MPP Report to the 24th Expert Committee on The Selection and Use of Essential Medicines

Executive summary

In 2019, the 22nd WHO Expert Committee on the Selection and Use of Essential Medicines (EC) requested the Medicines Patent Pool (MPP) to explore licensing possibilities for patented medicines added to the WHO Model List of Essential Medicines (EML) in order to support affordable access in LMICs. In 2021, the EC went one step further, requesting that MPP explore the possibility of also licensing a number of patented cancer medicines that were not yet recommended for EML inclusion but had potential for future inclusion. In addition, the 22nd EC asked MPP to explore whether and how its licensing model could be applied to biotherapeutics, so as to facilitate early entry of biosimilars in LMICs through voluntary licensing agreements. This report provides the EC with an update on the activities performed by MPP since the last EC meeting. It presents some of the licences that MPP has obtained, including its first licence for an essential medicine for cancer, and licences on three other WHO-recommended medicines, two of which have been submitted for EML inclusion this year. The report also updates the Committee on MPP's recent expansion into biotherapeutics following a detailed assessment of the potential applicability of its model. The report concludes with an overview of the medicines that have been submitted for EML inclusion at this year's EC that are patent protected.

Background

The Medicines Patent Pool (MPP) was established by Unitaid in 2010 as a public health organisation with a mandate to accelerate access to affordable and quality-assured HIV treatments in developing countries through an innovative voluntary licensing (VL) and patent pooling mechanism. It negotiates intellectual property (IP) licensing agreements with patent holders to allow generic manufacture and supply of medicines in low-middle income countries (LMICs). The MPP model seeks to ensure new treatments are more widely available at an affordable price several years prior to patent expiry. In addition, licences enable LMIC-focused innovation, such as the development of new fixed-dose combinations and special formulations for children needed in resource-limited settings.[1]

The purpose of this document is to provide the 24th WHO Expert Committee (EC) for the Selection and Use of Essential Medicines with an update on the progress made by MPP in facilitating affordable access to innovative medicines, especially in relation to the recommendations made by the previous Expert Committees.

In 2021, the 23rd EC requested MPP to explore licensing possibilities for newly added patented candidates in the Essential Medicines List, namely enzalutamide, ibrutinib, and the SGLT2 inhibitors. Additionally, the EC asked MPP to consider applying its licensing model to a number of patented medicines that were not yet recommended for inclusion, either because not cost-effective at current prices, or because of the lack of sufficient evidence, but that had potential for future inclusion. These candidates were cyclin-dependent kinase 4/6 inhibitors, daratumumab, osimertinib, PD-1/PD-L1 immune checkpoint inhibitors, and zanubrutinib.[2] In 2019, the 22nd Expert Committee asked MPP to explore whether and how its model could be applied to biotherapeutics, so as to facilitate early entry of biosimilars through voluntary licensing agreements in LMICs.[3]

[1] https://medicinespatentpool.org/what-we-do/licensing-for-public-health/
[2] https://www.who.int/publications/i/item/9789240041134
[3] https://www.who.int/publications/i/item/WHO-MVP-EMP-IAU-2019.05

This update will build on the Report that was submitted to the EC in 2021, and will focus on the developments that have taken place during the reporting period of 2021-2023.[4]

Specifically, it will cover the following areas:

1. Achievements in facilitating access to drugs already in the WHO EML;
2. Expansion of MPP's mandate to include biotherapeutics;
3. New submissions: licensing activities already ongoing and patent status of medicines submitted for inclusion in the 2023 model list.

1. Achievements in facilitating access to drugs already in the WHO EML

Since its establishment in 2010, the MPP has relied on the WHO Essential Medicines List and WHO Guidelines as key references to prioritize its actions and activities. Table 1 provides a list of all essential medicines for adults or children for which MPP has successfully negotiated licence agreements.

In 2022, MPP achieved a significant milestone in the non-communicable diseases (NCDs) space by signing the first-ever public health-oriented voluntary license agreement for a cancer medicine with Novartis. The licensed product, nilotinib, was included in the EML in 2017 for the treatment of Chronic Myeloid Leukemia in adults and in 2019 in the EML for children.[5] As of the submission of this report, the MPP team is completing the selection of generic manufacturers who will produce and provide the generic version of nilotinib in the countries covered by the license.

As this is the first license in the NCDs space, MPP is also supporting the identification of the proper regulatory pathway for quality assurance of generic versions of the product. Since the countries that are home to the Stringent Regulatory Authorities (SRAs) are not part of the licensed territory and the products are still patent protected in such countries, filing with SRAs is not a viable option. For HIV medicines, MPP licensees have traditionally been using the USFDA/PEPFAR expedited tentative approval pathway as well as the WHO Prequalification (PQ) Programme, whereas in other disease areas (like hepatitis C and COVID-19) WHO Prequalification has been the main mechanism being used. Reliance on WHO PQ can also facilitate subsequent national approvals through the Collaborative Registration Procedure. In the case of NCDs, most of the medicines included in the WHO EML have not yet been included in the WHO Prequalification Programme Expression of Interest. Options are currently being explored in discussion with the WHO Secretariat.

In addition, MPP has also obtained licences on three medicines recommended by WHO treatment guidelines, namely cabotegravir long-acting for HIV pre-exposure prophylaxis, and molnupiravir and nirmatrelvir for COVID-19, currently submitted for inclusion in the list. In the case of the two COVID-19 antivirals, generic versions have already been developed, have received approval and are being supplied in countries covered by the respective licences. In the case of cabotegravir, the sub-licensees have recently been announced and the generic versions will be developed in the coming years.

[4] https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/late-papers/l1_mpp-report.pdf?sfvrsn=79add055_3
[5] https://medicinespatentpool.org/licence-post/nilotinib

In relation to other medicines highlighted by the EC for licensing, MPP has reached out to the respective innovators and has been making the case for licensing, but no other licences have been concluded to date.

The full list of MPP in-licensing priorities can be found in the MPP Prioritization Report, on our website.[6]

Table 1. List of essential medicines for which MPP has licensing agreements with the patent holders (it should be noted that the patents on some of these medicines have since expired):[7,8]

Medicine(s)	Indication in the EML/EMLc
Abacavir (paediatrics)	HIV
Abacavir/lamivudine	HIV
Atazanavir	HIV
Atazanavir/ritonavir	HIV
Daclatasvir	Hepatitis C (pangenotypic)
Darunavir*	HIV
Dolutegravir	HIV
Glecaprevir/pibrentasvir	Hepatitis C (pangenotypic)
Lopinavir/ritonavir (adults and pediatrics)	HIV
Nilotinib	Chronic Myeloid Leukaemia
Raltegravir (paediatric)	HIV
Ritonavir	HIV
Tenofovir disoproxil fumarate	HIV /Chronic Hepatitis B/Post exposure prophylaxis
Tenofovir disoproxil fumarate/emtricitabine	HIV/Post exposure prophylaxis
Tenofovir disoproxil fumarate/emtricitabine /efavirenz	HIV
Tenofovir/lamivudine/efavirenz	HIV
Valganciclovir#	Cytomegaloviral retinitis

* Licence did not cover all relevant patents on the product; # Price agreement

In order to translate the effect of these access-oriented voluntary licence agreements into public health impact, we developed a new impact methodology to assess the public health and economic benefits of access-oriented voluntary license agreements. Our methodology examined licensing contributions to affordability, scale-up rates, and uptake volumes, and estimated the associated effects on health and cost savings.[9]

[6] https://medicinespatentpool.org/what-we-do/prioritising-medicines-for-licensing
[7] https://list.essentialmeds.org/
[8] https://medicinespatentpool.org/progress-achievements/licences
[9] Morin, Moak, Bubb-Humfryes, von Drehle, Lazarus, Burrone (2022) The economic and public health impact of intellectual property licensing of medicines for low-income and middle-income countries: a modelling study. The *Lancet Public Health*, **7(2):** E169-E176. https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(21)00202-4/fulltext

We, therefore, estimated that, between 2010 and 2021, MPP licenses enabled the supply of 26.91 billion doses of treatment in 148 countries, generating economic savings of 1.2 billion USD for the global health community. Based on our projections until 2030, we anticipate that these licenses will avert 160,000 deaths, 1.1 million DALYs, and generate economic savings of 3.5 billion USD for the global health community.[10]

2. Expansion of MPP's mandate to include biotherapeutics

Following the recommendation of the EC in 2019, MPP worked on a feasibility assessment that led its board to approve "*the inclusion of biotherapeutics in the scope of MPP's work on medicines that are either on the WHO EML or have strong potential for future inclusion.*"[11]

The assessment aimed to explore whether and how MPP model could be applied to biotherapeutics and includes considerations, requirements, and opportunities for public health non-exclusive licensing (in particular through the Medicines Patent Pool) to improve access to biotherapeutics in LMICs. The full assessment has recently been published in *The Lancet Global Health*.[12]

We would like to highlight a few key findings identified through the assessment, as they may be relevant also for Expert Committee when selecting essential medicines and reflecting on their use and affordability:

i. Identify biotherapeutic priority targets for licensing focusing on drugs that show the largest incremental benefit over the standard of care and any expected alternative pipeline candidate;

Identification of appropriate biotherapeutics for which licensing could contribute to access is critical. Given their likely higher complexity and cost, biotherapeutics would need to confer a substantial advantage in terms of efficacy, safety, and/or convenience over small molecule alternatives to justify a potentially higher cost. Further, the analysis of the added clinical benefit should not only be performed versus the current standard of care but should also take into consideration whether any small molecules are under development for the same therapeutic use that could be less costly to develop and that could be made available at more affordable prices.

ii. Support biosimilar development, including assistance around regulatory strategies, to reduce costs and timelines from development to market entry and explore the inclusion of technology transfer and access to reference product as part of licensing agreements;

Our findings suggest that for most biosimilars, development timelines and costs are driven to a large extent by the amount of clinical work required to obtain regulatory approval. In particular, the need in some cases to undertake phase 3 comparative efficacy trials contribute to driving up costs significantly. Nevertheless, the study noted that over recent years there is an evolution in the policies of some regulatory authorities in this regard. For example, the European Medicines Agency states that, in specific circumstances, a confirmatory trial may not be necessary if "similar

[10] https://medicinespatentpool.org/progress-achievements/impact
[11] https://medicinespatentpool.org/who-we-are/governance-team/governance-board-decisions
[12] Morin, Segafredo, Piccolis, Das, Das, Loffredi, Larbi, Mwamelo, Villanueva, Nobre & Burrone (2023) Expanding access to biotherapeutics in low-income and middle-income countries through public health non-exclusive voluntary intellectual property licensing: considerations, requirements, and opportunities. *The Lancet Global Health*, **11(1):** E145-E154, https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(22)00460-0/fulltext.

efficacy and safety can be clearly deduced from the similarity of physicochemical characteristics, biological activity, pharmacokinetic and pharmacodynamic profiles of the biosimilars with the reference product". Clinical trial waivers could substantially decrease both the costs and the time required for the development of biosimilars. And a full technology transfer increases the likelihood of obtaining a clinical trial waiver, particularly in the case of simpler biologics. However, the acceptance of clinical trial waivers in LMICs appears not to be widespread. More generally, a diversity in requirements in different countries can make the development of products for supply in multiple LMICs challenging and further drive-up costs.

In addition to potentially facilitating the regulatory pathway, a full technology transfer can also offer additional advantages for biosimilar manufacturers, including reducing the risk of failure. The findings also suggest that the costs for accessing the reference products needed to run both analytical comparability assays and preclinical and clinical trials in some cases constitute a substantial portion of the costs of development (reaching up to 73% of the total investment needed for certain products). Access to reference products at low prices (which potentially could be included in a licensing agreement, as has happened in a recent Medicines Patent Pool licence on a COVID-19 antiviral), could therefore be important to reduce development costs and enable more affordable biotherapeutics in LMICs.

iii. Expanding the use of biosimilars in LMICs, leveraging mechanisms aimed at early price reductions, aligning with country-and region-specific treatment priorities and relevant infrastructure-strengthening efforts.

In our assessment, we examined cost-effectiveness, procurement, supply chain, and health system requirements. Pricing is one of the key determinants of access to biotherapeutics. But the price of medicines is subject to considerable variations, which can have a positive (or negative) impact on their cost-effectiveness profile and on the number of patients accessing them. As observed with small molecules, registration, and market entry of multiple generics/biosimilars can contribute to substantially reducing prices. Data from multiple countries suggest that monoclonal antibody price reductions to attain cost-effectiveness can take time and are more likely with substantial biosimilar competition. Non-exclusive licensing to more than one manufacturer and supporting the pool of licensees could help to build competition more quickly, as has been demonstrated through MPP licenses for small molecule medicines. In addition to this effect on competition, as said earlier, licensing and technology transfer could reduce the costs of biosimilar development enabling steep and early price reductions in LMICs, and accelerating the path toward affordability and cost-effectiveness.

Assuming that biosimilars can be made available at a more affordable price, the successful uptake of a biotherapeutic in low-resource settings may require holistic and multistakeholder interventions aimed at strengthening the health system and its capacity for delivering care. This may be particularly the case for certain therapeutic areas in which highly effective biotherapeutics are available today, including some of those on the WHO EML. Aligning with national and regional priorities is critical to ensure that efforts are directed toward those biologics that can provide the greatest impact on public health in LMICs. The newly launched Access to Oncology Medicines (ATOM) coalition, convened by the Union for International Cancer Control, with several public, and private sector partners (including MPP), aims to provide coordinated efforts towards the provision of comprehensive cancer care in LMICs, including strengthening the supply chain, capacity building, advocacy, demand generation, and training.

As part of MPP's expansion into biologics, and in order to enhance its capacity to undertake technology transfer in this area, a new Technology Transfer team has been put in place at MPP which is currently overseeing, together with WHO, the implementation of the mRNA technology

transfer programme, a global initiative that aims to improve health and health security by establishing sustainable, locally owned mRNA manufacturing capabilities in and for LMICs.[13]

3. New submissions: licensing activities already ongoing and patent status of medicines submitted for inclusion in the 2023 model list

A total of 52 new medicines applications were submitted for review by the 24th Expert Committee for the Selection and Use of Essential Medicines. Three have already been licensed to the MPP (COVID-19 antivirals molnupiravir and nirmatrelvir/ritornavir and hepatitis treatment ravidasvir) while many others are no longer protected by patents. Table 2 lists the medicines that were submitted and that still have some active patents in LMICs. The expected date of patent expiry is also reported. However, these dates may vary depending on the countries in which they were filed/granted.

Table 2. List of medicines submitted for EML inclusion that are still protected by a primary or secondary patent

Reference of the application submitted and drug or class submitted	INN	Disease/Area	Primary patent expiry - compound(s)	Secondary patent expiry
A.4 Anti-Ebola Virus Disease Monoclonal Antibodies	Ansuvimab-zykl (mAb114)	Acute Ebola virus disease	2035	
	Atoltivimab, maftivimab, and odesivimab-ebgn (REGN-EB3)	Acute Ebola virus disease	2036	2041
A.5 Anti PD-L1 immune-checkpoint inhibitors	Pembrolizumab	Non-small cell lung cancer	2028	2032
	Atezolizumab	Non-small cell lung cancer	2029	2034
	Cemiplimab	Non-small cell lung cancer	2035	2038
	Durvalumab	Non-small cell lung cancer	2030	2037-2040
A.6 Baricitinib	Baricitinib	COVID-19	2029 - 2032	2032
A.8 CD-19-directed CAR-T cell therapy	Axicabtagene ciloleucel	Large B-cell lymphoma	TBD*	
	Tisagenlecleucel (square box)	Large B-cell lymphoma	2031	
	Lisocabtagene maraleucel	Large B-cell lymphoma	TBD*	
A.9 Ceftolozane/tazobactam	Ceftolozane/tazobactam	Bacterial infections due to MDR organisms	2023 (ceftozolane)	2032-2035
A.10 Multiple sclerosis disease-modifying therapies (DMTs)	Rituximab/ocrelizumab	Multiple Sclerosis	2004-2006/2023	2024-2030/2029, 2036
	Cladribine	Multiple Sclerosis	2005	2024-2041
	Glatiramer acetate	Multiple Sclerosis	2014-2015	2028, 2030
A.12 Cyclin-dependent kinase 4/6	Palbociclib	Hormone receptor positive/ HER2-negative advanced breast cancer	2023	2034
	Ribociclib	Hormone receptor positive/ HER2-negative advanced breast cancer	2027-2029	2031, 2036

[13] https://medicinespatentpool.org/what-we-do/mrna-technology-transfer-programme

	Abemaciclib	Hormone receptor positive/ HER2-negative advanced breast cancer	2029	2035-2038
A.13 Deferiprone	Deferiprone	Sickle cell disease and beta-thalassemia	Expired	2038
A.18 Glucagon-like peptide-1 (GLP-1) analogues	Liraglutide	Weight loss in obesity	2017	2022 (formulation) 2024 (MOT) 2025-2029 (devices)
	Semaglutide	Weight loss in obesity	2026	2023-2026 (solution) 2031,2033 (oral)
A.20 Imipenem/cilastatin/relebactam	Imipenem/cilastatin/ relebactam	Bacterial infections due to MDR organisms	2029 (Relebactam)	
A.24 Levetiracetam	Levetiracetam	Epilepsy	2005	2026
A.25 Molnupiravir	Molnupiravir	COVID-19	2035-2038	2024-2041
A.26 Naltrexone	Naltrexone	Alcohol use disorder	1986	Expired (Tablet) 2025 (formulation Extended release)
A.27 Nirmatrelvir/ritonavir	Nirmatrelvir/ritonavir	COVID-19	2041	
A.28 Ocrelizumab	Ocrelizumab	Multiple Sclerosis	2023	2029, 2036
A.30 Osimertinib	Osimertinib	Non-small cell lung cancer	2032	2035
A.34 Pretomanid	Pretomanid	MDR-TB or RR-TB	2016	2036(combi)
A.35 Quetiapine (square box)	Quetiapine	Bipolar disorder	2007	
	Aripiprazole	Bipolar disorder	2009	2022-2039
	Olanzapine	Bipolar disorder	2011	
	Paliperidone	Bipolar disorder	2009	2028
A.36 Ravidasvir	Ravidasvir	Hepatitis C	2029	
A.38 Remdesivir	Remdesivir	COVID-19	2029 2035	2031-2038
A.40 Risdiplam	Risdiplam	Spinal muscular atrophy	2033, 2035	2036
A.44 Tedizolid Phosphate	Tedizolid phosphate	Bacterial infections due to MDR organisms	2024	2030
A.45 Ticagrelor	Ticagrelor	Atherothrombotic events	2019 2024 (EP & US)	2027, 2036
A.46 Tislelizumab	Tislelizumab	Non-small cell lung cancer	2033	
A.47/A.48 Tocilizumab	Tocilizumab	COVID-19/Systemic onset juvenile idiopathic arthritis	2010	2023-2028
A.49 Toripalimab	Toripalimab	Nasopharyngeal and Oesophageal cancer	2034	2041

A.51 Ustekinumab	Ustekinumab	Severe psoriasis	2021	
A.52 Zanubrutinib	Zanubrutinib	Chronic lymphocytic leukaemia/small lymphocytic lymphoma	2034	2037

*To Be Defined, further analysis required

MPP looks forward to hearing the conclusions of the EC to update its list of licensing priorities. Small molecules and biotherapeutics that, according to the opinion of the EC, meet the clinical and public health relevance criteria and for which voluntary licensing could contribute to addressing some of the access gaps in LMICs, will be prioritized for MPP licensing. As happened in 2021, it would be important that the EC consider flagging not only medicines that are ready for EML inclusion, but also those that appear promising and for which interventions to facilitate future affordability could be important. As has been seen for other patented medicines that were added in the past, it is important to begin to work on addressing access issues early on, so as to avoid products being added to the EML that then continue to have limited access for several years.

Conclusion

Since 2010, MPP is contributing to improving access to affordable and quality-assured essential medicines. Over the years, the organization has expanded its focus to respond to urgent public health needs in LMICs, including NCDs, COVID-19, and biotherapeutics.

In 2022, MPP achieved a significant milestone by signing its first licence for an essential cancer medicine, nilotinib. This is a strategic opportunity to demonstrate the effectiveness of voluntary licensing in improving access to cancer medicines in LMICs. It is also hoped that this represents a first step for licensing in the NCDs field and that it will be possible to conclude additional licences for other prioritized NCDs medicines.

To conclude, MPP would like to reiterate two key asks. First, that the Committee continues to work on identifying promising new treatments early on where licensing could contribute to future affordability, given the huge current focus on equitable access. This was already done in 2021 for a number of cancer medicines and would ideally be done in relation to other disease areas too. Taking into consideration that it can take years for generic/biosimilar versions of licensed medicines to be developed, it is important to start working on licensing early in order to reduce the time lag from the availability of promising new treatments in high-income countries to their availability at affordable prices in LMICs.

Second, it would be important that when identifying medicines for which licensing effort should be explored, the Committee and/or the Secretariat also identify relevant quality assurance pathways so that, if licences are obtained, quality-assured generics or biosimilars can rapidly be developed and made available in LMICs.