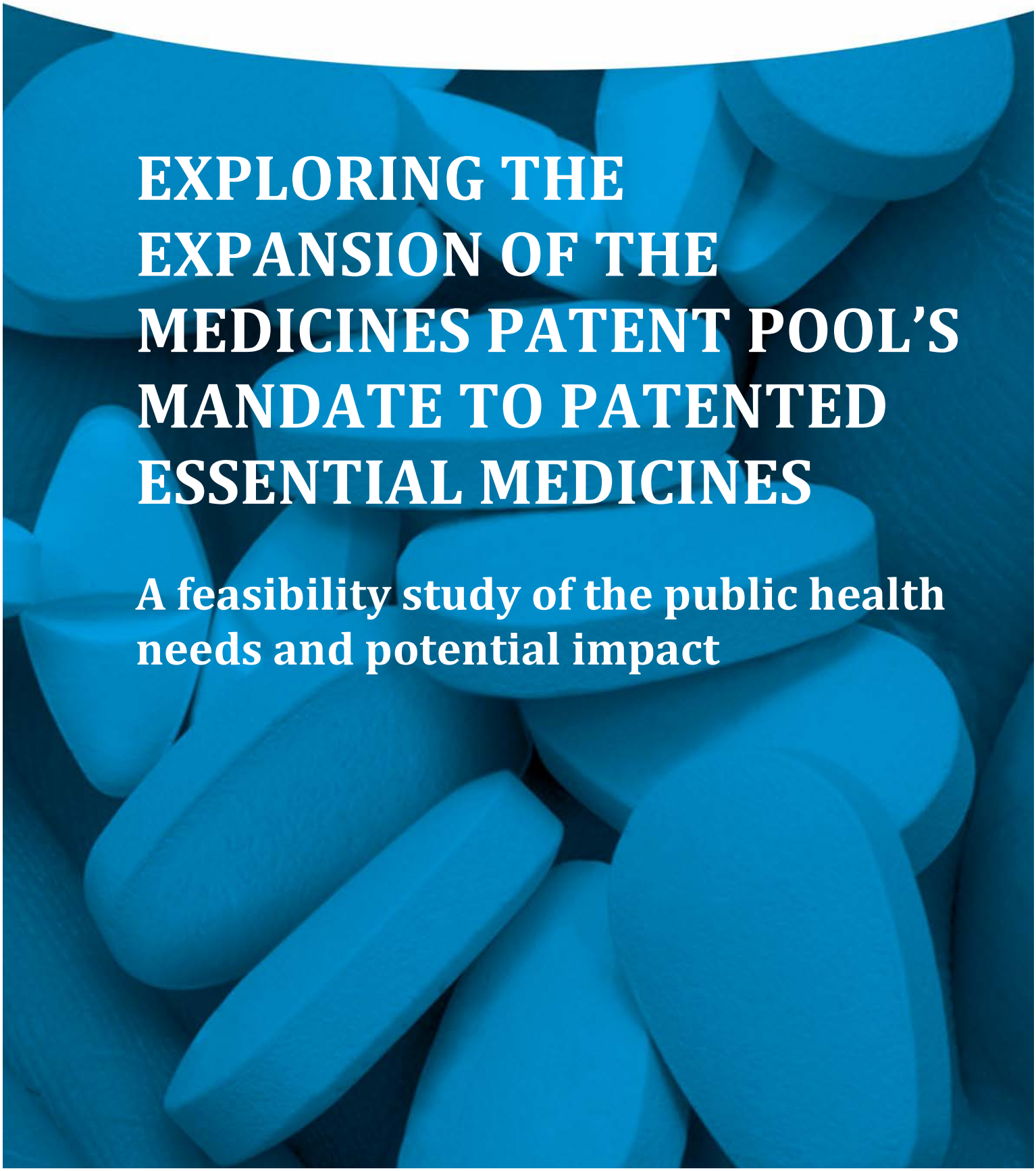
medicines patent pool



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

8 Other products in the WHO EML, highlighted by EML Committee or mentioned in discussions with stakeholders

8.1 Introduction

For the purpose of exploring the feasibility of expanding the MPP's mandate to include patented essential medicines beyond those for HIV, HCV and TB, we described some of the public health challenges in relation to a few products/therapeutic areas in the previous chapters, along with an analysis of the potential for MPP licensing. This chapter looks at a range of other medicines and therapeutic areas that were not covered in the case studies in previous chapters. It includes significantly less detail than in those case studies. It starts by outlining some of the other medicines in the WHO EML that have patent protection in certain LMICs. It then mentions other medicines that were not included in the WHO EML, in part as a result of concerns about the affordability of these medicines, such as the insulin analogues. Finally, we outline numerous other products or drug candidates that are on the market or under development that were highlighted in conversations with stakeholders and experts, for which MPP licences may offer a mechanism for increasing treatment access in the future.

8.2 Other patented medicines on the EML

A number of medicines in the WHO EML for HIV, TB, and hepatitis C, are under patent protection and are already within the MPP's current mandate. Outside of these three diseases, and apart from dasatinib, imatinib, nilotinib and trastuzumab discussed in the case studies, there are a number of other medicines on the EML that have patents in force in LMICs. Some of them are mentioned below. The list is by no means exhaustive, as there are instances of other essential medicines with patents in force in some jurisdictions (one example is moxifloxacin in Ukraine).

8.2.1 Rituximab

Rituximab is a biologic that was added to the EML in 2015,[1] and is an important treatment for certain types of blood cancer – diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and chronic lymphocytic leukaemia (CLL) – as well as for rheumatoid arthritis, a debilitating autoimmune condition that causes joint destruction. Rituximab reduces joint damage and pain and improves quality of life in rheumatoid arthritis.[2] Rituximab improves overall survival in chronic lymphocytic leukaemia,[3] follicular lymphoma,[4] and diffuse large B-cell lymphoma.[5]

We estimated that there are over 2.5 million prevalent cases and 244,000 incident cases that would theoretically be eligible for rituximab treatment in low-income, lower middle-income and Sub-Saharan African countries.

The original rituximab product was formulated as an intravenous infusion. A new, subcutaneous formulation of rituximab was approved in 2017. This formulation allows the drug to be given by an injection in a few minutes, rather than by infusion, which

takes hours.[6] This difference in administration time could offer savings in LMICs by reducing healthcare professional work time and reducing the time patients have to spend in a health facility.[7]

The main patents on rituximab appear to have recently expired in many LMICs, but in some jurisdictions, such as South Africa, method of treatment patents may still delay entry of biosimilars.[8] A patent protecting the subcutaneous formulation is set to expire in 2030 in several LMICs, including India. The subcutaneous formulation appears to also be covered by data exclusivity in a few countries.

At least three biosimilars of rituximab (intravenous formulation) have been approved in India, and many biosimilars are in development by various companies globally.[9] No generics are currently available for the sub-cutaneous formulation.

A role for the MPP may be possible in particular in relation to the sub-cutaneous formulation – though biosimilar manufacturers would likely need to undertake additional clinical trials to support regulatory approval of this new formulation. Technology transfer may be an important element for any potential MPP licence on biologics like rituximab.

8.2.2 Bevacizumab

Bevacizumab was added to the WHO EML in 2013 for its use in a relatively common eye condition – wet age-related macular degeneration.[10] However, bevacizumab is approved and used as a medicine to treat numerous cancers, including metastatic colorectal cancer, metastatic breast cancer, some types of metastatic lung cancer, advanced renal cell cancer, advanced ovarian carcinoma, and cervical cancer. Monthly prices of bevacizumab can reach $1,890 in the South African public market, $2,441 in Pakistan and over $4,000 in the Indian private market.

The primary patents for bevacizumab expire in 2017–2019 in the US, Europe, China, Brazil, and South Africa, and secondary patents are in force in some jurisdictions until 2025.

Numerous biosimilars of bevacizumab are in development, with two already approved in India, one in Russia, and one in Argentina.[11]

8.2.3 Bendamustine

Bendamustine was added to the WHO EML in 2015.[1] Bendamustine is used as a first-line treatment for chronic lymphocytic leukaemia in some patients, treatment for indolent non-Hodgkin's lymphoma that is refractory to rituximab, and for multiple myeloma.

Numerous patents have been granted for bendamustine formulations in LMICs, expiring in 2026. Additional method-of-treatment patents have been filed in some LMICs, which, if granted, would expire in 2033.[8] In the US, litigation resulted in a settlement between the proprietor (Teva) and multiple generics companies, under which generic versions will be permitted to enter the market from November 2019.[12] In India, generic

bendamustine is available from Natco, Emcure, Innova, RPG LS, and Dr Reddy's Laboratory, but is only available from a single supplier in a number of other LMICs.

8.2.4 Zoledronic acid

Zoledronic acid was added to the WHO EML in 2017 for malignancy-related bone disease. It is used to treat a number of bone diseases including high blood calcium, bone breakdown due to cancer, osteoporosis and Paget's disease. It is administered by injection.

The US FDA Orange Book lists several patents on zoledronic acid including one on the drug product expiring in 2028. Several generic manufacturers, however, appear to have entered the market.

8.2.5 Entecavir

Entecavir was added to the EML in 2015.[1] Entecavir is an oral, once-daily treatment for hepatitis B and is one of two WHO-recommended first-line treatments for hepatitis B (the other being tenofovir disoproxil fumarate (TDF), that has already been licensed to the MPP in view of its HIV indication). Entecavir is the only drug recommended for treatment of children below 12 years of age and is preferred for patients at risk of renal and bone toxicity.[13,14]

Globally, about 257 million people are living with HBV infection, some of them require long-term therapy. In 2015 alone, hepatitis B resulted in 887,000 deaths, mostly from liver cirrhosis and hepatocellular carcinoma (HCC).[15]

While primary patent for entecavir have expired in most LMIC jurisdictions, secondary patents expiring in 2021 have been granted in a number of LMICs and may delay generic market entry in some countries.[8]

8.2.6 Reproductive health

There are a number of contraceptives on the WHO EML that appear to have active patents in some jurisdictions: ulipristal acetate, the etonogestrel implant, and a new subcutaneous formulation for depot medroxyprogesterone acetate (DMPA-SC). Ulipristal acetate is an emergency contraceptive that was added to the EML in 2017.[16] It is protected by patents expiring in 2030. Teva challenged the patents protecting ulipristal in the US, but reached a settlement with the proprietor, Laboratoire HRA.[17] The terms of this settlement do not appear to be publicly available.

Depot medroxyprogesterone acetate has been included in the WHO EML in intramuscular injection form since 1985. A new formulation allows subcutaneous injection that women can administer themselves,[18] and was added to the WHO EML in 2017.[16] A patent protecting the new formulation will expire in 2020 in the US.[19]

The etonogestrel implant is a contraceptive implant that is inserted under the skin and offers effective contraception for 3 years. It was added to the WHO EML in 2015.[1] It offers benefits over the implantable contraceptive that was previously on the EML –

levonorgestrel – primarily in that its insertion and removal are easier. The etonogestrel implant appears to have geographically widespread patent protection until 2025-2027.[20] The originator (MSD) operates large discount programmes for donor agencies, all low-income countries, and some lower-middle-income countries.[21]

8.3 Patented medicines that were not included in the WHO EML partly due to affordability concerns.

In recent years, an application for adding the novel oral anticoagulants to the WHO EML was rejected by the WHO Expert Committee in part due to concerns around affordability. This case was discussed in Chapter 5. We outline below two further cases where the WHO EML Expert Committee or submission to the WHO highlighted affordability concerns over certain treatments being reviewed.

8.3.1 Insulin analogues.

For people living with type 1 diabetes, regular insulin injections are necessary for survival. Insulin may also be used in type 2 diabetes as one of the treatment options available for second- and third-line treatment.

Insulin analogues are newer forms of insulin in which the molecular structure has been altered leading to pharmacokinetic advantages such as more durable long-acting versions, faster rapid-acting versions, as well as more stable action in the body, potentially reducing the risk of hypoglycaemic events.[22] While the insulin analogues have come to dominate the market in high-income countries and increasingly also some LMICs,[23] in 2017, the WHO Expert Committee reviewed an application to add insulin analogues to the EML, and concluded that "the benefits in terms of reduced A1c and advantages of reduced hypoglycaemia of insulin analogues over human insulin were modest and do not justify the current large difference in price between analogues and human insulin".[16] Some have suggested that the rapid rate at which analogues are replacing human insulin in LMICs means that the issue of affordability needs to be urgently tackled.[23]

The patent landscape for insulin analogues is unclear. Two different analyses have reported that there appears to be little remaining patent protection for some of the insulin analogues, apart from patents on injection devices (pre-filled syringes, pens, and cartridges).[24,25] As insulins are biologic medicines, with a production process significantly more complex than that of small molecule (non-biologic) medicines, the details of the production process itself are highly important for successful manufacture of generic versions. These details are in general trade secrets, and as such pose a potentially indefinite, though partial, barrier to prospective biosimilar entrants.[25,26] Nevertheless, the first biosimilar insulin analogue (a biosimilar of insulin glargine) was recently approved in the US and the European Union, and multiple other biosimilars are in development.[27]

The field of insulin analogues is an area that may merit further exploration, in view of the importance of insulin for diabetes patients and the access challenges that have been widely reported in LMICs.[28–30] For example, engaging in technology transfer of certain

insulin analogues to biosimilar manufacturers in developing countries could be an interesting opportunity for the MPP to explore with industry partners.

8.3.2 Denosumab

The Union for International Cancer Control (UICC) prepared a review of bisphosphonates and submitted to the 21st WHO Expert Committee an application for the addition of the bisphosphonate zoledronic acid to the WHO EML.[31] Bisphosphonates are medicines that slow the breakdown of bone. This makes them useful in treating bone lesions, which are a common occurrence in certain cancers, occurring, for example, in nearly all cases of multiple myeloma, 75% of prostate cancer cases, and 70% of breast cancer cases.[31–33] Bisphosphonates prevent about a third of morbidity associated with bone lesions (such as fractures, pain, etc).[3134–37] The UICC review noted that denosumab, a biologic, is superior to bisphosphonates,[31,38] but has a far higher price, leading the UICC not to recommend denosumab for addition to the WHO EML "at this time due to the adverse economic impact this agent would have on health care budgets". Denosumab appears to be protected by substance patents lasting until at least 2022.[39]

8.4 Other patented medicines highlighted by stakeholders

In discussions with stakeholders and experts, a number of other medicines or therapeutic areas were flagged as having, in their opinion, potential for being considered essential medicines in the future and possibly representing candidates for MPP licensing. It should be noted that these medicines or therapeutic areas have not been analysed in detail and may represent the view of only a small number of stakeholders. The following are given as illustrative examples and are not intended to be an exhaustive list, nor are they intended to indicate cases in which the MPP could or should play a role. As they were mentioned by certain stakeholders, they are included here for completeness. For the cancer medicines mentioned below, the upcoming discussions of the EML working group on cancer could contribute to determining whether such treatments hold potential for future inclusion in the WHO EML.

8.4.1 Liver cancer

An estimated 813,000 people are currently living with liver cancer in LMICs.[40] Sorafenib is the only medicine that is recommended in European guidelines for treating primary liver cancer, apart from palliative medications.[41] Sorafenib is an oral, small-molecule medicine. The primary patent for sorafenib expires in 2020 in the US, and secondary patents may offer protection until 2028. In 2012, a compulsory licence was issued for sorafenib in India.[42]

8.4.2 Checkpoint inhibitors

Immune checkpoint inhibitors represent a new class of biologic medicine. Multiple medicines in this class have been approved in the past few years, and have shown benefit in cancers that previously had little options for treatment,[43] such as metastatic

melanoma and metastatic lung cancer.[44,45] Examples include ipilimumab, nivolumab, and pebrolizumab.

8.4.3 HER2-negative breast cancer

Palbociclib is an oral, small-molecule medicine approved for the treatment of HER2-negative, hormone-receptor positive breast cancer. Palbociclib offers overall survival benefits in patients who are not eligible for HER2-targeted therapies such as tratuzumab.[46] Patent protection for palbociclib expires in 2023 in the US.

8.4.4 Schizophrenia

An estimated 17.6 million people are currently living with schizophrenia in LMICs.[40] Multiple long-acting injectable (LAI) formulations of second-generation antipsychotics have become available in recent years. Some of these depot formulations, for example, paliperidone palmitate, have a duration of action as long as 3 months from a single injection. Depot formulations are useful in cases of low adherence to treatment.[47]

8.4.5 Multiple sclerosis

Natalizumab is biologic medicine approved for the treatment of relapsing-remitting multiple sclerosis (RRMS), the most common type of multiple sclerosis. In 2016, there were 962,000 people living with multiple sclerosis in LMICs.[48] RRMS is a debilitating neurological condition causing symptoms such as muscle weakness, fatigue, and visual problems, among others. In the landmark trial, natalizumab reduced the risk of worsening disability[z] by 42% in the first two years of treatment.[49] Natalizumab is protected by a patent expiring in 2024.

8.5 Areas where important new treatments may emerge soon

Experts and stakeholders highlighted a number of areas where promising drug candidates are in the pipeline, and, if approved, may represent important treatments for LMICs. We note a few illustrative examples that were highlighted to us below.

8.5.1 Sickle cell disease

One example is GBT440, a medicine for sickle-cell disease that has shown promise in early trials and is now in Phase III trials.[50] Sickle-cell disease is a condition in which red blood cells can become deformed, leading to a range of severe symptoms and complications, including anaemia, pulmonary infections, attacks of severe pain, and stroke before the age of 20 in 11% patients.[51] 99% of the estimated 3.8 million people with sickle cell disease cases occur in low- and middle-income countries.[48]

8.5.2 Endometriosis

[z] Worsening disability based on increases in the Extended Disability Status Scale sustained for at least 12 weeks.

Another example is elagolix, a treatment for endometriosis – a condition that affects 6-10% of women of reproductive age and causes severe pelvic pain and constipation, among other symptoms,[52] translating to significant economic losses.[53] Two phase III trials published in 2017 showed that elagolix conferred reductions in pain for a large proportion of women.[54]

8.5.3 Hepatitis B

While tenofovir and entecavir have higher barrier to resistance emergence than the older nucleoside analogues, these drugs alone are unable to achieve *functional cures* on their own and require long-term treatment. The management of treatment failures as well as the prospects for short-term therapy would benefit from new classes of direct-acting anti-HBV drugs, many of which are in Phase II or earlier-phase development. New treatment strategies for HBV may shift towards the use of a direct HBV-targeting drug in combination with an immunotherapy aimed at activating the immune system. This is reflected in the current HBV pipeline, where numerous immunomodulators are in Phase II. At present, the only Phase III candidate is besifovir, an oral treatment shown to be as effective current first-line treatment and possibly offering advantages in tolerability and toxicity.

Given that the MPP has already been working on expanding access to hepatitis B treatments through its licences on TDF and TAF (which are both also indicated for HIV), if promising new treatments were to enter the market, including treatments that could be used for a functional cure, the MPP would be well placed to play a role in facilitating access in LMICs.

8.6 Diagnostics

Shortcomings in access to diagnostics was a prominent and recurring issue across the range of areas considered in this feasibility study. Many of the stakeholders and experts consulted suggested that the MPP should consider whether it could play a role in increasing access to certain diagnostics in the therapeutic areas that the MPP works in, in collaboration with other stakeholders. This was mentioned not only in relation to therapeutic areas that would be new for the MPP, but also in relation to diagnostics for hepatitis C. The WHO is developing an Essential Diagnostics List,[55] which could potentially provide a starting point. However, the MPP has not, to date, undertaken an analysis of whether the MPP's patent pooling model could play a role in relation to diagnostics. There are many differences between medicines and diagnostic technologies, including differences in the role played by patent protection. We considered diagnostics to be beyond the scope of this feasibility study.

8.7 Note on vaccines

The MPP has separately commissioned a paper on vaccines, with a particular focus on the human papilloma virus vaccine and the pneumococcal conjugate vaccine, which are therefore not covered in this study.

8.8 Conclusions

In addition to dasatinib, imatinib, nilotinib and trastuzumab, which were discussed in an earlier chapter, and valganciclovir, for which the MPP has already signed an agreement in view of its use for an HIV-related co-infection, there are other medicines on the EML outside of HIV, hepatitis C, and TB that have patents granted or pending in some LMICs. These include bendamustine, bevacizumab, entecavir, rituximab, zoledronic acid, and three different contraceptives – ulipristal, DMPA-SC, and the etonogestrel implant. This list is not exhaustive, as others have secondary patents in some countries, and we were unable to review the patent status of all essential medicines in all countries.

Some of the products mentioned above are protected by secondary or device patents. Some patents are on specific formulations. MPP licensing agreements may enable increased access to these products in LMICs, although the potential MPP engagement in device patents would require more detailed evaluation beyond this analysis. Similarly, insulin analogues also appear to have device patents, and the possibilities for MPP involvement in that area through licensing and technology transfer could be explored further.

This chapter has also shown that there may be other recently-approved or pipeline medicines that could be promising candidates for MPP licensing, as was raised by different stakeholders and experts in our consultations. In some cases, these are (pipeline) products that are or could become important treatments for diseases with high prevalence in LMICs (e.g. hepatitis B). In other cases, the products target small patient populations but may offer improved efficacy over currently available treatments. In still other cases, these treatments may have limited available alternatives. Some of these may be products with potential for future inclusion in the WHO EML, although they have generally not been reviewed b the EML Committee.

However, one consideration that was repeatedly raised in consultations is the importance of the MPP to consider licensing important new medicines with strong potential for improving public health outcomes in LMICs early-on, which may mean negotiating licences before they are reviewed by the WHO. The key argument made was that there will in most cases be a period of time between the MPP identifying a promising new medicine, to that medicine being available as a quality-assured generic from MPP licensees. The sooner the process starts, the earlier populations lacking access could be treated. Moreover, as shown in previous chapters, the Expert Committee may delay EML inclusion due to affordability concerns or a need for additional data to justify inclusion. It would be important to have robust mechanisms in place for the early identification of new medicines with the potential to significantly improve public health in LMICs. This issue will be further discussed in the following chapter. If the MPP's mandate were expanded, the further exploration of mechanisms that could be used to identify candidates for MPP licensing, in close consultation with the WHO, would constitute an important element of the implementation plan.

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