



## **Medicines Patent Pool Submission to the discussion paper “Antimicrobial resistance: Invest in innovation and research, and boost R&D and access”**

The international community has stressed the imperative of increased research and development (R&D) of new antimicrobials, access strategies as well as fostering better stewardship in order to preserve their effectiveness. The discussion paper on AMR prepared by the Inter-Agency Coordination Group recognizes some of the main challenges along the R&D value chain. Voluntary licensing, including patent pooling instruments such as the Medicines Patent Pool (MPP), is suggested as a mechanism that may contribute to addressing some of these challenges.

This submission will focus on 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 innovation, affordable access and good stewardship of new antimicrobials.

### **The MPP’s Experience in Patent Pooling for HIV, hepatitis C and tuberculosis**

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 experience of the MPP in HIV has provided a concrete example of how patent pooling can contribute to addressing some of the innovation and access challenges relating to health technologies. While the design of the HIV patent pool was guided by the specific circumstances in HIV, some of these circumstances might also apply to other areas in public health such as AMR, although the model would likely require adaptations to align with international public health objectives in the field of AMR.

In the field of HIV, the MPP’s work on access relied on the fact that there were multiple new HIV medicines already on the market and a need for access in developing countries that could best be met through competition among multiple manufacturers to reduce the price to affordable levels. From an innovation perspective, the model sought to address the need for follow-on innovation in relation to products needed mostly in developing countries (e.g. pediatric formulations) and for products that require combining medicines patented by more than one entity (e.g. fixed dose combinations).

In November 2015, the mandate of the MPP was expanded to hepatitis C and tuberculosis (TB) and the model evolved to meet the needs in these therapeutic areas. In terms of innovation, while there had been multiple new hepatitis C treatments reaching the market, investments in tuberculosis R&D had been very limited, with only two new products reaching the market in the past forty years. Thus, while the first MPP license in HCV was for a marketed medicine with the aim of facilitating affordable access, the first MPP license in TB was for a medicine that had been stalled in clinical development for a number of years. The MPP license was expected to contribute to accelerating its development by facilitating access to the intellectual property by other potential developers promoting collaborative research and the development of new TB regimens.

Part of the work of the MPP in HIV, hepatitis C and TB was also relevant to concerns relating to antimicrobial resistance. For example, in HIV, the MPP holds numerous licenses 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. 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 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.

In the field of TB, patent pooling could also play an important role in facilitating the development of new treatment regimens, by pooling the necessary intellectual property and clinical data that may be needed. Combining patent and data pooling with push and/or pull incentives could contribute to the development of new regimens that are needed in the field of TB to improve current treatments for multi-drug resistance TB in particular.

Currently, the MPP holds licenses on 16 medicines 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 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.<sup>1</sup> 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.<sup>2 3</sup>

Last May, the MPP released the results of a feasibility study exploring the possibility of expanding its mandate to work on other patented essential medicines, including new antibiotics of public health priority.<sup>4</sup> The feasibility study provided the technical analysis for the MPP to expand its

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<sup>1</sup> 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](https://amr-review.org/sites/default/files/160525_Final paper_with cover.pdf) (accessed Feb 18, 2018).

<sup>2</sup> 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.

<sup>3</sup> 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).

<sup>4</sup> 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.

mandate beyond HIV, TB and hepatitis C. Over the coming months, the MPP will be working on prioritizing possible candidates for in-licensing, including exploring its possible role in relation to new antibiotics for combatting AMR.

In its feasibility 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.<sup>5</sup> 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.

### **Linking patent pooling to new financial incentives for R&D for antibiotics**

In the ongoing discussion on possible new incentive mechanisms that would contribute to strengthen the current antibiotic pipeline there is a general agreement, as approved by Member States at the UNHLM on AMR in 2016, that incentives should be designed “delinking the cost of investment in research and development on antimicrobial resistance from the price and volume of sales so as to facilitate equitable and affordable access” and should consider innovation, access and conservation holistically.<sup>6</sup> Public health-oriented patent pooling can contribute to de-linking the cost of R&D funding from sales and a number of proposals have identified patent pooling as a way in which IP on new antibiotics could be managed in a public health-oriented manner.

Licensing to the MPP could similarly be included as a possible requirement in milestone prizes offered by different innovative R&D financing mechanisms. Indeed, should a large end-stage prize for the development of antimicrobials eventually be established, 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 awarded an end-stage prize. For antibiotics that are meant to be kept as last resort or for limited use (e.g. *Watch* and *Reserve* categories), additional incentives may be required for licensees to develop and manufacture them and make them available to those in need without largescale use that may result in the development of resistance.

The MPP could also work closely in collaboration with recent mechanisms established to support R&D for new antibiotics, such as CARB-X or GARDP. CARB-X, an initiative to stimulate the early-stage pipeline for antimicrobials targeting priority pathogens, has 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, the Global Antibiotic Research & Development Partnership (GARDP) envisioned a role for MPP in AMR, both as a potential in-licensor of

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<https://medicinespatentpool.org/uploads/2018/05/Feasibility-Study-Expansion-of-the-MPP-Mandate-And-Appendix-2018.05.24.pdf> (accessed July 9, 2018)

<sup>5</sup> 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).

<sup>6</sup> United Nations General Assembly. Political Declaration of the high-level meeting of the General Assembly on antimicrobial resistance. 2016. [http://www.un.org/ga/search/view\\_doc.asp?symbol=A/71/L.2&referer=/english/&Lang=E](http://www.un.org/ga/search/view_doc.asp?symbol=A/71/L.2&referer=/english/&Lang=E) (accessed July 6, 2018).

promising candidate compounds for further development, as well as a licensee of products successfully developed by GARDP.<sup>7</sup>

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.<sup>8</sup> 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<sup>9</sup>. 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).<sup>10</sup> This is consistent with the standards used by the Global Fund, Unitaaid 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

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<sup>7</sup> 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)

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

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

<sup>10</sup> 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.

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 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 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 sublicense 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”.<sup>11</sup>

- *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

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<sup>11</sup> Industry Roadmap for Progress on Combating Antimicrobial Resistance –September 2016. 2016.

fixed-dose combinations of antibiotics has been reported in India.<sup>12</sup> 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 WHO and other experts, MPP licences could define permissible uses and permissible combinations.

## Conclusion

While the patent pool model has so far only been applied to specific diseases, the model can be adapted to other areas beyond HIV, HCV or TB. As demonstrated in the case of HIV, non-exclusive voluntary licensing through a patent pool can be a cost-effective mechanism to enhance access to needed health technologies in developing countries and facilitate innovation, such as the development of needed formulations, such as medicines for children or new fixed dose combinations.

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 mechanism to supporting these objectives, particularly if combined with incentives for the clinical development and manufacturing of new antibiotics.

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<sup>12</sup> 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.