criterion would be necessary if such a concern were to be addressed in MPP licences)

2.1.3. ***Marketing/promotional practices.*** Given the need to properly conserve new TB medicines, aggressive marketing/promotional practices by drug manufacturers may be counterproductive to the overall goals of stewardship.

- Do you agree with the above statement?

- What kind of activities and marketing practices in your opinion would be problematic in the TB context? When would you term marketing as too aggressive? If so, is there something that the MPP could do through its licences to address such practices (eg, provisions restricting or prohibiting certain practices)?

- Certain mechanisms have been proposed that would make the compensation going to the manufacturer of a drug independent of the volume of sales, so as to reduce the incentive for over-marketing a new drug. In effect, a manufacturer would receive a "flat-fee" regardless of volume. Do you feel that this is a good idea in the context of new TB drugs?

2.1.4. ***Selection of licensees.*** The MPP model has to date, in the field of HIV, relied upon robust generic competition through the selection of multiple licensees to promote access to its licensed products. Given both the smaller market in TB (in particular in MDR-TB), and certain stewardship concerns, this model may have to be adapted in the context of TB licences.

- Should the MPP consider limiting the number of licensees in the TB context as a mechanism for ensuring proper stewardship?

- What should be the main criteria by which the MPP select its licensees in TB? Eg, Demonstrated quality? Global reach? Expertise in manufacturing existing TB drugs? Ability to manufacture and supply local markets? Demonstrated ability to produce at low cost? Ability to make FDCs? Why? Any other criteria?

- Given that competition will likely be limited in TB, especially for MDR-TB drugs, in light of the small market, would it be desirable to include some affordability/accessibility requirements in MPP licences? What types of affordability/accessibility requirements might be appropriate, or should low prices be left to market competition as currently the case in HIV licences?

2.2. Regulatory oversight

The WHO paper discusses possible measures that could be imposed at the regulatory level, by the national (or regional) regulatory bodies, such as: (a) Limiting prescription or dispensing to certified institutions, trained providers, or specific healthcare settings; (b) Requiring demonstration of need through clinical algorithm or diagnostic test findings; and (c) Monitoring through a clinical registry of treated patients.

- In the TB context, do any of these potential measures seem particularly important?

- Are you aware of any similar precedent that has been applied on TB drugs, or some other drugs by national drug regulators in LMICs? What has been the experience?

- Even without independent action by drug regulators, is there a workable way that MPP could incorporate similar principles into its licences (without itself having to implement and monitor such requirements, which it lacks the capacity and infrastructure to do)?

- Are there other initiatives that could be taken at the national regulatory level that could contribute towards broader stewardship efforts?

2.3. Control and distribution

2.3.1. ***Global Drug Facility.*** The GDF, an initiative of the StopTB Partnership, is the largest public sector supplier of TB drugs, supplying treatment for roughly 35% of reported TB cases worldwide. Many of the services it provides further the goals of stewardship and access, including (i) the provision of competitively-priced, quality assured TB drugs; (ii) provision of tools for proper supply-chain management; (iii) technical assistance to national TB programmes; and (iv) product standardization and packaging to simply treatment, among other services.[52]

- Is there a way that the MPP could leverage the capabilities of the GDF to address some key stewardship concerns? What might be some ways to do this?

- Is the market share of the GDF likely to increase in the near future, particularly for new drugs for MDR-TB?

- Are you aware of the work of the Green Light Committee? Could you describe your understanding of it? What, in your view, is their role in the proper stewardship of new TB drugs?

- [*Particularly for governments – India, Brazil, Russia, South Africa*] What percentage of your country's national TB procurements is done through GDF? What are the reasons for/against GDF-mediated procurement?

- Are you aware of any national or regional-level programmes that offer similar capabilities (eg, quality assurance, supply chain management, technical assistance) as GDF?

- [*Particularly for Global Fund, WHO, UNITAID etc.]* Are you satisfied with current arrangements/deals/prices/availability of novel medicines ie bedaquiline (BDQ)/delamanid (DLM) such as Janssen's access programme for BDQ and Otsuka's

[52] For more information on GDF, see, *inter alia,* here and here.

price deal with GDF for DLM? Would such arrangements (where only the originator manufacturers TB medicines) be helpful for the cause of stewardship?

- [*Specifically for TB generics companies*] What has been your experience in providing TB drugs through the GDF? What share of your total TB drug sales are through GDF? What share of your total TB drug sales are into the private vs public sectors?

- [*Specifically for Janssen/Otsuka*] Bedaquiline/delamanid were recently made available for MDR-TB treatment through GDF.

    - What specific features of GDF made this an attractive proposition, from a stewardship perspective? From a commercial perspective? From an access perspective?

    - If, hypothetically, licensed generic versions of bedaquiline/delamanid were made similarly available through GDF, would this equally address your concerns?

    - If the safeguards within GDF could be replicated for procurements outside of GDF, would it address your concerns?

    - How sustainable do you view the donations [*Janssen*]/direct provision [*Otsuka*] through GDF to be on a longer-term basis, as use of your drugs are scaled up?

2.3.2. ***Public/private sector provision.*** Despite the existence of national TB programmes, many TB patients seek care within the private sector. For instance, in India, somewhere between 50-80% of TB patients seek care in private clinics, according to one study. However, the study found that the care provided in private clinics was sub-standard, with less than 6% of private clinicians in Mumbai writing a prescription for a correct TB drug regimen.

- Should the MPP consider limiting its licensees' ability to supply only into public-sector TB treatment programmes?

- If the MPP were to allow private sector sales, how, if at all, should the drugs' availability be controlled; eg, should they be made available at local pharmacies?

2.4. End-users

2.4.1. *Facilitating better adherence*

The WHO paper observed that "the size of packs and how they are sold by pharmacies also influence treatment adherence, and thus formation of resistance." Given this, what types of packaging requirements might make sense for new TB drugs licensed to MPP?

- Certain specified FDCs or co-packaged products only?

- Limitations on pack size? What might be appropriate limits?

- Are there broad guidelines that can be decided *a priori*, or would this be a drug-by-drug or regimen-by-regimen determination?

- Any other packaging/insert requirements (eg, warnings, instructions, etc.) that could be useful to achieving better adherence?

2.4.2. *Restrictions on other indications, including veterinary use*

Certain anti-TB agents will (or may) have efficacy in other indications, for example in other antibacterial indications. Would it make sense to restrict MPP licensees' ability to supply for other indications outside of TB?

The WHO paper recognises that any stewardship framework will have to adhere to the "one-health" approach. This approach recognizes that "human health and animal health are deeply intertwined," and treating the two separately "would be a profound mistake."[53]

- In the context of TB drugs, does it make sense to include restrictions to human use in MPP licences? In all cases, or a case-by-case approach? If latter, what factors should guide this decision?

3. Use of licensing terms as stewardship tool

The WHO paper notes that "reliance on intellectual property rights is…not a realistic option for controlling distribution – at least of existing medicines – as it would only affect a small faction of antimicrobial medicines on the market." Even for new drugs that are still under patent, however, the stewardship-related obligations included in a licence would, as a general matter, last only until the expiration of the underlying patents. How could the MPP, or the global community as a whole, help to ensure adherence to proper stewardship principles after patent expiry (or in countries where the product was never patented)?

4. Any other thoughts/observations?

[53] See Hoffman and Outterson, here.