

FRAMEWORK FOR PRIORITISATION OF CANDIDATE MEDICINES FOR IN-LICENSING UNDER AN MPP EXPANDED MANDATE

BACKGROUND

Every year, the Medicines Patent Pool (MPP) publishes a list of priority medicines for in-licensing, following an extensive prioritisation process that includes consultations with a number of experts, review of the most recent data on each product, and application of a detailed methodology.¹ To date, this has been done for HIV, hepatitis C and most recently tuberculosis (TB). An important part of prioritisation is the development of a sound methodology that enables the MPP to focus resources on medicines where its work could yield the greatest impact.

In May 2018, after a year-long process of consultations and the development of a feasibility study,² the MPP announced the expansion of its mandate to other patented essential medicines beyond the three diseases that had been part of its mandate since 2015 (HIV, hepatitis C and TB). The Board decision noted that: *“the MPP should make a phased expansion, initially into small molecules listed in the WHO Model List of Essential Medicines as well as medicines with strong potential for future inclusion in view of their clinical benefits and potential for public health impact in low- and middle-income countries.”*

As the MPP begins implementation of its expanded mandate, there is a need to prioritise carefully in view of the wide range of products that the expansion could potentially include and the need for the MPP to advance in a phased and sustainable manner.

Such prioritisation requires the development of a methodology that takes into consideration the public health needs in developing countries, the potential access challenges relating to specific medicines and the potential for the MPP to address such challenges through its public health-oriented licensing and patent pooling model. This document presents the proposed framework for MPP prioritisation and overview of the process that led to its development.

GENERAL PRINCIPLES FOR THE PRIORITISATION FRAMEWORK

In developing the framework, we were guided by a number of principles. These were as follows:

- The methodology should draw from the existing methodology being used by the MPP for prioritisation of candidate medicines in HIV, hepatitis C and TB. It should also draw from the methodology used by the WHO in selecting medicines for inclusion in its Model List of Essential Medicines (WHO EML).

¹ The most recent iteration of the prioritisation document is available at:

<https://medicinespatentpool.org/what-we-do/target-medicines/>

² MPP, Exploring the expansion of the Medicines Patent Pool’s mandate to patented essential medicines, 2018. Available at: <https://medicinespatentpool.org/resource-post/exploring-the-expansion-of-the-medicines-patent-pools-mandate-to-patented-essential-medicines/>

- It should result in the prioritisation of medicines for which an MPP intervention could yield the greatest impact on public health in low- and middle-income countries (LMICs).
- In its clinical assessment, where possible, the MPP should rely on existing assessments by the WHO in order not to duplicate work and to align with established global health priorities
- Where such WHO assessments are not available, assessments by other reputable public health institutions should be taken into consideration
- The methodology should take into account the multiple challenges to access that may affect the likelihood of an MPP licence resulting in public health impact, including those that may impact on possible uptake and market size
- It should consider existing access initiatives being implemented by pharmaceutical companies as well as other stakeholders
- It should be sufficiently flexible to be relevant across various disease areas, with the possibility of adaptations to specific areas, where appropriate.
- The MPP should continue to focus on patented medicines

The methodology as presently designed does not capture the expected likelihood of a patent holder being willing to engage in licensing with the MPP. The idea is that the framework should follow a public health approach and focus on the public health relevance of the medicine and the potential for the MPP to contribute to overcoming access challenges. An important subsequent step is to initiate discussions with the patent holders of any identified candidates resulting from the application of the methodology, in order to assess the probability of obtaining a license for each specific product. This should be done in an ongoing basis and in parallel with the further evolution/progress of the screening process.

CONSULTATIVE PROCESS

The MPP undertook consultations with a wide range of stakeholders in order firstly to build the framework and then to prioritise medicines and identify candidate medicines to which the framework could be applied. Such discussions already started during the development of the feasibility study that led to the MPP expansion.

The objectives of these consultations were to:

- (i) discuss the criteria the MPP could apply in its prioritisation;
- (ii) understand possible additional barriers to treatment access in different therapeutic areas, so that they could be incorporated in the framework;
- (iii) explore access needs on the ground;
- (iv) understand priority areas/products/conditions for key stakeholders;
- (v) identify medicines that could be good candidates for MPP licensing;
- (vi) verify whether certain patents are likely to be blocking;

Consultations with governments: In January 2019, the WHO convened a consultation with governments and other agencies on essential medicines lists. In that context, the MPP was able to present its plans for expansion and a session was devoted to discussing possible products on which the MPP could focus, and to better understand how to develop a prioritisation framework that would incorporate the key variables. In addition, prior to the

consultation, the WHO included questions requested by the MPP in the survey on essential medicines that it shared with governments and other stakeholders. This feedback fed into the framework.

Consultations with civil society and patient groups: The MPP undertook a stakeholder mapping exercise in some of the therapeutic areas where it may seek to work, based on the work undertaken during the feasibility study. In parallel to the stakeholder mapping, efforts are ongoing to engage with groups in the new disease areas and to consult on possible target medicines on which the MPP could work.

Consultations with its Governance Structures (wondering why Governance Structures is capitalised): In October 2018, the MPP presented initial ideas on how to adapt its prioritisation methodology to the Board and gathered feedback to work on the first draft of a prioritisation methodology. An outline of such a methodology was discussed with the Expert Advisory Group (EAG) in December 2018 and was followed up with exchanges with targeted members of the EAG.

Clinical experts: The MPP continued reaching out to clinical experts, including specialists in the possible new areas, to improve the prioritisation framework and to get a firmer understanding of priority products and possible challenges for diagnosis and treatment. This too built on contacts earlier established during the conduct of the feasibility study.

Consultations with generic manufacturers. Discussions with manufacturers sought to (i) better understand the extent to which certain secondary patents are likely to block generic market entry, and (ii) identify products for which manufacturers would be interested in obtaining licences from the MPP. These interactions helped to refine the framework, in particular with respect to how to address secondary patents.

While general interactions with select patent holders has continued during this period, discussions with patent holders on specific medicines take place once the MPP has identified possible candidates. In parallel to such discussions, the MPP will further consult with the generic manufacturers to assess willingness and feasibility for those specific medicines.

OVERVIEW OF THE PRIORITISATION FRAMEWORK

The framework was developed based on three key questions that it seeks to answer for each medicine that could be a candidate for in-licensing by the MPP. These questions are as follows:

1. How important is a given medicine (or the condition it treats) for LMICs?
2. Are there access challenges with respect to that medicine in LMICs?
3. Are MPP licences likely to lead to public health impact?

Under each question, there were a series of criteria that were developed, which are indicated in the table below.

Table 1 – Overview of the prioritisation criteria

PUBLIC HEALTH & CLINICAL RELEVANCE <i>How important is this medicine for LMICs?</i>	ACCESS CHALLENGES <i>Are there access challenges in LMICs?</i>	MPP VALUE ADD <i>Are MPP licences likely to lead to public health impact?</i>
<p>For medicines already reviewed by the WHO:</p> <ul style="list-style-type: none"> - WHO opinion on the clinical profile of the drug <p>For medicines not reviewed by the WHO:</p> <ul style="list-style-type: none"> - Opinion by other reputable entity - Disease burden in LMICs - Efficacy - Safety and tolerability - Ease of administration and scale-up in LMICs - Clinical relevance for special populations (if applicable): <ul style="list-style-type: none"> ○ Children ○ Other special populations 	<p>Access challenges in LMICs:</p> <ul style="list-style-type: none"> - Availability of product in LMICs - Affordability of product in LMICs - Existing access programmes (coverage, terms, sustainability) - Flagged by key stakeholder 	<p>Patent status in LMICs:</p> <ul style="list-style-type: none"> - Years of possible public health impact (patent expiry) - Geographical coverage of patents - Existence of generics <p>Potential for impact on access:</p> <ul style="list-style-type: none"> - Diagnostic needs - Health systems and infrastructure needs - Potential buyers - Market size

Annex 1 contains the detailed tables that include, for each criterion, the rationale, the key question(s) being answered, the scoring, explanations on how the criterion is applied and the data sources being used to collect the information.

IDENTIFICATION OF CANDIDATE MEDICINES FOR APPLICATION OF THE FRAMEWORK

The initial set of medicines that were put through the model were identified as follows:

- Patented medicines already included in the WHO EML
- Medicines assessed by the EML in 2015 or 2017 that were not included but noted as having relevant clinical benefits
- Patented medicines submitted for inclusion in the WHO EML in 2019
- Medicines flagged by certain stakeholders during consultations (governments, civil society, generics)
- Other medicines identified during the feasibility study

This led to the identification of a total of 52 medicines, which is the first set of medicines to be put through the model to identify a preliminary list of priority medicines for in-licensing.

In addition to the above, the MPP has undertaken a review of the products and pipelines of 16 pharmaceutical companies with potentially promising products, with at least three more planned for Q2. The objective of the product and pipeline reviews is to identify additional products that may be of interest to the MPP and that could be put through the framework at a subsequent date. Companies with products initially deemed to be potential candidates were prioritised for this analysis, so that initial discussions with those companies could be done on the basis of a good understanding of those companies' entire relevant portfolios. These medicines have not yet been put through the framework, and that is one of the next steps that have been identified.

It has also undertaken disease specific reviews for four diseases (hepatitis B, sickle cell, diabetes and new antibiotics) in areas that were considered promising for the MPP. Hepatitis B, for example, is an area in which the MPP already has two licences (TDF and TAF, both of which are also used for HIV treatment) and has high prevalence in LMICs. The application of the MPP model to any new hepatitis B medicines would be a natural extension of the MPP's current work. Sickle cell disease is particularly prevalent in malaria-endemic countries and diabetes is an exploding epidemic worldwide. A similar disease specific review could apply the approach to other therapeutic areas with a high burden of disease in LMICs, to identify any promising new treatments, including those in late-stage development, that for one reason or another may not have been considered for the WHO EML.

It should be noted that, given the decision of the Board on a "phased expansion" that would initially focus on small molecules, we have generally not focused on biologics for this initial prioritisation. The model, however, could in principle also be used for the prioritisation of biologics, but additional work would likely be needed to explore whether the model would be appropriate in that area (more on this under Next Steps below).

ADAPTATION OF THE FRAMEWORK FOR NEW ANTIBIOTICS

The above framework was partially adapted for new antibiotics, where certain criteria were modified. For example, whether a medicine has activity against a WHO priority pathogen was added as an important criterion for prioritising in the field of antibiotics. Similarly, questions relating to the market also need to take into consideration the need for stewardship of the medicine (which can further limit the market).

There are seven new antibiotics (including new combinations) that have been submitted for inclusion in the WHO EML in 2019. However, given the specific challenges in relation to antibiotics, as the MPP still explores its potential role in relation to antimicrobial resistance (AMR), it is too soon to undertake a full prioritisation of these medicines for in-licensing. A detailed analysis of each medicine has been undertaken for in-house purposes and will be expanded and concluded following decisions to be taken by the WHO EML .

NEXT STEPS

A number of next steps have been identified for the MPP to continue making progress on prioritisation and to continue engagement with the patent holders. These are as follows:

- **Apply the prioritisation framework to promising candidate medicines.** This would focus in particular on:
 - (i) medicines identified applying the methodology explained above
 - (ii) medicines identified in the company-specific product and pipeline reviews mentioned earlier
 - (iii) medicines identified in additional disease specific reviews that will be undertaken
 - (iv) additional cancer medicines that have obtained high scores on the European Society for Medical Oncology's Magnitude of Clinical Benefit Scale
- **Incorporate decisions to be taken by the WHO EML Committee in its meeting in April to the prioritisation framework.** It will be important for the MPP to take into account the Committee's decisions in its analysis and scoring of medicines.
- **Intensify engagement with patent holders.** Meetings will be conducted to explore opportunities and possible interest with patent holders. This may in some cases require the development of targeted business cases for individual medicines.
- **Continue to explore with key public health partners a potential role in relation to new antibiotics.** The MPP continues to interact with key stakeholders in the AMR space to explore a possible role for MPP licensing in relation to new antibiotics that take into account both access and stewardship considerations.
- **Undertake a market analysis on biologics.** While biologics were briefly analysed during the development of the MPP feasibility study, a more detailed market analysis would be needed to understand whether, and if so how, the MPP's model could be adapted to biologics. This may become important as a number of biologics are increasingly being identified by countries as medicines with significant affordability challenges. Many of the stakeholders consulted expressed an interest in the MPP exploring this possibility. It is therefore proposed to undertake a market assessment relating to antibiotics that could begin towards the end of 2019 or early 2020 depending on the availability of resources.

Annex – Prioritisation Framework

1. Public Health and Clinical Importance - How important is the medicine (or the condition it treats) in LMICs?				
Part A1: Medicines in the WHO EML, in WHO Guidelines or EML candidates on which a WHO body of experts (Expert Committee, WG etc) has provided opinions				
Sub-criteria	Key Question	Rationale	Explanation	Data Source
WHO opinion the clinical profile of this drug	1.1 Is the medicine recommended or considered essential by the WHO?	<p>Where the WHO (or its disease-specific expert working group) has expressed opinion on the clinical profile of a given medicine, the MPP does not intend to duplicate this effort but rather rely on this existing expert opinion.</p> <p>Where there is lack of WHO opinion, the MPP will resort to its own clinical criteria set out in Part A2.</p> <p>Regardless of whether or not there is WHO opinion, a medicine will also be assessed by criteria under Part B (if the scenario is applicable).</p>	<p>Medicines on the WHO EML or on WHO guidelines are high priority, followed by medicines with favourable clinical assessments that have not been included in WHO EML due to cost effectiveness or lack of sufficient data. Medicines rejected by the WHO EML for lack of clinical benefits or excluded from WHO guidelines are not a priority for the MPP.</p> <p>Medicines recommended by WHO as "preferred" treatments in a WHO Guideline score the highest.</p>	<p>WHO Essential Medicine List, prior WHO EML Committee reports</p> <p>WHO guidelines (if applicable to a given disease)</p>
Part A2: Medicines not yet in the WHO EML, nor endorsed by a WHO body of experts				
Sub-criteria	Key Question	Rationale	Explanation	Data Source
Endorsement by other parties	1.1 Has this drug (or its pharmacological class) been recommended by other major public health bodies or professional associations?	<p>In absence of WHO opinion, favourable opinions from a reputable public health body or professional association will be taken into consideration by the MPP.</p> <p>Designations of FDA Breakthrough Therapy or EMA PRIME (priority medicines) will also be taken into account.</p>	No penalty for no endorsement. Whether this leads to a No-Go depends on the context of the review and the weight carried by such opinion.	Reports, guidelines and analyses by reputable organizations in the specific field
Disease burden in LMICs	1.2 What are the incidence and prevalence of this disease?	The MPP seeks to focus on medicines with high disease burden in LMICs	Prevalence, incidence, DALYs are used to assess the disease burden in LMICs	Analysis from the Global Burden of Disease
Efficacy	1.3 How does the efficacy of this drug compare with that of standard-of-care (SOC) in LMICs?	The MPP would seek to focus on medicines that improve the standard of care in LMICs, including in particular medicines that offer benefits in terms of efficacy.	<p>Efficacy could mean primary, or primary and secondary endpoints depending on the disease and trial design. SOC is defined as the SOC used in LMICs. Where this is not applicable, SOC is what is in the EML for the same indication. If neither is applicable, then the framework uses SOC as defined in HICs prior to the entry of a new drug. Score is reduced if quality of evidence is low at the time of assessment</p> <p>Specifically for cancer drugs, it follow ESMO-MCBS (if applicable). Where ESMO assigned different MCBS by different indication, MPP will use the score for the indication that has been submitted for EML review, and/or indication that represent the greatest burden of disease in LMICs.</p>	Clinical trial results as published in peer reviewed journals or major conferences; ESMO MCBS for cancer medicines
Safety & tolerability	1.4 How does the safety and tolerability profile compare with those of SOC?	The MPP would seek to focus on medicines that improve the standard of care in LMICs, including medicines with improved safety and tolerability profiles	<p>The score is reduced if the quality of evidence is low at the time of assessment.</p> <p>This criterion is skipped for cancer medicines if the drug is for solid tumors, as ESMO-MCBS covers efficacy, toxicity and QoL, which will already be covered under the Efficacy criterion</p>	Clinical trial results as published in peer reviewed journals or major conferences; ESMO MCBS for cancer medicines
Ease of administration and scale-up in RLS	1.5 Is this drug / formulation relatively convenient to administer, and to scale up in resource-limited settings?	Medicines may have comparable efficacy and safety but have advantages over the standard of care in terms of convenience and extent to which it is adapted for scale-up in resource limited settings. For certain medicines, this may be the key value add from a public health perspective.	Factors to consider include: heat stability, food requirement, booster requirement, drug-drug interaction with WHO-preferred 1st line therapies of key co-morbidities; and if applicable: ease of administration by patient or community health workers without significant training or safety concern, infrequent dosing interval that could improve patient adherence.	Clinical trial results as published in peer reviewed journals or major conferences; ESMO MCBS for cancer medicines

Part B: Specific Populations				
<i>Note: Skip Part B if a drug is not applicable to these specific populations</i>				
Sub-criteria	Key Question	Rationale	Explanation	Data Source
Children	2.1 Infants and children (< 18y per FDA-EMA definition) - for a disease known to affect both adults and children	<p>This criterion builds upon MPP's existing commitment to paediatric drug development</p> <p>The criterion is skipped if a given disease or treatment eligibility is not applicable to children per WHO guidance</p>	No penalty for medicines with no paediatric investigation plan or pediatric study plan.	European Medicines Agency and US Food and Drug Administration
Subpopulations	2.2 Is this drug safe and effective in a given subpopulation such as known harder-to-treat subpopulation, or pregnant / breastfeeding women? (List not exhaustive).	<p>This criterion can be customized by disease as the need may be.</p> <p>The subpopulation could be categorized by disease severity, or patient characteristics, or other subtypes</p>	Lack of efficacy in this subpopulation may not be an automatic No-Go, depending on the importance and size of this population in LMICs, and the efficacy of the the SOC for the same population	FDA approved labels, clinical trial results as published in peer reviewed journals or major conferences

2. Access Challenges - Are there access challenges in LMICs?				
Sub-criteria	Key Question	Rationale	Explanation	Data Source
2.1. Availability	<i>Is the product available in LMICs?</i>	If medicine is generally not available in LMICs from originator, MPP licences could be a vehicle to make it available from generic manufacturers	In-country registration data is used as a proxy for availability. While it is understood that this would only capture a part of what it means for a product to be available to the population in a given country, it is considered a reasonable high-level proxy, particularly for products that are not donor-funded (and therefore less likely to be available through waivers)	Collected from national regulatory authorities in a few sample LMICs (already collected for certain products in MPP feasibility study)
2.2 Affordability	<i>Is the product affordable in LMICs</i>	If product is less affordable in LMICs, then there is a greater scope for an MPP intervention to contribute to bringing the price down	To assess affordability, we look at prices in a sample group of LMICs and compare that with a measure of per capita income or per capita expenditure on pharmaceuticals.	IMS Health and information collected for MPP feasibility study.
2.3 Existing originator access initiatives	<i>Are there effective access initiatives in place?</i>	If medicine is been made available through existing access initiative, there may be less of a need for an MPP intervention	The focus is on whether there are access initiatives in place, whether they cater for a large number of LMICs, whether they provide broad access in those countries whether they are active, whether they make the product affordable, and whether they are sustainable	Information collected from company websites, IFPMA database and Access to Medicines Index Report.
2.4. Flagged by External Stakeholder	<i>Has the importance of access to this product been flagged by external stakeholders?</i>	The MPP should prioritize products that are in high demand from key stakeholders	Specific requests or indications by leading stakeholders would help the MPP in focusing on products of public health importance in LMICs.	Discussions with stakeholders; EML submissions from key stakeholders; requests from governments or patient groups; reports from key stakeholders

3. Potential for MPP value add - Would MPP licences likely lead to public health impact?				
Sub-criteria	Key Question	Rationale	Explanation	Data source
PATENT STATUS				
IS THE PRODUCT PATENTED IN LMICS?				
3.1 Estimated number of years of potential MPP impact	<i>Is the product still under patent protection in LMICs?</i>	The MPP should focus its efforts on products that have longer time to patent expiry and therefore longer time for a licence to deliver impact	This takes into consideration both the number of years of blocking patent protection left, as well as the likely number of years for generic market entry. For the latter, we estimate 3 years for new products, 2 years for products under development, 1 year for product already available in certain countries. It considers patents on the molecule and secondary patents.	For patent expiry: FDA Orange Book and analysis of listed patents For generic market entry: company websites, USFDA, interactions with generic companies
3.2. Geographical coverage of patents	<i>How widely is the product patented in LMICs?</i>	The MPP should focus its work on products that are patented in LMICs where its licences can contribute to facilitating access to more affordable treatments	Focuses on certain sample countries, namely: ARIPO, Brazil, China, EAPO, Guatemala, India, Indonesia, Morocco, Philippines, South Africa, Thailand, Ukraine and Vietnam	Esp@cenet, Pat-INFORMED, national patent office databases
IMPACT ON ACCESS				
WOULD MPP LICENCES LIKELY IMPROVE ACCESS IN LMICS?				
3.3. Diagnostic needs	<i>Does the product require complex diagnostics that are likely limited in LMICs?</i>	The MPP prioritizes products for which diagnosis is relatively simple or for which access to the products could contribute to improved diagnostic capacity in LMICs	Products that can be diagnosed easily and at first presentation by a general physician or specialist nurse and do not require sophisticated diagnostic tools would be classified as having limited diagnostic requirements. Products requiring some infrastructure, some expertise, diagnostic tools that are more sophisticated and may not be available everywhere would be moderate Products requiring sophisticated diagnostic tools, including, for example, identification of a specific gene mutation would be considered complex. This may also include conditions for which it is difficult to undertake clinical diagnosis.	Recommendations for diagnosis from WHO or other reputable body; information from EML submission. (For some products, analysis already included in the MPP feasibility study)
3.4. Health systems and infrastructure needs	<i>Does the use of the product require significant infrastructure, highly specialized personnel or sophisticated health systems?</i>	The MPP seeks to prioritize products with potential for scale-up in LMICs	Considers whether administration of the treatments is complex, whether it requires hospitalisation, whether it needs to go hand in hand with surgery, radiotherapy or other intervention that may only be available in few centres in certain LMICs, whether requires a specialist or can be administered by a generalist or healthworker.	Recommendations for treatment from WHO or other reputable body; information from EML submission. (For some products, analysis already included in the MPP feasibility study)
3.5. Potential buyers for the product	<i>Would there be potential buyers/uptake for this product?</i>	The MPP would focus on products for which licences could result in product uptake	Considers whether public systems already finance the product or the SOC that this product may replace; or whether the product (or the SOC it would replace) is generally being bought in LMICs.	IMS Health to understand whether current SOC is being procured. Otherwise data to be collected from a sample number of countries. Data for certain countries already in MPP feasibility study.
3.6. Market size	<i>Is the market for the product likely to be big, leading to economies of scale for production/sale?</i>	The MPP model would likely work best and lead to greatest price reductions when the market size is large enough to attract generic manufacturers and to have economies of scale	Given the challenges in making a thorough estimate of market size, it is a basic assessment of the likely/possible market size based on disease burden, and the other sub-criteria mentioned above	Global Burden of Disease; IMS Health, treatment recommendations from WHO or other reputable body