MPP Report to the WHO Expert Committee on the Selection and Use of Essential Medicines

Executive summary

In 2019, the Report of the WHO Expert Committee on the Selection and Use of Essential Medicines acknowledged the significant role played by the Medicines Patent Pool (MPP) in facilitating affordable access to essential medicines in the field of HIV and hepatitis C virus (HCV) and noted that licensing to MPP could contribute to facilitating access to some of the cancer medicines, the novel oral anticoagulants, the new antibiotics, the heat-stable formulation of carbetocin and medicines for tuberculosis that are listed on the WHO Model List of Essential Medicines (EML). The Committee also recommended that MPP explore the application of its model to biotherapuetics so as to facilitate early entry of biosimilars through voluntary licensing agreements in LMICs. This report provides an update on MPP's progress in facilitating access to essential medicines in LMICs. It also provides an update on its ongoing assessment relating to biotherapeutics, identifies some of the medicines submitted for inclusion in the EML that have patents filed or pending in low-middle income countries (LMICs) and mentions some challenges that need to be addressed to improve the likelihood that the licensing of patented essential medicines (particularly in the field of NCDs) can result in public health impact on the ground.

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 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 aim of this document is to provide an update to the 23rd WHO Expert Committee (EC) for the Selection and Use of Essential Medicines on the progress made by MPP in facilitating affordable access to medicines included in the WHO EML, in view of the EC's recommendations in 2019. More specifically, it focuses on:

1. Achievements to date in facilitating access to drugs already in the WHO EML;
2. Mandate expansion to other disease areas of the EML;
3. Ongoing activities and opportunities to increase access to essential medicines for non-communicable diseases;
4. Ongoing assessment for expansion into biotherapeutics;
5. Overview of patent status of medicines submitted for inclusion in the 2021 EML.

1) Achievements to date in facilitating access to drugs already in the WHO EML

Since its establishment, MPP has been working closely with WHO in identifying medicines for licensing, mapping patents on essential medicines, supporting the development of affordable versions of WHO-recommended products and scaling up access to those medicines in LMICs.

Table 1. List of essential medicines for which MPP has licensing agreements with the patent holders:[2,3]

Medicine(s)	Indication in the EML/EMLc
Abacavir (paediatrics)	HIV

[1] https://medicinespatentpool.org/what-we-do/licensing-for-public-health/
[2] https://list.essentialmeds.org/
[3] https://medicinespatentpool.org/progress-achievements/licences/

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Abacavir/lamivudine	HIV
Atazanavir	HIV
Atazanavir/ritonavir	HIV
Daclatasvir	Hepatitis C (pangenotypic)
Darunavir*	HIV
Dolutegravir	HIV
Glecaprevir/pibrentasvir	Hepatitis C (pangenotypic)
Lopinavir/ritonavir	HIV
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

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

A practical example to illustrate MPP's role in facilitating affordable access to an EML drug is the agreement between MPP and ViiV Healthcare on the HIV medicine dolutegravir (DTG). The licence was signed in 2014, less than one year after USFDA approval. In just 4 years from USFDA approval, MPP licensees had not only developed generic versions of DTG but also a new fixed-dose combination of tenofovir/lamivudine/dolutegravir (TLD) which combines the WHO-preferred treatment regimen into a single pill.[4] Both DTG and TLD are now in the WHO EML (added in 2017 and 2019 respectively) and, as of December 2020, 11 MPP sublicensees had received quality assurance and supplied over 330 million packs of generic DTG or TLD in 113 countries.[5]

Between January 2012 and June 2020, 141 countries have benefitted from access to MPP-licensed products. Generic partners have distributed over 15 billion tablets of HIV and hepatitis C medicines, saving international procurers USD 1.66 billion.[6]

2) MPP mandate expansion to other disease areas of the EML

In 2017, MPP undertook a feasibility study exploring the public health need for, and potential feasibility and impact of, expanding its work into patented essential medicines in other therapeutic areas beyond HIV, TB and HCV. The assessment included an analysis of epidemiology, treatment, market, patent and pricing landscape in LMICs, supplemented with case studies from several countries to better understand local environments.

The findings of the feasibility assessment[7], published in May 2018, showed that there was a substantial public health need in LMICs for access to affordable, quality-assured generic versions of certain medicines that were currently patent-protected, which could contribute to reducing morbidity and mortality. The feasibility study identified five categories of medicines for which public health-oriented licensing could be an important strategy to improve access. These categories include:
i) Patented medicines in the WHO EML;
ii) Patented medicines that are not included in the EML yet because of insufficient cost-effectiveness;
iii) Patented medicines that show promising clinical data and may be included in the EML in the future;
iv) Patented cancer medicines under consideration by a specific working group of the EC;
v) New antimicrobials.

[4] https://medicinespatentpool.org/news-publications/mpp-publications/
[5] https://medicinespatentpool.org/progress-achievements/access-to-medicines-tracker#Interactive-Table/
[6] https://medicinespatentpool.org/progress-achievements/impact/
[7] https://medicinespatentpool.org/resource-post/exploring-the-expansion-of-the-medicines-patent-pools-mandate-to-patented-essential-medicines/

For each group, a case study was selected and developed.[8] The study led to a phased expansion of MPP's mandate to small molecules in the EML and those with strong potential for future inclusion.

3) Ongoing activities and opportunities to increase access to essential medicines for non-communicable diseases

In 2019, the 22nd EC acknowledged the role of the MPP as a mechanism to facilitate affordable access to innovative and essential medicines in LMICs, highlighting specific products where MPP could make a difference: *"licensing through the MPP could contribute to facilitating access to some of the cancer medicines, the novel oral anticoagulants, the new antibiotics and the heat-stable formulation of carbetocin"* and "*licensing through the MPP of patented essential medicines for the treatment of tuberculosis (e.g. bedaquiline) would also be a welcome contribution to improving access."*[9] In addition, newly added medicines for the treatment of chronic obstructive pulmonary disease also had patents filed or granted in LMICs.

Table 2. List of essential medicines of the disease areas flagged as priorities by the Expert Committee for MPP

Product/class	INN *Alternatives	Patent expiry - compound(s) (primary)	Patent expiry - (secondary)	Indication
bedaquiline	bedaquiline	2023	2025-27	Tuberculosis
carbetocin	carbetocin		2031 (heat stable formulation)	Post-partum hemorrhage
Direct Oral Anticoagulants (DOACs)*	dabigatran*	2018; 2023 (mesylate salt)	2024	- Prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation - Treatment of venous thrombo-embolism
	apixaban*	2019 (generic); 2022 (specific)	2031	
	edoxaban*	2022	2028	
	rivaroxaban*	2020	2024, 2026	
EGFR TKI*	erlotinib*	2016	2020	Lung cancer
	afatinib	2021	2024	
	gefitinib	2016	2023	
dasatinib	dasatinib	2020	2024, 2025	- Imatinib-resistant chronic myeloid leukaemia
nilotinib	nilotinib	2023	2026	- Imatinib-resistant chronic myeloid leukaemia
lenalidomide	lenalidomide	2018	2024-2028	Multiple Myeloma
plazomicin	plazomicin	2028		- Carbapenem resistant infections
Long Acting Muscarinic Agent*	tiotropium*	2010	2021, 2023	Chronic obstructive pulmonary disease
	umeclidinium*	2025		
	glycopirronium*	2016	2021 treatment regimen; 2025 dry powder formulations	
	aclidinium*	2020 (in LMICs)	2028 Use by inhalation for COPD; 2029 compo for inhalation and use in COPD	

* therapeutic equivalence within the class

Since 2019, MPP has been working in the context of its expanded mandate to apply its licensing model in new therapeutic areas, including those highlighted by the WHO Expert Committee. A key first step was to develop a robust evidence-based framework for the prioritisation of medicines for in-licensing to ensure MPP focuses its resources on medicines where its work could yield the greatest health impact. As in HIV and hepatitis C, the clinical part of this prioritisation work relies on the assessments performed by the WHO Expert Committee and on WHO guidelines, where such assessments exist. In addition, MPP

[8] Burrone E. Dzintars Gotham , Andy Gray , Kees de Joncheere , Nicola Magrini , Yehoda M Martei , Charles Gore & Marie Paule Kieny . Patent pooling to increase access to essential medicines. Bull World Health Organ 2019;97:575–577

[9] Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019

assesses whether there are access challenges with any given medicine in LMICs, and whether MPP licensing could contribute to addressing such challenges.[10]

It should be noted that the purpose of MPP licensing is to enable future affordability of promising patented medicines, bearing in mind that after a license is negotiated several years are needed for a quality-assured affordable generic version to be on the market (more on this below). At times, this has meant licensing of medicines not yet recommended by WHO (e.g. those identified as promising by WHO-led Conference on Antriretroviral Drug Optimization) or not yet approved (e.g. investigational tuberculosis treatment sutezolid) for which licensing could contribute to further development and/or future affordable access.

In the context of its prioritization, MPP undertakes an analysis of the patents status of medicines included in the EML. Such information is then published on MedsPaL (MPP's free patents and licences database), which is now the source for patent data on the online version of the WHO EML.

In addition to those highlighted by the EC, MPP also identified the SGLT2 inhibitors (which had received a positive clinical assessment from the EC in 2017 but were rejected because of the need of additional confirmatory trials in patients at high risk of cardiovascular events) and enzalutamide (reviewed by the EC in 2017 and 2019 and rejected mainly due to the unfavourable cost-effectiveness profile compared to abiraterone) as promising candidates to focus on.

In 2019/20, MPP initiated exploratory talks with patent holders to gather industry perspectives on the voluntary license model and to explore their potential willingness to partner with MPP to facilitate access in LMICs. MPP has longstanding relationships with companies operating in the field of HIV, HCV and TB. However, expanding into new therapeutic areas has meant building relationships with new companies and new teams who have never relied on voluntary licensing as an access strategy before. As was the case for HIV, this approach takes time, and requires the development of detailed business cases to each company making the case for licensing. This process was severely hampered by the COVID-19 pandemic, as it significantly delayed efforts with industry partners as well as other supportive stakeholders (including governments and civil society groups) many of which shifted priorities and resources to respond to the pandemic. In addition, for some of the products identified, patent expiry is relatively soon, and there may be limited scope for MPP intervention.

In the course of this first year and a half working in these new areas, a few key challenges have emerged that are outlined here for discussion and consideration of the EC.

i. **Timelines from licence to access can be long and it is important to begin identification of promising new treatments early on.** Typically, it has taken generic manufacturers 3 to 4 years to develop a generic version of a new medicine and obtaining approval from a stringent regulatory authority (SRA) or from WHO Prequalification. Waiting for a medicine to have proven its full clinical potential and to be considered cost-effective for inclusion in the WHO EML before it is prioritized for licensing risks delaying access significantly, as work on obtaining the license and then developing and registering the generic version takes several years. As a result, a medicine considered essential that is included on the EML, may not become accessible and affordable in LMICs for some time. This is why it is critical to begin to work on access beforehand. In areas like HIV, it has been possible to rely on WHO mechanisms to identify promising new medicines early on, enabling affordable access to be possible shortly after inclusion on the WHO EML. This is also an important lesson that is being learnt in the context of COVID-19, where early identification of promising treatments is done through ACT-A. In other areas, early assessments by WHO could enable early identification of promising new medicines,

[10] https://medicinespatentpool.org/uploads/2019/05/Prioritisation-Framework-MPP-New-Areas.pdf

which if made available as generics in LMICs through voluntary licences, could be important for public health. This could help to accelerate access to important new treatments in LMICs.

ii. **Need to ensure there is a regulatory pathway for quality assurance for patented essential medicines in NCDs.** For products identified by the Expert Committee where MPP could play a role, the traditional regulatory pathways that have been used in HIV and hepatitis C (namely US FDA's accelerated tentative approval under PEPFAR and WHO Prequalification) are currently not available. For NCD essential medicines for which patents have expired, approvals from SRAs can provide an avenue for quality assurance. For the patented ones, however, that is not the case. Prioritizing such medicines for WHO Prequalification could be an avenue to explore.

iii. **Need for listing in WHO EML to go hand in hand with broader efforts to improve access holistically**. While improving the availability and affordability of medicines in LMICs can be an important trigger to spur access, there are many challenges for access to NCD essential medicines in LMICs that also need to be addressed, including those linked to health systems capacity and diagnosis and the lack of public funding for the procurement of such medicines. All of these can have an impact on the ability of licences to lead to access in LMICs and therefore on the strength of the business case to provide licences. It is critical therefore to establish broad partnerships that will contribute to ensure that new products, if made available at affordable prices from licensed manufacturers, can indeed result in improving access on the ground. In recent years, broad initiatives have begun to be established that seek to address a range of different access challenges in a given field by combining the efforts of a broad range of stakeholders. One example is the Global Strategy to Accelerate the Elimination of Cervical Cancer. Similar initiatives for other NCDs can be an important way to approach access holistically and to ensure that the inclusion of a medicine in the WHO EML effectively leads to impact.

4) Ongoing assessment for expansion into biotherapeutics

In 2019, the report of the Expert Committee noted that *"in the case of cancer, it would be important that the MPP also explore the application of its model to biotherapeutics so as to facilitate early entry of biosimilars through voluntary licensing agreements in LMICs."*[9] Following the recommendation, and acknowledging that a growing number of biologics were added to the WHO EML, MPP initiated an assessment to evaluate its mandate expansion in this field. MPP's assessment seeks to understand whether, and if so how, MPP's licensing model could play a role in facilitating affordable access to new biotherapeutics in LMICs. The first phase of the study focused on the key differences in the development, registration, IP protection, manufacturing and distribution of biosimilars as compared to small molecule generics that could impact on the application of MPP's licensing model to biotherapeutics.

Biologics have undoubtedly contributed to tremendous medical progress over the last decades, but, despite the potential public health impact that these treatments could have, the international community has not yet succeeded in implementing models to facilitate affordable and sustainable access in LMICs.[11] The study highlighted some of the following issues:
Complexity: biologics are more complex molecules that require more complex, lengthy and costly development and manufacturing processes.
IP Protection: As is the case for small molecules, biologics are generally protected through several patents on the active ingredient, the formulations, the manufacturing processes and methods of use. In addition, trade secrets are particularly important in the case of biotherapeutics.
Regulatory pathway: with few exceptions, the current regulatory pathways for approval of biosimilars by SRAs are longer and considerably more costly than those for small molecule generics.

[11] Expanding access to monoclonal antibody-based products A global call to action. A report developed by IAVI and the Wellcome Trust. Available at: https://wellcome.org/reports/expanding-access-monoclonal-antibodies

Cost: the costs of independently developing a biosimilar that meets SRA requirements (without technology transfer) can be over 30 times higher than those of developing a standard small molecule. While those higher costs are primarily driven by expensive clinical trials, they are also due to lengthy and challenging analytical work, cell line development and procurement of batches of the reference product.
Small market: public procurement for biologics in most LMICs has genererally been limited and price declines not as pronounced as for small molecules.
Potential licensees: to date, few companies based in LMICs have succeeded in developing biosimilars and having them approved by SRAs such as EMA. The number, however, is rapidly increasing, as more companies develop the necessary expertise.
Technology transfer: technology transfer could play an important role in accelerating development and improving affordability of biosmilars in LMICs.
Opportunities: The study identified several opportunities that could contribute to reducing costs and timelines for developing biosimilar versions of important biotherapeutics and that could help to accelerate access and expand potential demand.

MPP is continuing with a second phase of its exploration focusing on several case studies to identify opportunities and challenges to further define the potential framework for intervention. These case studies will further inform a Board decision expected in October 2021.

5) Overview of patented medicines submitted for inclusion in the WHO EML in 2021

Approximately 40 applications were submitted for review by the 23rd Expert Committee for the Selection and Use of Essential Medicines. Some have already been licensed to the MPP (such as paediatric glecaprevir/pibrentasvir and paediatric sofosbuvir/daclatasvir) while many others are no longer protected by patents. Table 4 lists the medicines that were submitted and that still have some active patents in LMICs. Among these, are a number of cancer medicines, some of which have received high scores from the ESMO Magnitude of Clinical Benefits Scale (ESMO-MCBS), a scale that is used by the WHO's EML working group on cancer[12] in identifying potential medicines for inclusion. 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 4. List of medicines submitted for EML inclusion that are still protected by a primary or secondary patent

Drug or class submitted	INN	Disease/Area	Patent expiry – compound /primary	Secondary patent expiry
Anti- PD1 immune checkpoints inhibitors	Pembrolizumab#	non small cell lung cancer	2028	
	nivolumab#		2026	
	atezolizumab#		2029	
	durvalumab#		2030	
BRAK/MEK inhibitors	dabrafenib+ trametinib	metastic melanoma	Dabrafenib: 2029 Trametinib: 2025	dabrafenib: 2030-33 trametinib: 2030-33
	vemurafenib+ cobimetinib		Vemurafenib: 2024-26 Cobimetinib: 2026	Vemurafenib: 2030 Cobimetinib : 2036
	encorafenib+ binimetinib		Encorafenib: 2029 Binimetinib: 2023	Encorafenib: 2030-34 Binimetinib: 2030-33
cefiderocol	cefiderocol	infections due to multi-drug resistant organisms	2029	2035
Cyclin-dependent kinase (CDK) 4/6 inhibitors	palbociclib	HR+ /HER2- breast cancer	2023	2034
	ribociclib		2027-29	2031-36
	abemaciclib		2029	
daratumumab	daratumumab#	multiple myeloma	2036	
enzalutamide	enzalutamide	prostate cancer	2026-27	2033
ibrutinib	ibrutinib	chronic lymphocytic leukaemia	2026$	2031-36

[12] WHO EML cancer medicines working group (CMWG): report of the meeting 22-23 March 2018, Geneva, Switzerland

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zanubtrutinib	zanubtrutinib	chronic lymphocytic leukaemia & mantle cell lymphoma	2034	
osimertinib	osimertinib mesylate	EFGR+ non small cell lung cancer	2032	2035
Paliperidone and risperidone	paliperidone	schizophrenia	Expired	2028
	risperidone (long-acting)		Expired	2021
pertuzumab	pertuzumab[#]	metastatic breast cancer	2020 (extension to 2025-6 in some countries)	2023-29
Rabies monoclonal antibodies – rabies post-exposure prophylaxis	docaravimab[#]/miromavimab[#]	rabies post-exposure prophylaxis	2039	
	rabishield[#]	rabies post-exposure prophylaxis	2026	
SGLT2 inhibitors	dapagliflozin	type 2 diabetes	2020-23	2027-28
	canagliflozin	type 2 diabetes	2024	2027-31
	empagliflozin	type 2 diabetes	2025	2026-34
tislelizumab	tislelizumab[#]	urothelial carcinoma; Hodgkin lymphoma	2033	
tocilizumab	tocilizumab[#]	juvenile idiopathic arthritis	Expired	2022-28
varenicline	varenicline	smoking cessation	Expired	2022
everolimus	everolimus	subependymal giant cell astrocytoma	Expired	2022-26

[#] biotherapeutics

[$] Note that a generic version was recently approved for use in the United States.

MPP looks forward to hearing the conclusions of the EC to update its list of licensing priorities. Small molecules that, according to the opinion of the Committee, meet the clinical and public health relevance criteria and for which access gaps in LMICs could be addressed through voluntary licensing, will be prioritized for MPP licensing. As suggested above, 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 early to engage on access issues so as to avoid products being added to the EML that then continue to have limited access for several years. Moreover, if the MPP Board supports its mandate expansion to biotherapeutics, listed patented biologics will also be considered as potential priorities.

Conclusion

Since 2010, MPP has contributed significantly to facilitating affordable access to new essential medicines in LMICs in HIV and HCV. In 2019, the WHO Expert Committee flagged a number of newly added patented medicines as areas where MPP could potentially contribute to supporting affordable acces in LMICs. Further, a number of additional patented medicines have been submitted for inclusion in the WHO EML at this session, including a number of biotherapeutics. MPP will continue to make the case for licensing with the patent holders in order to support efforts at making EML medicines more available and affordable in LMICs. And as part of its ongoing assessment, MPP will continue to explore opportunities to support affordable access to biotherapeutics in LMICs.

Finally, MPP considers it important that: (i) the Committee consider the importance of identifying promising new treatments early (including those with affordability challenges, or requiring further clinical data to confirm importance, that may not be ready for EML inclusion); (ii) consideration be given to the most appropriate mechanisms for quality assurance for patented new treatments identified by the Expert Committee; and (iii) that inclusion in the WHO EML (or early identification of promising future EML treatments) represents a key element of a broader plan to support and facilitate access that takes into consideration all the different dimensions of access.