Medicines Patent Pool Submission to the discussion paper "Reduce untentional exposure and the need for antimicrobials, and optimize their use"

The MPP is a United Nations-backed public health organization funded by Unitaid, working to improve access to affordable and appropriate HIV, hepatitis C and tuberculosis medicines in low- and middle-income countries. The MPP has previously worked on antimicrobial resistance in the context of HIV and TB. In HIV, the MPP holds several 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 was recommended by the WHO for first-line use in countries with high levels of pre-treatment resistance to one class of medicines[1].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. Recently, the MPP has expanded its mandate to work on other patented essential medicines, including future new antibiotics of public health priority that could contribute to addressing antimicrobial resistance.

The submission below will try to answer some of the questions included in the consultation paper "*Reduce unintentional exposure and the need for antimicrobials, and optimize their use*" focusing on questions 5, 6 and 7 and the potential role that the Medicines Patent Pool (MPP) could play as part of the AMR response, with a particular focus on how the MPP could contribute to good stewardship of new antimicrobials while facilitating affordable access. These points were also included in the MPP's submission to the IACG discussion paper on "Antimicrobial resistance: Invest in innovation and research, and boost R&D and access", where we focused on the use of licensing approaches to support innovation, access and stewardship. However, given that these points are particularly relevant in the context of this new discussion paper, we are hereby re-submitting them for consideration by the relevant IACG working group.

The MPP's Experience in Supporting Innovation, Access and Swtewardship

Currently, the MPP holds licenses on 16 medicines for HIV, HCV and TB with nine patent holders, including pharmaceutical companies, universities and public research organizations. These licenses enable 25 partner generic companies and one product development partnership to develop, register, manufacture, and supply WHO-recommended products in a large number of LMICs. The MPP's work has delivered 17 million patient years of treatment and resulted in $535 million in savings from the procurement of more affordable quality-assured medicines.

The experience of the MPP in HIV has provided a concrete example of how licensing and patent pooling can contribute to addressing some of the innovation and access challenges relating to health technologies.

As mentioned in the introduction, antimicrobial resistance was already part of the work of the MPP in HIV, hepatitis C and TB. The MPP is therefore already implementing, monitoring, and enforcing stewardship-related obligations in its current licenses with drug manufacturers. These

[1] World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, 2nd edn. WHO Press, 2016
http://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf;jsessionid=939637CE96EB31

practices include the careful evaluation and selection of licensees through its Expression of Interest system, strict quality requirements, and provisions for pharmacovigilance. Through these binding requirements and close monitoring of licensees' compliance, the MPP has demonstrated success in ensuring its licensees adhere to such obligations and has sought remedies up to and including termination of licenses for those who fail to perform. However, the model may also require significant adaptation in the AMR field beyond HIV.

The potential role of the MPP in contributing to innovation, access and stewardship for new antimicrobials, including new antibiotics

Recent high-level reports have recommended that the MPP could play an important role in new mechanisms for financing antimicrobial R&D. 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.[2] 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] [4]

Last May, the MPP released the results of the feasibility study exploring the possibility of expanding its mandate to work on other patented essential medicines, including new antibiotics of public health priority.[5] In the study the MPP looked at its role in relation to new antibiotics taking into consideration the categorization made by the WHO Committee on the Selection and Use of Essential Medicines on antibiotics for Access, Watch and Reserve.[6] MPP licenses could be tailored to the specific public health needs that a new antibiotic can contribute to addressing while ensuring a proper balance between innovation, access and stewardship. Stakeholder feedback during the conduct of the feasibility study, confirmed that there could be a role for MPP to play, through its licences, 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

[2] The Review on Antimicrobial Resistance Chaired by Jim O'Neill. Tackling drug-resistant infections globally: final report and recommendations. 2016. https://amr-review.org/sites/default/files/160525_Final paper_with cover.pdf (accessed Feb 18, 2018).
[3] Chatham House. Towards a New Global Business Model for Antibiotics Delinking Revenues from Sales: Report from the Chatham House Working Group on New Antibiotic Business Models. 2015.
[4] DRIVE-AB. Revitalizing the antibiotic pipeline: Stimulating innovation while driving sustainable use and global access. 2018. http://drive-ab.eu/wp-content/uploads/2018/01/DRIVE-AB-Final-Report-Jan2018.pdf (accessed Feb 19, 2018).
[5] The Medicines Patent Pool Foundation. 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. https://medicinespatentpool.org/uploads/2018/05/Feasibility-Study-Expansion-of-the-MPP-Mandate-And-Appendix-2018.05.24.pdf (accessed July 9, 2018)
[6] World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/ (accessed July 6, 2018).

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[7].

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.[8] 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 license agreement with a manufacturer. However, MPP could nevertheless make an important contribution by addressing certain aspects of stewardship that can be influenced through licensing agreements, while contributing to facilitating access to needed new antibiotics in LMICs. Potential areas in which antimicrobial stewardship could be promoted through MPP licensing are explored further below:

- *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[9]. In its licenses 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).[10] This is consistent with the standards used by the Global Fund, Unitaid and the Global Drug Facility (GDF). The MPP would continue to implement strict quality standards in any licenses for new antibiotics.

- *Release of active pharmaceutical ingredients into the environment*

The O'Neill Review on AMR observed that improper treatment of wastewater by manufacturers of antimicrobial 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." MPP licenses in antimicrobials could

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[8] The Medicines Patent Pool Foundation. TB Stewardship Report. 2016. https://medicinespatentpool.org/uploads/2017/07/STEWARDSHIP-REPORT_FINAL-1.pdf (accessed March 8, 2018)

[9] Laxminarayan R, Duse A, Wattal C, *et al.* Antibiotic resistance—the need for global solutions. *Lancet Infect Dis* 2013; **13**: 1057–98.

[10] 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.

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.

- *Marketing and promotional practices*

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.

- *Selection of licensees and affordability*

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.

- *Definition of permissible buyers*

If 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".[11]

- *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.[12] New antimicrobials may also have potential applications in veterinary use, but such use may not be conducive to good

[11] Industry Roadmap for Progress on Combating Antimicrobial Resistance –September 2016. 2016.
[12] McGettigan P, Roderick P, Kadam A, Pollock AM. Access, Watch, and Reserve antibiotics in India: challenges for WHO stewardship. *Lancet Glob Heal* 2017; **5**: e1075–6.

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stewardship. In close consultation with the WHO and other experts, MPP licences could define permissible uses and permissible combinations.

Conclusion

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. Within the new categorization systems for antibiotics adopted in the Essential Medicines List in 2017, the MPP may be uniquely positioned to implement and enforce access and stewardship obligations which can contribute to support the appropriate use of antibiotics for newly developed antibiotics. Licences could be tailored to different antibiotics of public health priority depending on whether they fall under the Access, *Watch* or *Reserve* categories of the WHO. New incentive mechanisms for the development of new antibiotics could be linked to licensing via the MPP to support access and stewardship of the end of the product.

The MPP is already implementing, monitoring, and enforcing stewardship-related obligations in its current licenses 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. Further areas would likely need to be considered in the AMR context, as described above.

In the context of efforts to support the development of new antibiotics it is important that due consideration be given to ensuring that any new antibiotics of public health priority are available to those who need them in LMICs. Support to overcome innovation challenges in AMR should therefore integrate access considerations, as well as considerations relating to appropriate use, from the outset. Public health oriented licensing via the MPP can be a mechanisim to supporting these objectives, particularly if combined with incentives for the clinical development and manufacturing of new antibiotics.