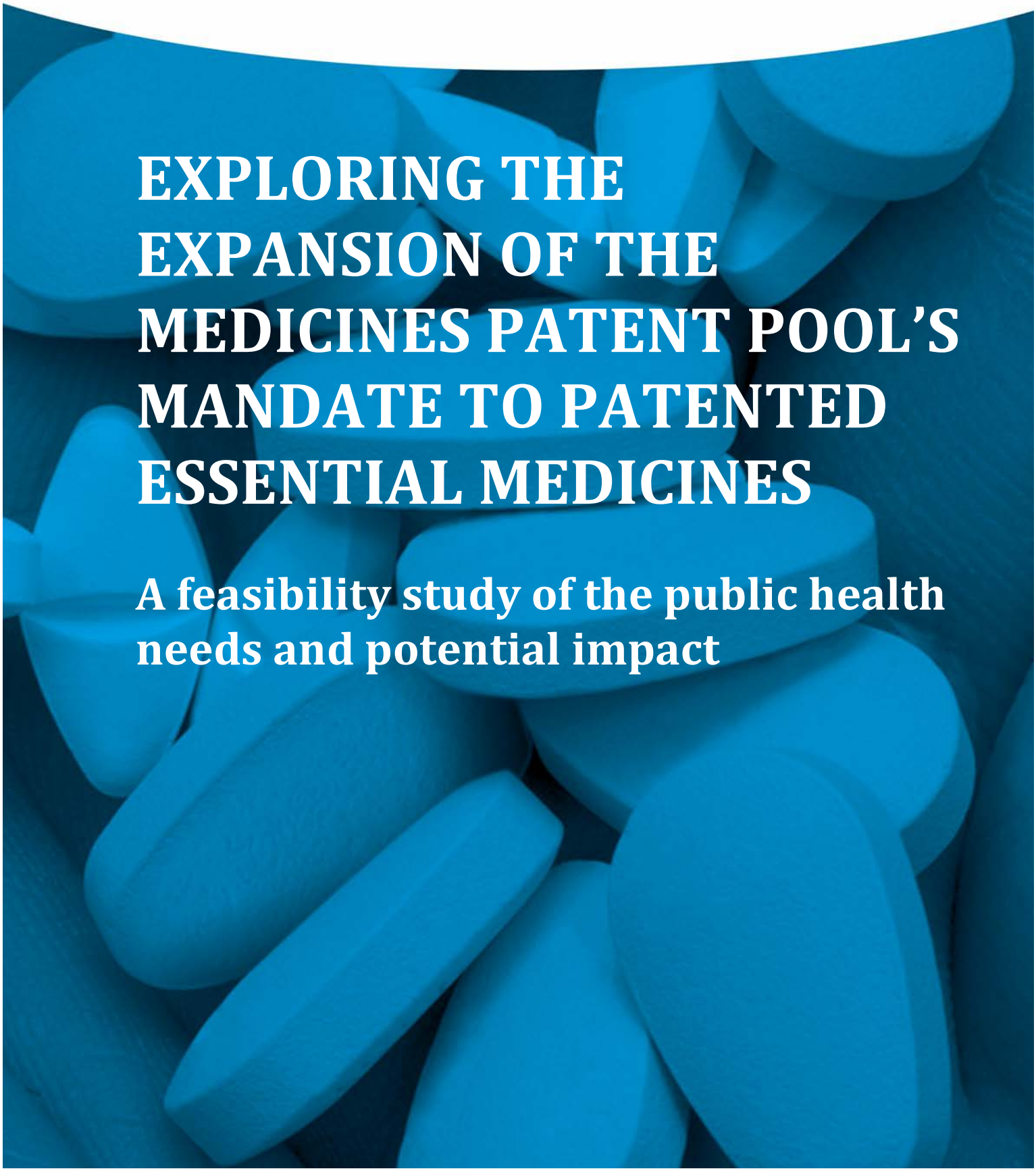
medicines patent pool



EXPLORING THE EXPANSION OF THE MEDICINES PATENT POOL'S MANDATE TO PATENTED ESSENTIAL MEDICINES

A feasibility study of the public health needs and potential impact

7 New antibiotics to combat antimicrobial resistance

7.1 Background

Antibiotics comprise a significant part of the WHO Essential Medicines List (EML). The EML includes 61 antibiotic medicines, antibiotic groups, or combinations. Of these, 20 are TB treatments. None of the antibiotics currently listed, outside of TB, are patented. The absence of patented antibiotics on the EML is indicative of systematic underinvestment in the discovery of new antimicrobials over the last several decades.[1–6] This underinvestment, in turn, has contributed to growing antimicrobial resistance (AMR), in which the medicines that are currently available are less and less effective in treating infections.

The rising threat of AMR has received greater attention in recent years, with discussions at the United Nations,[7] World Health Assembly,[8] the G7,[9] the G20,[10] and elsewhere[11] highlighting the gravity of the situation. The international community has stressed the imperative of increased research and development (R&D) of new antimicrobials, as well as fostering better stewardship in order to preserve their effectiveness. Novel initiatives, such as the Global Antibiotic Research and Development Partnership (GARDP) and CARB-X, have been established to facilitate the development of new antimicrobials against priority pathogens, and other incentive mechanisms have been proposed to stimulate greater R&D in antimicrobials, for example, large end-stage prizes.[1,3,12]

The increased focus on the need to respond to rising antimicrobial resistance will likely translate to a growing pipeline of new drug candidates to target priority pathogens in the coming years. And, given the clear public health need for these drugs, antimicrobials that effectively target drug-resistant microbes will likely be added to the WHO EML soon after regulatory approval. This chapter will focus on the potential role that the MPP could play in relation to these drugs, with a particular focus on how the MPP could contribute to both affordable access and good stewardship of new antimicrobials.

7.2 The challenges of development, access and stewardship in AMR

Although precise data are unavailable, it is conservatively estimated that 700,000 people die every year from drug-resistant infections, and this number is estimated to reach 10 million by 2050 (Figure 1).[1] These figures include the estimated number of deaths from drug-resistant strains of HIV and TB, but also includes projected deaths from other drug-resistant forms of bacteria.

Figure 1. Deaths attributable to antimicrobial, compared to other causes.

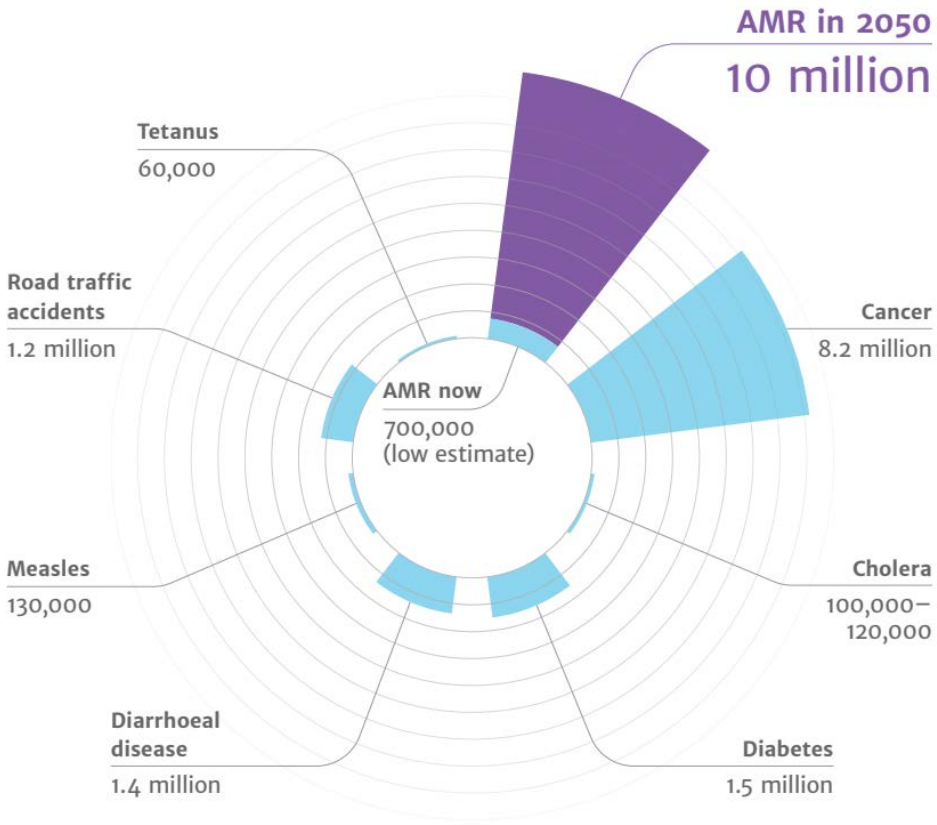


Figure reproduced from the O'Neill AMR Review.[1]

In an effort to guide and promote R&D to combat AMR, the WHO published a priority pathogen list (PPL) in 2017, highlighting those bacteria (apart from drug-resistant TB, which remains the largest global killer in AMR) for which there is an urgent need for new treatments (Table 1).[13] All three critical priority pathogens in the PPL, and seven of the nine listed as critical or high priority are Gram-negative bacteria. The WHO Expert Panel consequently noted that "future R&D strategies should particularly focus on the discovery and development of new antibiotics specifically active against multidrug- and extensively drug-resistant Gram-negative bacteria."[13] At the same time, the panel noted that antibiotic stewardship programmes are urgently required.[13]

Table 1. WHO priority pathogen list.[13]

Antibiotic	Key antibiotic to which there is resistance
Critical priority	
Acinetobacter baumanii	Carbapenem
Pseudomonas aeruginosa	Carbapenem
Enterobacteriaceae	Carbapenem, 3rd-generation cephalosporins
High priority	
Enterococcus faecium	Vancomycin,
Staphylococcus aureus	Vancomycin, methicillin
Helicobacter pylori	Clarithromycin
Campylobacter species	Fluoroquinolones
Salmonella species	Fluoroquinolones
Neisseria gonorrhoeae	3rd-generation cephalosporins, fluoroquinolones

Medium priority	
Streptococcus pneumoniae	Penicillins*
Haemophilus influenza	Ampicillin
Shigella species	Fluoroquinolone
*non-susceptible. Adopted from the WHO *Antibacterial agents in clinical development* report.[14]	

Following the publication of the PPL, the WHO published a pipeline report that analysed antibiotics in clinical development in terms of their expected activity against priority pathogens and their level of innovativeness[v].[14] Although the report identified a number of potentially valuable agents, the analysis concluded that the current pipeline was insufficient to meet the rising challenge of AMR. For example, given an estimated phase 1 success rate of 14%,[14] only one or two of the ten anti-Gram-negative compounds in phase 1 are likely to eventually be approved.

In an effort to facilitate antibiotic stewardship efforts, the 2017 EML adopted a new categorization system for antibiotics.[15] The new classification categorises antibiotics into three groups – *Access*, *Watch* and *Reserve* – to balance the need for broad access to some antibiotics against the need to preserve other classes of antibiotics as a last resort for highly resistant cases. The *Access* category includes antibiotics that are the first- or second-choice treatment for common infectious syndromes, for which the aim should be to have affordable and quality-assured versions widely available. The *Watch* category includes antibiotic classes that are considered to be especially susceptible to the development of resistance, but which are still important in some indications (the *Access* and *Watch* categories have some overlap). The third, *Reserve* category includes last-resort antibiotics and antibiotic classes that are to be used when alternatives have failed or would be inadequate. Newly developed antibiotics may automatically fall under the *Watch* or *Reserve* categories due to their class – for example, pipeline fluoroquinolones (a class included in the *Watch* category), or pipeline oxazolidinones (a class included in the *Reserve* category).

While sound stewardship of antimicrobials is critically important, access to existing antimicrobials remains limited in low- and middle-income countries (LMICs). An estimated 5.7 million deaths occur annually from infections that would in most cases have been treatable with existing antimicrobials if they were accessible (Table 2).[16]

[v] In the WHO report on the antibiotic pipeline, innovativeness is described in terms of the medicine not having cross-resistance to existing antibiotics, being of a new chemical class, having a new target, or having a new mechanism of action.[14]

Table 2. Global deaths due to infections amenable to treatment with existing antimicrobials (thousands).

Lower respiratory tract infections*	2,466
Tuberculosis	1,290
Malaria	855
Neonatal infections and sepsis	366
Meningitis	304
Gastrointestinal infections*	221
Sexually transmitted infections*	142
Maternal infections and sepsis	24
Total:	5,668
*Excludes cases due to viral causes. Table from Daulaire et al.[16]	

Thus, while there is a need to develop new antimicrobials to treat drug-resistant infections and ensure that they are used appropriately, there is also a need to expand access to existing and recently-approved antimicrobials, particularly in LMICs. As Daulaire et al note: "Ensuring universal and appropriate access to essential medicines is a necessary precondition to any policy on restricting the use of antimicrobials in low-income settings; absent this, any restriction is likely to be ethically and politically challenged, or simply ignored."[16] This is the 'policy tripod' of aims in tackling antimicrobial resistance (Figure 1): improving access to existing antimicrobials, boosting the development of new antimicrobials, and developing effective stewardship practices to protect existing antimicrobials from becoming ineffective.[17]

Figure 2. The 'policy tripod' for tackling antimicrobial resistance.

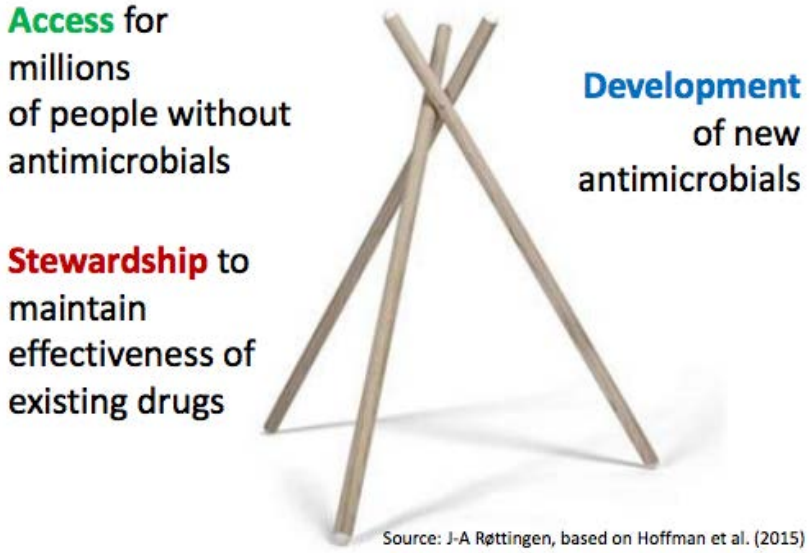


Figure from Peter Beyer.[18]

7.3 The potential role of the MPP in contributing to access and stewardship for new antimicrobials

The MPP has previously worked on antimicrobial resistance in the context of HIV and TB. In HIV, the MPP holds numerous licences on second-line antiretrovirals – i.e. antiretrovirals used in patients whose HIV infection has developed resistance to first-line treatment – as well as products such as dolutegravir, which is recommended by the WHO for first-line use in countries with high levels of pre-treatment resistance to one class of medicines.[19] In TB, the licence signed by MPP and the Johns Hopkins University on sutezolid includes provisions to ensure that commercialization of the product follows proper stewardship.

We consulted with a number of key stakeholders in the area of AMR (Table 2). This list supplements the large number of stakeholders that the MPP consulted during the preparation of its TB Stewardship Report,[20] which examined how MPP licences could contribute to both affordable access and responsible stewardship for new TB drugs.

Table 2. Stakeholders consulted specifically in the area of AMR, as part of this feasibility study.

Manica Balesagaram, Global Antibiotic Research & Development Partnership (GARDP)
Peter Beyer and Nicola Magrini, WHO
Kevin Outterson, CARB-X
Tim Jinks and Jeremy Knox, The Wellcome Trust
Anna Zorzet and Helle Aagaard, ReAct
Sanne Fournier-Wendes, Unitaid
Ursula Theuretzbacher, Center for Anti-Infective Agents
Gabrielle Breugelmans and Adrian Alonso Ruiz, Access to Medicines Index/AMR Benchmark
Numerous other civil society organisations and originator and generic pharmaceutical companies with whom semi-structured interviews were conducted in the course of the overall study (see *Acknowledgements*).

The stakeholder feedback echoed much of what was gathered during the preparation of the TB Stewardship Report: that there was a potential role for MPP, through its licences, to play in promoting good stewardship practices while enabling affordable access to new antimicrobials. For example, a number of stakeholders pointed out that many of the developers of pipeline antimicrobials identified in the WHO Pipeline Report were smaller biotechnology companies, with little to no presence in LMICs and no current plans for stewardship or access in these countries. Indeed, the AMR Benchmark published recently by the Access to Medicine Foundation found that only two of 28 antibiotics in late stages of clinical development had any access or stewardship plans in place.[21]

Stakeholder feedback also indicated that the MPP's model would need to be adapted to address the specific challenges in antimicrobial resistance. In antibiotics, for instance, the MPP should not aim to make new antibiotics broadly available from multiple manufacturers. Rather, the MPP should target just products of public health priority, particularly those for which there are limited or no existing alternatives or that significantly improve on existing options. And, rather than broadly licensing to multiple manufacturers to promote wide availability and generic competition, the MPP would

need to limit the number of licensees to ensure that the products are made affordably available to those who need them while preventing overuse.

7.3.1 Role of the MPP in relation to initiatives to stimulate antibiotic R&D

Recent high-level reports have recommended that the MPP could play an important role in new mechanisms for financing antimicrobial R&D.[1,3,12] The Review on Antimicrobial Resistance Chaired by Jim O'Neill recommended that incentive mechanisms such as market entry rewards should be linked to requirements to ensure access and stewardship – for example, by requiring recipients of payouts to license their discovery to the MPP under appropriate provisions.[1] Analyses from Chatham House, a prominent international affairs think tank based in the United Kingdom and DRIVE-AB, a consortium supported by the European Innovative Medicines Initiative, made similar recommendations.[3,12]

CARB-X is an initiative to stimulate the early-stage pipeline for antimicrobials targeting priority pathogens, established by two divisions of the US Department of Health and Human Services,[W] and funded by one of these divisions along with the Wellcome Trust. CARB-X indicated that it would contractually require its grantees to develop an access and stewardship plan for its drug candidates that advance through the pipeline and viewed licensing to the MPP as one key option for grantees to fulfil this requirement. Likewise, GARDP envisioned a role for MPP in AMR, both as a potential in-licensor of promising candidate compounds for further development, as well as a licensee of products successfully developed by GARDP.

7.3.2 Role of the MPP in relation to good antimicrobial stewardship

An access and stewardship licensing framework for the AMR context would build upon the substantial work that the MPP has already completed in exploring how stewardship-related practices could be integrated into its licensing model.[20] The development of such a framework would begin with the recognition that many of the most important measures for ensuring proper stewardship of new antimicrobials lie outside of the licensing context; for example, strengthening regulatory systems in LMICs, expanding the availability of proper diagnostics, and developing and implementing sound treatment guidelines will be key to achieving good stewardship but cannot be addressed in a licence agreement with a manufacturer. However, interviews with stakeholders indicated that the MPP could nevertheless make an important contribution by addressing certain aspects of stewardship that can be influenced through licensing agreements. Potential areas in which antimicrobial stewardship could be promoted through MPP licensing are explored further below.

[W] These two divisions are the Biomedical Advanced Research and Development Authority (BARDA) and the National Institute of Allergy and Infectious Diseases (NIAID).

7.3.2.1 Quality standards

Ensuring that a drug meets quality standards, that it is safe and effective, contains the correct amount of active ingredient, has a stable shelf-life, and is manufactured in accordance with current Good Manufacturing Practices (cGMP) – is a central pillar of ensuring responsible antimicrobial stewardship.[24] 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).[X] This is consistent with the standards used by the the Global Fund, Unitaid and the Global Drug Facility (GDF). The MPP would continue to implement strict quality standards in any licences for other antimicrobials.

7.3.2.2 Release of active pharmaceutical ingredients into the environment

The O'Neill 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."[1] The AMR Industry Alliance recognised the importance of reducing the environmental impact from the production of antibiotics and committed to establish targets for limiting discharge by 2020.[25] The AMR Benchmark, in turn, is tracking the pharmaceutical industry's performance with regard to such commitments.[21] MPP licences in antimicrobials could seek similar commitments from its licensees regarding environmental discharge and incorporate rigorous standards for acceptable levels of discharge once these are developed in the coming years.

7.3.2.3 Marketing and promotional practices

Concerns have been raised that aggressive sales promotion could result in overuse of an antibiotic.[12] In particular, it would be appropriate to have strict controls on the sublicensee's promotion and marketing for antibiotics that have been (or are likely to be) classified as "Watch" or "Reserve" in the WHO EML. In order to ensure that MPP sublicensees do not engage in inappropriate promotional activities, the MPP could, as part of its Expression of Interest (EOI) process, ask potential sublicensees to submit marketing plans that are in line, for example, with the recommendations in the WHO's Ethical Criteria for Medicinal Drug Promotion, or other relevant standards, and in line with national laws and regulations. Such plans could then become binding obligations as part of the licensing agreement. Prohibitions on over-promotion may need to be coupled with an incentive mechanism that would delink the licensee's revenue from the volume of sales, such as, for example, advance purchase commitments.[12] This sort of

[X] For example, 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 could be included in MPP licences covering other antimicrobials.

delinkage mechanism, of course, would have to be implemented by or in partnership with donors, governments, or procurement agencies capable of financing such a mechanism.

7.3.2.4 Selection of licensees

For its HIV and HCV licences, the MPP selects licensees through its Expression of Interest (EoI) system, which allows the organisation to assess a potential licensee's ability to promptly bring a quality-assured product to market at an affordable price in the countries included in the licence.[Y] This existing framework can be leveraged to require interested licensees to submit additional information that is relevant to good stewardship, such as marketing plans (as discussed above) and manufacturing environmental controls.

Unlike with MPP-licensed products with high sales volumes, such as medicines used in first-line HIV treatment where the MPP seeks a large number of licensees in order to generate market competition, in antimicrobials the MPP may need to limit the number of licensees in order to better control the medicines' use in line with good stewardship. Under this practice, because the number of licensees – and thus competition – would be limited, there may be a need for additional measures to ensure that the end product is made available at an affordable price. This could be done, for example, by specifying a 'cost-plus' formula that establishes the maximum allowable price based on the manufacturer's production costs, while ensuring a sustainable profit margin for the licensee.

7.3.2.5 Definition of permissible buyers

If guidelines such as the WHO EML recommend that an antimicrobial licensed to the MPP is used only in restricted settings (e.g. only in hospitals), it may be appropriate for the MPP to define in sublicence agreements the types of entities to whom sub-licensees may sell the product. This would be in line with the AMR Industry Alliance Roadmap, in which the signatories have committed to "collaborate with governments, their agencies and other stakeholders to reduce uncontrolled antibiotic purchase, such as via over-the-counter and non-prescription internet sales".[25] Permissible buyers could be limited to, for example, public-sector hospitals, tertiary care centres, or certain NGOs. Specific restrictions included in sublicences would need to be sensitive to factors such as a product's recommended scope of use or the level of public provision of healthcare in a given country.

7.3.2.6 Limitations on irrational combinations and use

The inappropriate use of antimicrobials, including in irrational combinations, can contribute to the development of resistance. Recently, for example, an alarming proliferation of irrational fixed-dose combinations of antibiotics has been reported in India.[26] New antimicrobials may also have potential applications in veterinary use, but such use may not be conducive to good stewardship. In close consultation with the

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

WHO and other experts, MPP licences could define permissible uses and permissible combinations.

7.4 Conclusion

As recognised in the MPP's earlier TB Stewardship Report,[20] the use of patent licences is an imperfect tool for enforcing stewardship obligations. Such obligations could only be enforced on drugs that are under patent and as long as patents are in force. Moreover, such obligations would not be binding on non-licensees based in jurisdictions in which the product is not patented. However, stewardship-related activities at the manufacturing, commercialisation, and distribution levels could make an important contribution towards good stewardship, and, to the extent that a patent licence can place binding requirements for stewardship, it would seem counterproductive not to use this tool.

Within the aforementioned constraints, the MPP is uniquely positioned to implement and enforce stewardship obligations. The MPP is already implementing, monitoring, and enforcing stewardship-related obligations in its current licences with drug manufacturers in the fields of HIV, hepatitis C and TB. These practices include the careful evaluation and selection of licensees through its EoI system, strict quality requirements, and provisions for pharmacovigilance. Through these binding requirements and close monitoring of licensees' compliance, the MPP has demonstrated success in encouraging 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 chapter.

The MPP's work in the field of AMR could be further strengthened if the MPP were to partner with existing initiatives, such as the Access to Medicine Foundation's AMR Benchmark. In HIV, the Access to Medicine Index (ATMI) has recognised that MPP-negotiated licences set the standard for public health-oriented licensing. Licensing to the MPP could similarly be included as requirements in milestone prizes offered by CARB-X and other innovative R&D financing mechanisms. Indeed, should a large end-stage prize for the development of antimicrobials eventually be established, several stakeholders felt that the MPP could play an important role as the mechanism to ensure equitable access and responsible stewardship, particularly in LMICs, by manufacturers for any new antimicrobial that is rewarded an end-stage prize.

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