



medicines
patent
pool

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**

Executive summary

I. Introduction

The Medicines Patent Pool (MPP) was established with the support of Unitaid in 2010 as a public health organisation with a mandate to accelerate access to affordable, appropriate, and quality-assured HIV treatments in developing countries. The MPP was the first (and is the only) voluntary licensing and patent pooling mechanism in the public health space. It negotiates intellectual property (IP) licensing agreements with patent holders to allow generic manufacture and supply of medicines in low- and middle-income countries (LMICs). The MPP model is based on collaborative agreements and ensures new treatments are more widely available 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.

In 2015, with its successful track-record in HIV and following extensive consultation, MPP's funder Unitaid supported the expansion of the organisation's mandate to hepatitis C and tuberculosis. In both areas, important new medicines had recently been brought to market, and there were significant access challenges in LMICs.

Currently, the MPP holds licences on 16 medicines with nine patent holders, including pharmaceutical companies, universities and public research organizations. These licences 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.¹

In 2016, the World Health Organization (WHO) and the Lancet Commission on Essential Medicines Policies recommended the expansion of the MPP's mandate to include all patented essential medicines.^{2,3} These recommendations were made against the backdrop of new medicines for cancer being added to the WHO Model List of Essential Medicines (EML) and concerns being raised about access in LMICs. That same year, pharmaceutical company GlaxoSmithKline announced an intention to license essential medicines for lower middle-income countries and to explore licensing of its pipeline cancer medicines to the MPP. Finally, several high-level reports proposing ways to better address antimicrobial resistance (AMR) indicated that the MPP could play an important role in this area. The MPP, therefore, decided to undertake an evidence-based assessment exploring the public health need for, and potential feasibility and impact of, expanding the work of the MPP into patented essential medicines in other therapeutic areas. The study was financed by the Swiss Agency for Development and Cooperation.

This study focuses on a number of medicines on the WHO's Model List of Essential Medicines (EML) and medicines with potential for future inclusion. It seeks to understand current public health needs, and the extent to which improved access to certain medicines could contribute to improving public health outcomes in LMICs. It also explores a potential role for the MPP in promoting access and stewardship for new antimicrobials.

II. Methodology

The starting point for this feasibility study was to identify essential medicines that are included in the WHO's EML, are used in the treatment of diseases other than HIV, HCV and TB, and are under patent protection. As the WHO EML is updated every two years, it was important that the study also extend the analysis to treatments that may be considered essential medicines in the future. To do so, we relied on the WHO Expert Committee's assessments, identifying medicines that were highlighted by the Committee for offering relevant clinical benefits.

Our analysis centred on case studies of specific medicines and corresponding therapeutic areas. These case studies explored the public health challenges in LMICs in relation to these therapeutic areas, by analysing the relevant disease burden, the treatment landscape in LMICs and current access challenges. The public health analysis is complemented with an analysis of the market, patent, and pricing landscapes. In order to ensure that the case studies included an on-the-ground perspective, they drew on national background papers that were commissioned from selected expert clinicians in LMICs. We also conducted interviews with a wide range of stakeholders that contributed to a more rounded understanding of the situation for different medicines and therapeutic areas. For some of the medicines, we modelled the potential public health and economic impact of MPP licensing.

The case studies focused on the following categories of products, as evaluated by the WHO EML Expert Committee:

1. **Patented medicines included in the EML.** In this category, the case study considered medicines for the second-line treatment of chronic myeloid leukaemia (dasatinib, nilotinib). These medicines were added to the WHO EML in 2017.
2. **Patented medicines that the WHO Expert Committee considered as having relevant clinical benefits but lacking sufficient data.** This case study focused on one new class of medicines used for the treatment of type 2 diabetes, the sodium-glucose cotransporter 2 inhibitors (SGLT2Is; canagliflozin, empagliflozin, dapagliflozin), which the WHO Expert Committee highlighted as potentially having clinical benefit for patients at high risk of cardiovascular events, reducing mortality.
3. **Patented medicines that have clinical benefits but did not meet the WHO Expert Committee's comparative cost-effectiveness criterion.** This case study considered novel oral anticoagulants (NOACs; dabigatran, rivaroxaban, apixaban, edoxaban). In 2015, the WHO Expert Committee concluded that "the evidence indicates a favourable, overall clinical benefit of the NOACs over warfarin" but that "the large difference in costs between NOACs and warfarin was disproportional to the observed incremental benefit".⁴ MPP licensing for this category of medicines could potentially contribute to reducing concerns over their affordability in LMICs.
4. **Patented medicines for which the WHO Expert Committee recommended a therapeutic area review by a separate working group.** This case study considered medicines for lung cancer, prostate cancer, multiple myeloma, and breast cancer. The WHO Expert Committee will reassess these medicines, along

with other cancer therapies, at its next meeting in 2019, following a review by a separate cancer working group. The cancer working group will seek to clarify what constitutes a clinically relevant therapeutic effect that would be sufficient to justify adding a cancer medicine to the EML.

5. **New antibiotics for combating antimicrobial resistance.** Given the prominence of antibiotics in the WHO EML and the growing recognition of the need to develop new therapies, we considered the potential role that MPP licensing could play in relation to new antibiotics of public health priority. In this context, we paid particular attention to ways of aligning potential MPP work in this field with efforts to promote good antimicrobial stewardship and addressing antimicrobial resistance, while facilitating access to those in need.

The medicines discussed in the cases studies are illustrative for the purposes of analyzing the feasibility of expansion. Further prioritization would be required, in consultation with stakeholders, if the MPP were to expand its mandate. A number of these may not be suitable candidates for the MPP, as outlined in the case studies.

Table 1. Overview of case studies based on WHO EML Committee assessments.

| Category | Case study |
|--|---|
| 1. Patented medicines included in the WHO EML | Second-line medicines for chronic myeloid leukemia (CML) |
| 2. Patented medicines that the WHO Expert Committee considered as having relevant clinical benefits but lacking sufficient data | New oral medicines for type 2 diabetes (SGLT2 inhibitors) |
| 3. Patented medicines that have clinical benefits but did not meet the WHO Expert Committee's comparative cost-effectiveness criterion | Novel oral anticoagulants (NOACs) |
| 4. Patented cancer medicines for which the WHO Expert Committee recommended a therapeutic area review by a separate working group | Breast cancer |
| | Lung cancer |
| | Multiple myeloma |
| | Prostate cancer |
| 5. New antibacterials to combat anti-microbial resistance | New antibacterials |

III. Patented medicines currently included in the WHO EML

Currently, there are approximately 45 medicines on the WHO EML, across all therapeutic areas, that may be protected by patents in at least some jurisdictions. Of these, 13 are covered by patents on the active molecule itself (compound patents) whereas others are covered by secondary patents. These numbers will continue to evolve as new medicines are added to the EML and as patents on listed medicines expire. These patented medicines on the EML are primarily for different cancers, HIV, hepatitis B and C, reproductive health and tuberculosis. Two cancer medicines (dasatinib and nilotinib) have compound patents and are the focus of the case study discussed below.

Case study on medicines for chronic myeloid leukaemia

Dasatinib and nilotinib are medicines that were recommended by the EML Committee as second-line treatment for Philadelphia chromosome-positive chronic myeloid

leukaemia (Ph+ CML), which affects about 200,000 people in LMICs.⁵ Both were added to the EML in 2017,⁶ and are protected by patents expiring between 2020 and 2030. Ph+ CML can be treated with oral medicines to achieve almost normal life expectancy.⁷

The main first-line treatment for Ph+ CML is imatinib, a medicine that recently lost patent protection in most jurisdictions. However, an estimated 23% (or up to 40% according to some sources) of patients with CML will likely become resistant or intolerant to standard-dose imatinib.^{8,9} In these patients, dasatinib and nilotinib are preferable to other treatment options.¹⁰⁻¹³ In addition to second-line use, these medicines are also approved for first-line treatment and dasatinib is also indicated for the treatment of another form of leukaemia (acute lymphoblastic leukaemia).^{10,14}

Access to dasatinib and nilotinib appears to vary greatly across LMICs and generic versions are currently not available. A number of stakeholders, including some governments, mentioned challenges in accessing them at affordable prices. In some countries, dasatinib and/or nilotinib are available through originator donation or discount initiatives. These initiatives have played an important role in facilitating access to treatment and diagnosis in certain countries. Where originator access initiatives were not in place, however, the drugs are either unavailable or accessible to few people in the private market. Competitive generic manufacture could be a more sustainable approach to enabling access that potentially could build on these existing access initiatives.

The LMIC market for dasatinib and nilotinib is comparatively small, which may limit its attractiveness for generic manufacturers. However, in the case of imatinib, several manufacturers developed and marketed generic versions in some LMICs years before they entered high-income countries.¹⁵ This has resulted in significant price reductions: for example, the Indian state of Tamil Nadu procures imatinib for \$8 per patient per month.¹⁶ Additionally, several manufacturers appear to be developing generic versions of dasatinib and nilotinib.¹⁷

Using a model that combines a number of assumptions regarding clinical parameters, treatment access, and market dynamics, we estimated that MPP-enabled generic versions could deliver up to 150,000 patient-years of treatment in LMICs.

MPP licences on dasatinib and/or nilotinib could therefore contribute to facilitating access to important and highly effective essential medicines for cancer in LMICs at affordable prices, through a sustainable model that could complement existing access programs.

IV. Patented medicines that the WHO Expert Committee considered as having relevant clinical benefits but lacking sufficient data

For some medicines submitted for addition to the EML, the Committee may consider that the available evidence is not strong enough to recommend immediate inclusion, but that additional evidence may justify inclusion in the future if further studies confirm the benefits shown in earlier data. This was the case for one class of oral medicines

indicated for the treatment of type 2 diabetes, which is covered in the following case study.

Case study on medicines for the treatment of type 2 diabetes

Type 2 diabetes affects around 300 million people living in LMICs and represents around 90% of cases of diabetes. Its economic impact is also considerable, projected to cause an estimated US\$1.1 trillion in economic losses in LMICs in 2030.¹⁸

The first-line treatment for type 2 diabetes is metformin – a safe and effective medicine that is available from multiple manufacturers at very low prices in most LMICs. However, most people with type 2 diabetes will require the addition of a second-line medicine a few years after beginning treatment.¹⁹

In 2017, the WHO Expert Committee reviewed the six main classes of second-line treatment. All six classes lower blood sugar levels, which is the primary goal of treatment. However, of these six classes, the Committee highlighted that “SGLT-2 inhibitors have shown a relevant clinical benefit as second-line therapy in patients at high risk of cardiovascular events, with a reduction in overall mortality” but concluded that “this finding needs to be confirmed in other trials, prior to selectively supporting this class of medicines in patients with type 2 diabetes”.⁶

The effect of SGLT2 inhibitors in reducing cardiovascular events and overall mortality is significant, since people with type 2 diabetes are at higher risk of cardiovascular events compared to people who do not have diabetes.²⁰ The SGLT2 inhibitors also offer other advantages over some of the older classes such as causing fewer hypoglycaemic events.^{21,22} In addition, SGLT2 inhibitors cause weight loss, which is desirable in most people with type 2 diabetes.

The availability and affordability of the newer drug classes for type 2 diabetes treatment is low in LMICs.²³ This applies to the SGLT2 inhibitors as well as to other newer agents, such as the GLP-1 agonists and to a lesser extent the DPP-4 inhibitors. Most of these medicines are under patent protection in several low- and middle-income countries, including those with significant manufacturing capacity, with patents protecting SGLT2 inhibitors expiring between 2023 and 2029.

Our modelling suggested that MPP licensing of SGLT2 inhibitors could potentially enable 1.1–3.3 million people to access treatment. Based on available data on the cardiovascular benefits of these medicines, this uptake could avert 31,000–126,000 cases of major adverse cardiovascular events, conferring 68,000–275,000 additional QALYs.

Based on this analysis, the MPP could potentially have a significant public health impact if it were to license patented, newer second-line medicines for type 2 diabetes, such as the SGLT2 inhibitors and facilitate the development, registration, and supply of quality-assured generic versions for use in LMICs. Licensing could enable the introduction of this class of medicines in countries where current market penetration is extremely low or non-existent, contributing to a better standard of care for people with type 2

diabetes, in particular those with high cardiovascular risk, through a win-win mechanism that could benefit all stakeholders.

V. Patented medicines that have clinical benefits but did not meet the WHO Expert Committee's comparative cost-effectiveness criterion

Comparative cost-effectiveness is one of the criteria used by the WHO Expert Committee to assess medicines when multiple treatments are available for the same indication.²⁴ In some cases, the WHO Expert Committee has identified medicines as offering relevant public health benefits but considered that they were not cost-effective compared to treatments that are already on the EML. For these medicines, availability at lower prices, particularly in LMICs, could change the cost-effectiveness analysis. Given the MPP's mandate to facilitate access to more affordable treatments in LMICs through voluntary licensing, this category of products represents a potentially interesting area of focus. The following case study reviews one class of products that falls into this category, the novel oral anticoagulants. Reviews of recent WHO Expert Committee reports showed that some of the insulin analogues and denosumab may be considered in the same category.

Case study on novel oral anticoagulants (NOACs)

Novel oral anticoagulants are new blood thinner medicines that are given to people with conditions that put them at high risk of a blood clot. In people with non-valvular atrial fibrillation (NVAf) – a common heart rhythm disturbance – NOACs are used to substantially reduce the risk of a stroke, and in people who have previously suffered a clot in the leg or lung (a venous thromboembolism; VTE), NOACs are used to reduce the risk of recurrence. In both cases NOACs are now preferred in the United States and Europe over an older class of anticoagulants – vitamin K antagonists – of which the most widely used example is warfarin.^{25–29}

The number of people with NVAf is on the rise in LMICs and is estimated to reach 17.8 million in LMICs by 2020, with each person having an annual risk of stroke of 1–8%, depending on the region.³⁰ In addition, there are at least 6 million cases of venous thromboembolism annually in these countries. Both strokes and VTEs are often fatal. Compounding this significant burden, LMICs face multiple challenges in treating and preventing stroke and VTE. For example, in many countries there are limited facilities to treat and rehabilitate those with stroke.³¹

In 2015, the WHO EML Expert Committee noted the relevant clinical benefits of the NOACs but decided not to include them in the EML, indicating as one of their main concerns the considerably higher price of NOACs compared to warfarin.⁴

One of the most important advantages of NOACs over warfarin is that they do not require regular monitoring, due to significantly more stable and predictable pharmacokinetics and pharmacodynamics. This may be particularly important in LMICs, where access to regular monitoring (which is required with warfarin) can be limited. National background papers commissioned for this study noted that there is hesitation to prescribe warfarin to people needing anticoagulation in view of this challenge. In

addition, NOACs likely confer a lower risk of bleeding³²⁻³⁶ have fewer interactions with other medications and fewer dietary restrictions. Low availability and unaffordable prices in LMICs were reported as major barriers and their use has remained very limited. Lack of reversal agents for most of the NOACs (though they are under development) was also raised as a potential challenge for the scale-up of NOACs.

One of the four approved NOACs, dabigatran, has recently become available as a generic in India. However, other NOACs, which are still under patent protection, may offer certain advantages for scale-up in LMICs. We estimated that MPP licensing agreements on NOACs could facilitate 0.5–1.6 million additional patient-years of treatment for patients with NVAF, preventing 10,000–31,000 cases of SSE. For the VTE indication, we estimated that 234,000–702,000 additional patients could be treated, preventing 94,000–281,000 VTE events.

NOACs therefore represent an interesting example of medicines with strong potential for improving public health outcomes in LMICs that were not included in the WHO EML partly due to affordability concerns. Early MPP licensing in such cases could contribute to making such medicines available sooner at affordable prices in LMICs through a collaborative public health mechanism, with suitable royalties. Given the lower monitoring requirements of NOACs over alternatives, this could enable more people in need to access anticoagulation therapy, therefore reducing the risk of strokes and other sometimes fatal complications in LMICs.

VI. Patented medicines for which the WHO Expert Committee recommended a therapeutic area review by a separate working group

In 2017, a number of cancer medicines were submitted to the WHO Expert Committee for inclusion in the WHO EML. The Committee “considered that listing of these medicines was premature and recommended the establishment of an EML cancer medicines working group to coordinate comprehensive evaluation of cancer medicines for the EML.”⁶ The working group would support WHO in establishing some guiding principles in relation to the potential inclusion of second-line cancer treatments, clarifying what constitutes a clinically relevant therapeutic effect for inclusion in the EML. Some or all of these medicines will likely be re-evaluated at the next meeting of the Committee and are therefore candidates for future inclusion. We analysed the potential for MPP licensing of medicines that fit in this category, which covered treatments for lung cancer (erlotinib, gefitinib, afatinib, crizotinib), prostate cancer (abiraterone, enzalutamide), multiple myeloma (lenalidomide) and breast cancer (pertuzumab, ado-trastuzumab emtansine, lapatinib).

Most of these medicines are licensed for use in patients with advanced cancer and, in some cases, restricted to second-line use. In the majority of patients, the therapies are not curative, and the EML cancer working group is considering how to define a therapeutic effect that is sufficient to justify addition to the EML.

Most of the medicines reviewed in this section offer certain improvements over therapies currently listed in the WHO EML. Advantages, depending on the medicine,

include increases in overall survival, more favourable tolerability and/or an oral route of administration, removing the need for hospital-based infusions and potentially lower overall costs to health systems.

The medicines considered for lung cancer and breast cancer require, in general, biopsy, molecular diagnostics and trained pathologists, which is often not widely available in some LMICs. However, national background papers revealed that this diagnostic infrastructure is becoming increasingly available at least in the main cancer centres. Additionally, greater access to these medicines may facilitate investments in such infrastructure.

Information gathered by cancer experts in LMICs suggested that access to these medicines in LMICs is limited. MPP licences could potentially play a role in improving access in countries where licences could facilitate the development a competitive generic market, which could make the medicines more affordable to local populations. This would have to go hand-in-hand with a number of other interventions to facilitate proper diagnosis, treatment and care for cancer patients, including expanding capacity for surgery and radiotherapy, which are central to the treatment of many cancers. In certain cases, generics have already become available in some countries because patents have expired, have not been granted, or existing secondary patents may not be blocking (e.g. abiraterone). In such cases MPP licensing would likely not be needed or could be limited to specific countries.

For some of these medicines, markets are likely to be small due to indications that are limited to patients with specific tumour characteristics. Additionally, the breast cancer medicines considered in this study, like many new cancer medicines, are biologics, which pose additional challenges. These challenges are discussed in the following section.

Taking into consideration any recommendations made by the EML cancer medicines working group and the WHO Expert Committee in 2019, the MPP could explore licensing those medicines that are considered to offer sufficient therapeutic benefit and contribute to improved access in LMICs.

VII. Biologics and similar biotherapeutic products

Many of the stakeholders interviewed raised concerns about the limited access to several important biologics in LMICs and argued that this may therefore be an area in which the MPP could explore opportunities to improve access through its licensing model. However, there are important differences in the development, manufacture, and regulatory approval of similar biotherapeutic products (SBP) compared to 'small molecule' generics that need to be considered.

One of the greatest challenges for SBPs is that, in general, manufacturers are required to conduct more extensive studies to demonstrate comparable efficacy and safety compared to the reference (originator) product. Various other regulatory challenges exist, which vary by country.^{37,38} The expertise needed to develop and safely manufacture SBPs, as well as the high capital expenditures for biologics may also be a major challenge.³⁹

On the other hand, a large number of SBPs are under development. The WHO and some LMIC governments are making efforts to encourage the development of domestic production capacity of SBPs. The WHO has developed guidelines for SBP regulatory review,⁴⁰ and has recently announced a pilot programme for the prequalification of SBPs.⁴¹ Some governments have initiatives to help develop local SBP production capacity.^{37,42}

In terms of MPP's potential for working in SBPs, some of the challenges mentioned above could be substantial and may reduce the potential impact MPP licences could have in facilitating access to more affordable treatments in LMICs. However, including strong technology transfer components in licensing agreements may allow some of these challenges to be partially overcome. MPP licensing agreements on biologics could potentially draw from the experience that some originator companies have in partnering with LMIC manufacturers to supply local markets. This is an area that would require further exploration.

VIII. New antibacterials to combat antimicrobial resistance (AMR)

The EML includes 61 antibiotic medicines, antibiotic groups, or combinations. The absence of patented antibiotics on the EML (except those for TB) is indicative of systematic underinvestment in the discovery of new antibiotics over the last several decades.⁴³⁻⁴⁸ This underinvestment, alongside misuse and overuse, has contributed to growing antimicrobial resistance (AMR), in which the medicines that are currently available are less and less effective in treating certain infections.

Combating the spread of antimicrobial resistance is an international global health imperative. The threat of widespread antimicrobial resistance has been the subject of increasing focus and recent high-level reports have highlighted the need for the development of new antibiotics alongside strategies to enable access while ensuring proper stewardship and rational use.^{43,45,49} Some reports identified patent pooling through the MPP as one way to contribute to addressing the access-innovation-stewardship 'tripod', as a key part of novel mechanisms for financing antimicrobial development.

Stakeholder feedback indicated that the MPP's model could be adapted to address the specific challenges in antimicrobial resistance in LMICs. In antibiotics, for instance, the MPP should target only those products of public health priority, particularly those for which there are limited or no existing alternatives or that significantly improve on existing options. Rather than broadly licensing to multiple manufacturers to promote wide availability and generic competition, the MPP would likely need to limit the number of licensees to prevent overuse, while still ensuring that the products are made affordably available to those who need them.

While licensing cannot address many important aspects of proper stewardship of new antibiotics (such as strengthening regulatory systems in developing countries and expanding the availability of proper diagnostics), tailored licensing approaches for specific antibiotics of public health significance could contribute to good stewardship in a number of ways. These could include, for example, ensuring: that manufacturers meet

quality standards, that manufacturers do not engage in inappropriate promotional practices, that manufacturing is conducted under rigorous standards for the treatment of wastewater, that only appropriate combination products are developed, and that the products are only distributed through appropriate channels.

IX. Other products in the WHO EML and other products mentioned in discussions with stakeholders

For certain products on the WHO EML, while the main patents may have expired, secondary patents have been filed or granted in certain countries and could delay the development of a competitive market. These products are primarily cancer medicines, reproductive health products and medicines for hepatitis B. The MPP could potentially play a role in facilitating broader availability of such products at affordable prices in LMICs.

In addition to the medicines discussed in the case studies mentioned above, a number of other medicines or therapeutic areas were highlighted in discussions with stakeholders and experts as having, in their opinion, potential for being considered essential medicines in the future and therefore possibly representing candidates for MPP licensing. It should be noted that such medicines or therapeutic areas were not analysed in detail and may represent the view of only some stakeholders. They are mentioned in the study for completeness, but a more thorough evaluation would be required.

Several stakeholders consulted suggested that the MPP consider a role in increasing access to certain diagnostics, medical devices or vaccines. In diagnostics, the WHO is developing an Essential Diagnostics List,⁵⁰ which could potentially provide a starting point. This study, however, does not explore the role of the MPP in improving access to diagnostics. The MPP commissioned a separate study to explore whether there could be a role in the licensing of essential vaccines.

X. Discussion

There is a substantial public health need for access to new, patented medicines beyond HIV, hepatitis C and tuberculosis in LMICs. The case studies presented in the feasibility study have outlined how accelerating access to selected medicines in cardiovascular disease, diabetes and cancer could contribute to improving public health outcomes and reduce morbidity and mortality. Instances were also identified where the MPP's potential role may be more limited or may not be necessary, for example where generic manufacturers are already becoming widely available on the market.

Some of the medicines analysed are treatments for diseases that represent a large and growing health burden in LMICs. In other cases, where the disease in question is not as prevalent, such as for some cancer subtypes, the medicines discussed represent important treatments for patients that may otherwise have few alternatives. In addition, some of the NCDs discussed in the cases studies are associated with catastrophic health expenditure for the individuals. Expanding the treatment and prevention of NCDs, in the context of universal health coverage schemes, would likely have significant knock-on effects on LMIC health systems.

The MPP could also play an important role in addressing what is considered by many to be one of the most pressing challenges in global health today, that of increasing resistance to antimicrobials, by facilitating access to, and good stewardship of, new antibiotics of public health priority.

However, certain health system factors may pose challenges to achieving public health impact through MPP licensing. In some disease areas and some regions, resource-constrained health infrastructure, limited diagnostic capacity, and a lack of expert staff may limit the detection of cases that could be treated with MPP-enabled generics and the likelihood of people receiving the best available treatment. This challenge would likely be more pronounced for some of the medicines discussed in this study (e.g. certain cancers) than for others.

Moreover, several stakeholders highlighted the lack of international funding mechanisms for NCDs such as those that have been established in the area of HIV, TB and malaria, as another significant challenge that would likely limit market uptake of new treatments. MPP's work would therefore need to be integrated in a broader framework of interventions within the Universal Health Coverage agenda, that seek to improve diagnosis, screening, treatment and care for the disease area in question. Partnering with governments and key global, regional and national organisations would be an important part of the MPP's strategy if it were to work in NCDs.

From a market perspective, many of the medicines considered in this study appear to have limited commercial markets for originator manufacturers in many of the LMICs for which data were collected. In a number of cases, the medicines were not registered locally, were unavailable in the public sector or were affordable only to a limited proportion of the population in the private market. MPP licensing could contribute to making patented essential medicines more widely available from quality-assured suppliers in such countries, while compensating originator companies through reasonable royalty rates, which may vary according to income or disease burden. Licensing early on, as has been the case in HIV, could also be important in order to accelerate access to those in need.

Access-oriented licensing is a relatively new approach for increasing access to medicines in LMICs, which has primarily been used in the fields of HIV and hepatitis C. It would therefore be important to consult further with patent holders and other stakeholders to increase/strengthen confidence in the model for essential medicines beyond those disease areas, develop opportunities for win-win strategies and ensure that concerns around market leakage can be addressed.

The cases studies presented in the study are illustrative and further prioritization would be required, in consultation with stakeholders, to identify suitable opportunities for MPP licensing.

XI. Conclusions

Based on the analysis presented in this feasibility study, there appears to be a strong case for the MPP to expand its mandate to include patented essential medicines in other therapeutic areas, beyond its current work in HIV, TB and hepatitis C. Patented

medicines added to the WHO EML in its biennial revisions could be natural candidates for MPP licensing. In addition, the MPP could explore licensing patented medicines that the WHO Expert Committee highlights as having clinical benefits but have not yet been included on the list given concerns about the high prices for these medicines or the need for additional data to confirm clinical benefits.

As some of the case studies note, there appear to be instances where patent holders' commercial interests in the countries analysed may be limited and where MPP licensing could lead to win-win solutions that benefit all stakeholders. Suitable royalty provisions could play a role in providing adequate compensation.

Developing robust ways to prioritize medicines in close consultation with WHO and other key stakeholders would be important, while drawing upon the WHO EML Expert Committee to identify promising medicines for in-licensing as early as possible, as was the case in HIV. Some flexibility should remain to explore opportunities where a given medicine has strong potential for improving public health outcomes in LMICs and where patent holders are willing to engage early-on.

In the field of AMR, partnerships with existing and new initiatives to stimulate the development of novel, effective antibiotics, would be important. The MPP's role in this area could focus on exploring the licensing of new antibiotics of public health priority, with a view to contributing to the appropriate stewardship of new antibiotics to prevent misuse and overuse while facilitating access to those who need them.

The MPP would also need to monitor closely the evolving area of international quality standards and identify appropriate quality assurance standards for use in licenses on essential medicines. This will require working closely with the WHO Prequalification Programme, as it expands the range of medicines it reviews, and monitoring ongoing discussions at WHO on updating the definition of 'stringent regulatory authorities'. These discussions could inform appropriate standards for MPP's future licensing agreements.

Given many of the challenges relating to biologics, the MPP could initially consider focusing its activities under an expanded mandate on the licensing of small-molecule medicines, for which the current model would likely be more easily adaptable and where the challenges for facilitating the development of competitive markets may be smaller. In parallel, the MPP could consider developing licensing approaches that would potentially be suitable for biologic products in the future.

Certain adaptations to the model would also be required to address the specific circumstances of each product and public health objectives being pursued. Tailored approaches could include, for example: the inclusion of terms to support good antimicrobial stewardship practices; targeted licences to address specific challenges in specific countries; greater use of differentiated royalties; limiting the number of licensees where there are small markets and introducing affordability provisions where competition alone may not achieve affordable prices.

Finally, partnerships with governments, public health organisations and patient groups in relevant disease areas would likely be important to gain an understanding of the

public health needs as well as facilitating uptake when MPP-enabled generics reach markets. A number of recent initiatives in the field of NCDs and AMR could represent interesting opportunities for synergies with MPP's approach.

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