

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

Table of contents

Ack	nowledgments
Acr	onyms
Exe	cutive summary
1	Introduction22
2	Methodology
3 chro	Patented medicines included in the EML: <i>Case study on medicines for</i> onic myeloid leukaemia
4 rele <i>med</i>	Patented medicines that the WHO Expert Committee considered as having evant clinical benefits but needing additional data: <i>Case study on novel</i> <i>licines for type 2 diabetes</i> 48
5 Exp on n	Patented medicines that have clinical benefits but did not meet the EML ert Review committee's comparative cost-effectiveness criterion: <i>Case study</i> novel oral anticoagulants64
6 thei pros	Patented medicines for which the WHO Expert Committee recommended a capeutic area review by a separate working group: <i>Case studies on lung cancer, state cancer, multiple myeloma and breast cancer</i> 80
7	New antibiotics to combat antimicrobial resistance
8 mer	Other products in the WHO EML, highlighted by EML Committee or ntioned in discussions with stakeholders114
9	Discussion and conclusions124

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Acronyms

AF	Atrial fibrillation
ALL	Acute lymphocytic leukaemia
AMR	Antimicrobial Resistance
API	Active pharmaceutical ingredient
ARIPO	African Regional Intellectual Property Organization
ARV	Antiretroviral
ATMI	Access to Medicines Index
CARB-X	Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
CML	Chronic myeloid leukaemia
CPL	Countries in past MPP licences
DALY	Disability-adjusted life year
DPP-4	Dipeptidyl peptidase 4 inhibitor
EAPO	Eurasian Patent Organization
EML	Essential Medicines List
EOI	Expression of interest
ERP	Expert Review Panel
FISH	Fluorescent in-situ hybridisation
GARDP	Global Antibiotic Research and Development Partnership
GLP1A	Glucagon-like peptide-1 receptor agonists
HAI	Health Action International
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
INR	International normalized ratio
LMIC	Low- and middle-income countries
MACE	Major adverse cardiovascular event
MPP	Medicines Patent Pool
NEML	National essential medicines list
NICE	UK National Institute for Health and Care Excellence
NOAC	Novel oral anticoagulant
NSCLC	Non-small cell lung cancer
NVAF	Non-valvular atrial fibrillation
OAPI	Organisation Africaine de la Propriété Intellectuelle
PCR	Reverse transcriptase polymerase chain reaction
PE	Pulmonary embolism
PH+ CML	Philadelphia chromosome-positive chronic myeloid leukaemia
PPL	Priority Pathogens List
QALY	Quality adjusted life years
R&D	Research and development
SGLT2I	Sodium-glucose cotransporter 2 inhibitors
SG-TKI	Second-generation tyrosine kinase inhibitor
SBP	Similar biotherapeutic product
SRA	Stringent regulatory authority
SSE	Stroke and systemic embolism
SU	Sulphonylureas
T2D	Type 2 diabetes
ТВ	Tuberculosis
T-DM1	Trastuzumab emtansine

TKI	Tyrosine kinase inhibitor
UICC	Union for International Cancer Control
UK	United Kingdom
USFDA	United States Food and Drug Administration
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WHO	World Health Organization
WIPO	World Intellectual Property Organization

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.

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

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

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

11

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 qualityassured 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 costeffectiveness 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 bleeding,³²⁻³⁶ 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.

Combatting 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, resourceconstrained 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.

XII. References

1 Medicines Patent Pool. https://medicinespatentpool.org/what-we-do/global-licence-overview/update-on-progress-of-mpp-sublicensees/ (accessed May 17, 2018).

Wirtz VJ, Hogerzeil H V, Gray AL, *et al.* Essential medicines for universal health coverage. *Lancet* 2017; 389: 403–76.

3 World Health Organization. WHO Submission to the UN SG High Level Panel on Access to Medicines. 2016. https://static1.squarespace.com/static/562094dee4b0d00c1a3ef761/t/56e746279f7266a586c2b893/1457997352 055/WHO_HLP_Submission_7Mar2016.pdf (accessed Feb 16, 2018).

4 World Health Organization. The Selection and Use of Essential Medicines: Report of the WHO Expert Committee. 2015. http://apps.who.int/iris/bitstream/10665/189763/1/9789241209946_eng.pdf?ua=1 (accessed Oct 17, 2017).

5 Vos T, Abajobir AA, Abate KH, *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1211–59.

6 WHO EML Expert Committee. Report of the WHO Expert Committeeon Selection and Use of Essential Medicines. WHO Tech. Rep. Ser. 2017.

http://www.who.int/medicines/publications/essentialmedicines/EML_2017_EC21_Unedited_Full_Report.pdf?ua=1 (accessed Sept 14, 2017).

Kantarjian H, Cortes J. Chronic Myeloid Leukemia. In: Abeloff's Clinical Oncology, 5th edn. 2014: 1944–57.
 National Institute for Health and Care Excellence. Dasatinib, nilotinib and high-dose imatinib for treating

imatinib-resistant or intolerant chronic myeloid leukaemia. 2016.

https://www.nice.org.uk/guidance/ta425/chapter/4-Committee-discussion (accessed Sept 19, 2017).
 9 Hochhaus A, Larson RA, Guilhot F, *et al.* Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. *N Engl J Med* 2017; 376: 917–27.

10 Rosti G, Castagnetti F, Gugliotta G, Baccarani M. Tyrosine kinase inhibitors in chronic myeloid leukaemia: which, when, for whom? *Nat Rev Clin Oncol* 2016; 14: 141–54.

11 European Society for Medical Oncology. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; 28: 41–51.

12 NCCN Guidelines Version 1.2018 Chronic Myeloid Leukemia.

13 Loveman E, Cooper K, Bryant J, Colquitt JL, Frampton GK, Clegg A. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: a systematic review and economic evaluation. *Health Technol Assess* 2012; 16: iii–xiii, 1-137.

Hughes TP, Saglio G, Kantarjian HM, *et al.* Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. *Blood* 2013.

15 Gabble R, Kohler J. 'To patent or not to patent? the case of Novartis' cancer drug Glivec in India'. *Global Health* 2014; 10: 3.

16 Tamil Nadu Medical Services Corporation Ltd. Specialty 2016-17.

http://www.tnmsc.com/tnmsc/new/user_pages/drugtender.php?drugcat=sdg2016.

17 U.S. Food and Drug Administration (FDA). DMF List 3Q2017.

https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/drugmasterfilesdmfs/def ault.htm (accessed Oct 24, 2017).

Bommer C, Sagalova V, Heesemann E, *et al.* Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030. *Diabetes Care* 2018; : dc171962.

19 Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 1999; 281: 2005–12.

20 Di Angelantonio E, Kaptoge S, Wormser D, *et al.* Association of Cardiometabolic Multimorbidity With Mortality. *JAMA* 2015; 314: 52.

21 Methods and Applications Group for Indirect Treatment Comparisons. Application for the revision of second line treatments of type II diabetes. 2017.

http://www.who.int/selection_medicines/committees/expert/21/applications/s18_T2D_antidiabetics_rev.pdf?ua=1 (accessed Sept 14, 2017).

Polonsky W, Henry R. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence* 2016; Volume 10: 1299–307.

International Diabetes Federation. Access to Medicines and Supplies for People with Diabetes: a global survey on patients' and health professionals' perspective. 2016.

World Health Organization. Revised procedure for updating WHO's Model List of Essential Drugs. 2001. http://apps.who.int/medicinedocs/documents/s22165en/s22165en.pdf (accessed March 8, 2018). 25 Huisman M V, Rothman KJ, Paquette M, *et al.* The Changing Landscape for Stroke Prevention in AF: Findings From the GLORIA-AF Registry Phase 2. *J Am Coll Cardiol* 2017; 69: 777–85.

American Academy of Family Physicians. Pharmacologic Management of Newly Detected Atrial Fibrillation. 2017. https://www.aafp.org/dam/AAFP/documents/patient_care/clinical_recommendations/a-fib-guideline.pdf (accessed Jan 19, 2018).

27 You JJ, Singer DE, Howard P, Lane DA, Eckman MH. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST J* 2012; 141: e531S–e575S.

Kearon C, Akl EA, Ornelas J, *et al.* Antithrombotic Therapy for VTE Disease. *Chest* 2016; 149: 315–52.
 Kirchhof P, Benussi S, Kotecha D, *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; 37: 2893–962.

Healey JS, Oldgren J, Ezekowitz M, *et al.* Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *Lancet* 2016; 388: 1161–9.

World Health Organization. Assessing national capacity for the prevention and control of noncommunicable diseases. 2016. http://apps.who.int/iris/bitstream/10665/246223/1/9789241565363-eng.pdf (accessed Oct 5, 2017).

32 Cohen AT, Hamilton M, Mitchell SA, *et al.* Comparison of the novel oral anticoagulants apixaban, dabigatran, edoxaban, and rivaroxaban in the initial and long-term treatment and prevention of venous thromboembolism: Systematic review and network meta-analysis. *PLoS One* 2015; 10: e0144856.

33 Proietti M, Romanazzi I, Romiti GF, Farcomeni A, Lip GYH. Real-World Use of Apixaban for Stroke Prevention in Atrial Fibrillation. *Stroke* 2018; 49: 98–106.

Larsen TB, Skjøth F, Nielsen PB, Kjældgaard JN, Lip GYH. Comparative effectiveness and safety of nonvitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ* 2016:i3189.

35 Yao X, Abraham NS, Sangaralingham LR, *et al.* Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation. *J Am Heart Assoc* 2016; 5: e003725.

Hicks T, Stewart F, Eisinga A. NOACs versus warfarin for stroke prevention in patients with AF: a systematic review and meta-analysis. *Open Hear* 2016; 3: e000279.

Pharmaceutical Product Development LLC. Developing Biosimilars in Emerging Markets: Regulatory and
 Clinical Considerations. 2013. http://healthtrustpg.com/biosimilars/pdf/ppd.pdf (accessed Feb 21, 2018).
 Welch AR. 6 Tips For Navigating Emerging Market Biosimilar Regulations. Biosimilar Dev. 2016.

https://www.biosimilardevelopment.com/doc/tips-for-navigating-emerging-market-biosimilar-regulations-0001 (accessed Feb 21, 2018).

39 Rader RA. Biosimilar Markets and Regulation: Which Countries Are Going All In? Bioprocess Int. 2017. http://www.bioprocessintl.com/manufacturing/biosimilars/biosimilar-markets-regulation-countries-going/ (accessed Feb 21, 2018).

40 World Health Organization. Guidelines on evaluation of similar biotherapeutic products (SBPs). http://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf (accessed Feb 21, 2018).

41 World Health Organization. WHO to begin pilot prequalification of biosimilars for cancer treatment. 2017.
42 Welch AR. A Deep Dive Into Brazil's Biosimilar PDPs. Biosimilar Dev. 2017.

https://www.biosimilardevelopment.com/doc/a-deep-dive-into-brazil-s-biosimilar-pdps-0001 (accessed Feb 21, 2018).

43 The Review on Antimicrobial Resistance Chaired by Jim O'Neill. Tackling drug-resistant infections globally: final report and recommendations. 2016. https://amr-review.org/sites/default/files/160525_Final paper_with cover.pdf (accessed Feb 18, 2018).

44 Renwick MJ, Simpkin V, Mossialos E. International and European Initiatives Targeting Innovation in Antibiotic Drug Discovery and Development: The Need for a One Health – One Europe – One World Framework. 2016. http://static.diariomedico.com/docs/2016/02/12/2016-report-on-antibiotic-rd-initiaitives-1.pdf (accessed March 26, 2018).

DRIVE-AB. Revitalizing the antibiotic pipeline: Stimulating innovation while driving sustainable use and global access. 2018. http://drive-ab.eu/wp-content/uploads/2018/01/DRIVE-AB-Final-Report-Jan2018.pdf (accessed Feb 19, 2018).

46 Silver LL. Challenges of Antibacterial Discovery. *Clin Microbiol Rev* 2011; 24: 71–109.

47 Coates AR, Halls G, Hu Y. Novel classes of antibiotics or more of the same? *Br J Pharmacol* 2011; 163: 184–94.

48 Outterson K, Gopinathan U, Clift C, So AD, Morel CM, Røttingen J-A. Delinking Investment in Antibiotic Research and Development from Sales Revenues: The Challenges of Transforming a Promising Idea into Reality. *PLOS Med* 2016; 13: e1002043.

49 Chatham House. Towards a New Global Business Model for Antibiotics Delinking Revenues from Sales: Report from the Chatham House Working Group on New Antibiotic Business Models. 2015.

https://www.chathamhouse.org/sites/files/chathamhouse/field/field_document/20151009NewBusinessModelAnti bioticsCliftGopinathanMorelOuttersonRottingenSo.pdf (accessed Feb 15, 2018).

50 World Health Organization. WHO to develop Essential Diagnostics List. 2017.

http://www.who.int/medicines/news/2017/WHO_develop_essential_diagnostics_list/en/ (accessed Feb 20, 2018).

1 Introduction

1.1 Background to the study

1.1.1 The Medicines Patent Pool

The Medicines Patent Pool (MPP) is a public health organisation established in 2010 to accelerate access to affordable, appropriate, and quality-assured HIV treatments in developing countries through public health voluntary licensing and patent pooling. The innovative financing mechanism Unitaid supported the establishment of the MPP at the request of the international community to respond to the significant gap between the number of people living with HIV eligible for therapy and those receiving care. Concerns about high costs for the newer HIV treatments, some of which were on the World Health Organization's Model List of Essential Medicines (EML) were coupled with a need for medicines with better efficacy, tolerability, and a higher barrier to resistance.

The MPP's licences with patent holders enable multiple HIV medicine manufacturers to enter low- and middle-income countries (LMICs) markets several years prior to patent expiry with quality-assured formulations. In addition to facilitating access to treatments, the MPP model enables innovation that addresses specific needs in LMICs. This includes the development of new fixed-dose combinations (FDCs) and special formulations for children, a neglected population given limited treatment options adapted for different age-groups and weight bands.

The MPP was the first public health patent pool and was created in response to calls for the implementation of novel mechanisms to facilitate innovation, access, and technology transfer.¹ Multiple positive endorsements from public health agencies, international organisations, as well as high-level declarations supported the launch of the MPP which helped establish its role as an integral part of the international response to the HIV epidemic.²⁻⁴

1.1.2 Expansion of the MPP's mandate to hepatitis C and tuberculosis

Following extensive consultation, in November 2015 the Unitaid Executive Board decided to fund the expansion of the MPP mandate to include hepatitis C and tuberculosis (TB). In both therapeutic areas, new and promising medicines had recently been granted regulatory approval, or were in late-stage development, and had patents pending or filed in several developing countries. Some of these medicines had been recently added to the EML and there was a pressing need to increase access in LMICs. Public health-oriented licensing was identified as one way to address some of those needs. Shortly after the expansion, the UN Political Declaration on HIV/AIDS "welcome[d] the broadening of the scope of work of the Medicines Patent Pool [...] to promote voluntary partnerships to address hepatitis C and tuberculosis."²

1.1.3 The MPP's current model

The MPP's work starts with the identification of a priority list of approved and pipeline medicines for in-licensing in consultation with the World Health Organization (WHO) and other experts, including in governments and civil society. Prioritization is based on the analysis of medical needs, market challenges, and patent status in LMICs.

Once the MPP finalises its list of priority medicines, the organisation approaches relevant patent holders to explore the possibility of obtaining a licence, with a detailed rationale as to why and how licensing to the MPP would contribute to facilitating access to the medicine and to improving public health in LMICs. To date, the MPP has negotiated licensing agreements with nine patent holders^B covering 16 medicines for the treatment of HIV, hepatitis C virus (HCV), and tuberculosis. This includes 12 medicines/combinations that are included in the WHO EML (Table 1). In addition to these licensing agreements, the MPP has partnerships with two other patent holders in the form of non-assert declarations and a price discount agreement.

Medicine(s)	Year of MPP licence agreement	Year of addition to the EML
Abacavir (paediatrics)	2013	2002/2007/2017
Abacavir/lamivudine	2013	2015
Atazanavir	2013	2009
Atazanavir/ritonavir	2013 and 2015	2017
Daclatasvir	2015	2015
Dolutegravir	2014	2017
Lopinavir/ritonavir	2015	2002/2007/2009
Raltegravir (paediatric)	2015	2017
Ritonavir	2015	2002
Tenofovir disoproxil fumarate	2011	2007
Tenofovir disoproxil fumarate/emtricitabine	2011	2007 (treatment) 2017 (prophylaxis)
Tenofovir disoproxil fumarate/emtricitabine /efavirenz	2011 and 2015	2007
Tenofovir/lamivudine/efavirenz	2011	2017
Valganciclovir *	2013	2015

Table 1. Medicines in the WHO EML licensed to the MPP.

* Special access agreement for HIV programmes for 138 low- and middle-income countries.

Licences with patent holders are negotiated from a public health perspective and have been recognised for their pro-access terms and for providing the greatest flexibility and transparency.^{5,6} Key terms and conditions in MPP licences include:

• Broad geographical coverage in LMICs to enable a large number of countries/patients to benefit from access to affordable treatment and to facilitate economies of scale for manufacturing

^B The MPP has licences from: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Johns Hopkins University, MSD, NIH, Pharco, Viiv Healthcare. In addition, the MPP has an agreement with Roche and collaborated on non-assert declarations with Janssen and Boehringer Ingelheim.

- Ability to sublicense manufacturing rights in a non-exclusive and nondiscriminatory manner to multiple manufacturers to facilitate robust competition
- Strict quality assurance requirements
- Where necessary, reasonable royalty terms, including differentiated royalties according to a country's per capita income
- Freedom for manufacturers to develop suitable paediatric formulations or other fixed-dose combinations that meet public health needs.

In addition, a key characteristic of MPP licences is that they are all published on the MPP website, setting a new precedent for licensing transparency in pharmaceuticals and public health.

Following the issuance of a licence, the MPP publishes an expression of interest inviting qualified manufacturers to apply for a sublicence. The process seeks to ensure that sublicences are granted to companies or product developers that have the capacity, willingness and commitment to develop appropriate formulations, obtain regulatory approval, and make them available in the licensed territory. To date, 24 manufacturers and one product development partnership have signed sublicences with the MPP (Figure 1).

Figure 1. The MPP model.



The MPP also helps to facilitate and accelerate the development process through the publication of market projections jointly with the WHO, the provision of technical support to sublicensees where needed and quarterly meetings with manufacturers to review progress in development and address any issues. This helps to shorten the development timelines, enabling people with HIV in the developing world to access the best available treatments more rapidly.⁷

As of December 2017, MPP's generic manufacturer partners had supplied more than 17 million patient years of treatment and allowed savings of US\$553 million through the procurement of more affordable treatments.⁸ MPP licences have also enabled the

development of new fixed-dose combinations that are now recommended by the WHO. One example is the combination tenofovir / lamivudine / dolutegravir (or TLD). Only four years after the approval of the HIV medicine dolutegravir, the first generic manufacturers have already obtained US FDA approval for the new combination TLD, providing a new FDC that is ideally suited for scale-up in developing countries.⁹

1.1.4 Calls for expansion into patented essential medicines

In 2016, the WHO recommended to the UN High Level Panel on Access to Medicines that consideration be given to "the expansion of the mandate of the Medicines Patent Pool to all disease areas, and for all patented essential medicines on the WHO Essential Medicines List to be licensed into the [Medicines Patent] Pool", with the MPP's work recognised as a "major advancement for access to medicines".¹⁰

In November 2016, the Lancet Commission on Essential Medicines Policies made a similar recommendation, concluding that there appeared to be "a wide scope for patent pooling for other essential medicines (as defined by WHO or national committees)" and calling for the expansion of the MPP into an Essential Medicines Patent Pool.¹¹

The recommendations from the WHO and the Lancet Commission, as well as preliminary conversations with a number of stakeholders, highlighted a perception that the MPP's patent pooling and voluntary licensing model could potentially be adapted to essential medicines in therapeutic areas beyond HIV, TB and HCV. In the same year, the pharmaceutical company GlaxoSmithKline announced an intention to license any essential medicines for lower middle-income countries and to license future cancer medicines to a patent pool and to explore this with the MPP.¹²

In December 2016, the MPP's Board decided to undertake an evidence-based assessment that would explore the feasibility and potential public health and economic impact of expanding the MPP's mandate to include patented essential medicines in other therapeutic areas. This study would support an informed decision on whether the mandate should be expanded.

1.2 Essential medicines

1.2.1 The concept of essential medicines and the WHO Model List of Essential Medicines (EML)

The WHO defines essential medicines as "those drugs that satisfy the priority health care needs of the majority of the population" and that are "intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford."¹³ Target 3.8 of the UN Sustainable Development Goals is to "[a]chieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all."

The WHO EML, first issued in 1977,¹⁴ is intended to serve as a model for the development of national essential medicines lists and a large number of countries have

developed their own lists, including, in some cases, EMLs at the provincial level. National essential medicines lists are usually associated with treatment guidelines and often guide the procurement of medicines in the public sector, reimbursement schemes, or other mechanisms linked to a country's medicines policy. At the global level, the WHO EML provides a valuable framework for multiple public health actors, including international organisations, for the prioritization of medicines for various programmes and activities.¹¹

1.2.2 The WHO EML Expert Committee and criteria for inclusion in the List

The WHO EML is updated every two years by the WHO Expert Committee on the Selection and Use of Essential Medicines. The current procedure for development of the list and general criteria for inclusion were established in 2001 by the WHO Executive Board, with further clarifications provided by the Committee in its subsequent meetings. The medicines included in the WHO EML are selected on the basis of public health relevance, evidence on efficacy and safety and comparative cost-effectiveness.¹⁴

The WHO Executive Board clarified the application of the comparative cost effectiveness criterion in 2001. Absolute cost is not considered a reason for excluding a medicine. However, comparative cost-effectiveness is assessed when multiple treatments are available for the same indication. The patent status of a medicine is also not considered in the selection of medicines for inclusion.¹⁴ In 2013, the Expert Committee defined the criterion of public health relevance to include not only consideration of medicines for diseases with a high prevalence, but also medicines for diseases that may be less common but for which there are highly effective medicines.^{15,16}

The number of medicines on the WHO EML has been growing steadily over the years. Today, the core and complementary lists combined contain 433 medicines.

1.2.3 Evolution in the inclusion of new patented medicines in the WHO EML

Historically, the vast majority of medicines included in the EML were medicines that had been on the market for many years, and for which patent protection had expired in developing countries or had never been widely granted^C.¹⁷

In 2002, the inclusion of 12 new, patented antiretroviral medicines (ARVs) for the treatment of HIV marked an important turning point in this respect. These ARVs had been included in the WHO HIV treatment guidelines but were generally unavailable and/or unaffordable in the vast majority of developing countries. The WHO Expert Committee recognised the limited experience in treating HIV in resource-limited settings but noted the significant public health needs.¹⁸ These ARVs were under patent protection in some LMICs, with expiry dates many years beyond the date of their addition to the EML.¹⁹ Since then, several additional ARVs have been added to the EML, many of which have been licensed to the MPP.

^c Many LMICs did not grant patents on pharmaceutical products until the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) entered into force.

In 2013, the patented medicine bevacizumab was added to the EML for its use in ophthalmology^D.¹⁵ The 2015 revision of the EML resulted in the inclusion of several new patented medicines outside of the area of HIV treatment. This was triggered by the approval of the first new medicines for TB in over forty years, the approval of ground-breaking new hepatitis C treatments, inclusion of hepatitis B medicines and a review of the oncology section of the EML. In oncology, bendamustine, imatinib, rituximab, and trastuzumab (in addition to 12 other older cancer medicines) were added to the EML.²⁰ The working group responsible for recommending medicines for inclusion noted that "although some of the medicines are currently under patent protection and are only sold at a high price, there are some good examples of initiatives to expand the availability of such medicines to lower-income settings at an affordable price." The proponents also recalled the case of ARVs, noting that inclusion in the EML could be a critical step to improving affordability.²¹

1.2.4 The 2017 revision of the EML

The 2017 revision of the WHO EML resulted in the addition of a number of new, patented medicines to the list, including three medicines for HIV, one for HCV, two for chronic myeloid leukaemia (nilotinib and dasatinib), one for emergency contraception and at least one other cancer medicine with secondary patents (zoledronic acid). In the case of the HIV medicine dolutegravir, the Committee highlighted the existence of MPP licences in its recommendation for inclusion, noting that nine generic manufacturers held sublicences on the product and would be bringing quality-assured generics to the market.²² The MPP had signed a licence on dolutegravir with patent holder ViiV Healthcare in 2014, three years before it was submitted to the WHO EML in 2017. By the time the Committee discussed the listing of dolutegravir, several MPP licensees had already developed the product and had filed for WHO Prequalification.

In addition to the two leukaemia medicines, several other recently approved cancer medicines were submitted but were ultimately not added, pending a comprehensive evaluation of cancer treatments by a dedicated 'cancer working group'. It is expected that this working group will support the WHO in establishing guiding principles on the inclusion of second-line cancer treatments, clarifying what constitutes a therapeutic effect significant enough to justify a medicine's addition to the EML. Thus, numerous cancer medicines submitted to the 2017 Committee – such as those for lung cancer, breast cancer, and prostate cancer – will likely be reconsidered at the next meeting of the Committee as part of a review of cancer medicines.²²

In total, we have estimated that approximately 45 medicines on the WHO EML may be protected by patents in some jurisdictions, of which 13 are covered by compound patents. This does not include consideration of patented vaccines that are also listed on the WHO EML. These numbers should not be considered an exhaustive analysis (see Methodology chapter for how these were identified). The numbers will also continue to evolve as new medicines are added to the EML, and patents on listed medicines expire.

^D Listed in the WHO EML for age-related macular degeneration but is also used for the treatment of colon cancer, lung cancer, glioblastoma, renal-cell carcinoma, and numerous other cancers.

1.2.5 National Essential Medicines Lists

Many countries have developed national essential medicines lists (NEMLs), which are used in different ways depending on local legislation and practices. Often, they guide the procurement and supply of medicines in the public sector and medicine reimbursement schemes. In certain cases, countries may also have national or provincial level reimbursement lists that are distinct from the NEML.²³

While the WHO EML is often used as a basis for the development of national lists, several studies have shown significant differences between NEMLs. In the case of imatinib, for example, 30% of the reviewed NEMLs had already included the medicine prior to its inclusion on the WHO list in 2015.²⁴

Due the link between NEMLs and government reimbursement, several stakeholders noted during consultations that governments often hesitate to have new, highly-priced medicines added to NEMLs in view of the impact this may have on health budgets. Several examples of this were cited, including, for example, the direct-acting antivirals for hepatitis C or certain medicines for cancer or diabetes. Conversely, a few countries have NEMLs that include many of the new cancer medicines, sometimes leading to significant budgetary pressures.

1.3 Aims and scope

The aim of this study is to assess the public health need for, feasibility and potential impact of, expanding the MPP's mandate to include patented essential medicines in other therapeutic areas beyond HIV, TB, and hepatitis C. The methodology for this feasibility study and main sources are outlined in **Chapter 2**.

The starting point for this feasibility study was to identify essential medicines that are included on the WHO's EML, are used in the treatment of diseases other than HIV, HCV, and TB, and that are under patent protection. For this, we used earlier studies that analysed previous editions of the EML, and supplemented these with our own analyses of the new patented medicines added in the most recent editions (Table 2).^{17,25}

Medicine	Main use(s)	Year added to EML
Artemether- lumefantrine	Malaria	2002
Bendamustine	Cancers of the blood	2015
Bevacizumab	Macular degeneration, colorectal cancer	2015
Dasatinib	Leukaemia	2017
Entecavir	Hepatitis B	2015
Etonorgestrel impant	Contraceptive	2015
Imatinib	Leukaemia	2015
Nilotinib	Leukaemia	2017
Omeprazole	Gastrointestinal reflux disease	2009
Oseltamivir	Influenza	2011
Pegylated interferon	Hepatitis C	2013
Progesterone vaginal ring	Contraceptive	2015
Rituximab	Cancers of the blood, rheumatoid arthritis	2015
Tenofovir disoproxil fumarate	Hepatitis B (and HIV)	2015 (for hepatitis B)
Trastuzumab	Breast cancer	2015
Ulipristal acetate	Emergency contraceptive	2017
Valganciclovir	Citomegalovirus retinitis (CMVr)	2015
Zoledronic acid	Malignancy-related bone disease	2017

Table 2. Examples of medicines added to the EML in recent years with patents in force at time of addition, outside of HIV, TB, and hepatitis C (not exhaustive).

Vaccines are excluded from the table.

In addition, the human papilloma virus and the pneumococcal conjugate vaccines are also considered important essential medicines as per the WHO EML with patent protection in some LMICs, but are not covered in this study, as vaccines will be the focus of a separate assessment.

As the WHO EML is updated every two years, it was important that this study reviewed not only medicines that are on the list today, but also included an analysis of treatments that may be considered essential medicines in the future. To do so, we relied on the WHO Expert Committee's own assessments, identifying medicines that were highlighted by the Committee for offering relevant clinical benefits.

We identified the following medicines, falling into four categories, for exploratory case studies:

- 1. Patented medicines included in the EML: Examples of medicines that are on the EML, were under patent protection at the time of addition to the EML, and are outside of the therapeutic areas of HIV, TB, and hepatitis C, are shown in the table above. In **Chapter 3**, we present an in-depth case study on two patented medicines recently added to the EML: dasatinib and nilotinib, used for the treatment of chronic myeloid leukaemia (CML).
- 2. Patented medicines that the WHO Expert Committee considered as having relevant clinical benefits but needing additional data to confirm findings: These are medicines that appear to offer benefits over medicines already on the list, but for which inclusion in the EML was considered premature at the time they were

reviewed. In this category, we considered the case of a new class of medicines used for the treatment of type 2 diabetes – the SGLT2 inhibitors. In 2017, the WHO Expert Committee concluded that "SGLT2 inhibitors have been reported to be associated with a relevant clinical benefit as intensification therapy in patients at high risk of cardiovascular events, leading to a relevant reduction in overall mortality. This finding needs to be confirmed in other trials, prior to selectively supporting this class of medicines in patients with type 2 diabetes."²² **Chapter 4** will provide an analysis of medicines in this category, with a focus on new medicines for type 2 diabetes.

- 3. Patented medicines that have clinical benefits but did not meet the EML Expert Review committee's comparative cost-effectiveness criterion: In this category, we considered the case of the novel oral anticoagulants (NOACs). In 2015, the Committee assessed an application for the inclusion of the NOACs and concluded that the "evidence indicates a favourable, overall clinical benefit of the NOACs over warfarin" but also that "the large difference in costs between NOACs and warfarin was disproportional to the observed incremental benefit."²⁰ MPP licensing for this category of medicines could potentially contribute to reducing concerns over their affordability in LMICs. A case study on this category of productss is available in **Chapter 5**.
- <u>4.</u> Patented medicines for which the WHO Expert Committee recommended a therapeutic area review by a separate working group: In this category, we considered the case of medicines for lung cancer (erlotinib, gefitinib, afatinib, crizotinib), prostate cancer (abiraterone, enzalutamide), breast cancer (trastuzumab emtansine, pertuzumab, lapatinib) and multiple myeloma (lenalidomide) which the WHO Expert Committee in 2017 recommended could be reviewed as part of the work of a new Cancer Working Group.²² For some such medicines, the Committee noted clinical benefits (e.g. more favourable tolerability profile, or greater efficacy) but also certain challenges (e.g. a lack of screening and diagnostic infrastructure). Comprehensive evaluation by the EML Cancer Working Group may result in these or other cancer medicines being added to the list in 2019. These medicines are discussed in **Chapter 6**.

In addition to the medicines described above, this study also analysed the potential role that MPP licensing could play in antimicrobials, with particular attention to aligning any potential work with efforts to tackle antimicrobial resistance. In 2017, the WHO Expert Committee undertook a thorough review of antibiotics and introduced a new classification, categorizing antibiotics into three groups – *Access, Watch* and *Reserve* – to balance the need for broad access to some antibiotics with the need to preserve other classes of antibiotics as last resort in case of resistance. Given that the international community has prioritised the need for developing new antibiotics,²⁶ it is likely that certain new antibiotics, once developed, would be important candidates for inclusion in the WHO EML. Various reports have indicated that mechanisms such as the MPP could play a role in ensuring the appropriate supply of new antibiotics to LMICs while contributing to proper stewardship to avoid the development of resistance.²⁷ In **Chapter 7**, we consider how the MPP could play a role in relation to new antibiotics in the context of the *AWaRe* framework established by the EML Committee.

Chapter 8 provides a brief outline of a few other patented medicines in the EML that are not covered in the above case studies. It also covers other medicines or candidate drugs highlighted by different stakeholders that may be candidates for inclusion in the EML in the future. These medicines have in general not been reviewed by the WHO EML Committee, have not been analysed in detail and are mentioned in the study for completeness.

In **Chapter 9**, we provide a general discussion of the public health and market considerations that are relevant to a potential expansion of the MPP's mandate and draw some general conclusions.

While vaccines have not been analysed in this study, they are the subject of a separate ongoing assessment.

As the future composition of the EML is not known, this analysis should be considered illustrative. We have focussed on specific products and therapeutic areas in order to explore some of the publc health needs in LMICs at present and the potential role the MPP could play. However, if the MPP's mandate were to be expanded, further prioritization processes would be needed to identify, in consultation with stakeholders, specific target products for MPP licensing.

1.4 References

World Health Organization. Global strategy and plan of action on public health, innovation and intellectual property. 2008. http://apps.who.int/medicinedocs/documents/s21429en/s21429en.pdf (accessed March 13, 2018).
 United Nations General Assembly. Political Declaration on HIV and AIDS: On the Fast Track to Accelerating the Fight against HIV and to Ending the AIDS Epidemic by 2030. 2016.

http://www.unaids.org/sites/default/files/media_asset/2016-political-declaration-HIV-AIDS_en.pdf (accessed March 13, 2018).

World Health Organization. Global Strategy and Plan of Action on Public Health, Innovation and Intellectual
 Property. 2011. http://www.who.int/phi/publications/Global_Strategy_Plan_Action.pdf (accessed March 13, 2018).
 Deauville G8 declaration: Renewed commitment for freedom and democracy. 2011.

https://photos.state.gov/libraries/unitedkingdom/164203/2011/Deauville_Declaration_FINAL_ENGLISH.pdf (accessed April 20, 2018).

5 Access to Medicine Foundation. The Access to Medicine Index. 2014.

https://accesstomedicinefoundation.org/media/atmf/2014-Access-to-Medicine-Index.pdf (accessed March 12, 2018).

6 World Health Organization. Global health sector strategy on HIV 2016-2021. 2016.

http://apps.who.int/iris/bitstream/10665/246178/1/WHO-HIV-2016.05-eng.pdf?ua=1 (accessed March 12, 2018). 7 Burrone E, Perry G. Ensuring new medicines reach those in most need. *Lancet HIV* 2015; 2: e362–3.

8 KPMG statement. 2017. https://medicinespatentpool.org/uploads/2017/06/KPMG-statement_13-Oct-2017.pdf (accessed March 11, 2018).

9 Press release. Mylan Receives Tentative Approval for 'TLD' Under PEPFAR. 2017.

https://www.prnewswire.com/news-releases/mylan-receives-tentative-approval-for-tld-under-pepfar-300500233.html (accessed March 12, 2018).

10 World Health Organization. WHO Submission to the UN SG High Level Panel on Access to Medicines. 2016. https://static1.squarespace.com/static/562094dee4b0d00c1a3ef761/t/56e746279f7266a586c2b893/1457997352 055/WHO_HLP_Submission_7Mar2016.pdf (accessed Feb 16, 2018).

11 Wirtz VJ, Hogerzeil H V, Gray AL, *et al.* Essential medicines for universal health coverage. *Lancet* 2017; 389: 403–76.

12 GlaxoSmithKline. Increasing medicine access across the world's poorest nations. 2016. https://au.gsk.com/en-au/behind-the-science/access-to-healthcare/increasing-medicine-access-across-the-worlds-poorest-nations/ (accessed Feb 16, 2018).

13 World Health Organization. Essential medicines. http://www.who.int/topics/essential_medicines/en/ (accessed March 12, 2018).

14 World Health Organization. Revised procedure for updating WHO's Model List of Essential Drugs. 2001. http://apps.who.int/medicinedocs/documents/s22165en/s22165en.pdf (accessed March 8, 2018). 15 World Health Organization. Report of the WHO Expert Committee on the Selection and Use of Essential Medicines. 2013. http://apps.who.int/iris/bitstream/10665/112729/1/WHO_TRS_985_eng.pdf (accessed Jan 30, 2018).

16 Magrini N, Robertson J, Forte G, *et al.* Tough decisions on essential medicines in 2015. *Bull World Health Organ* 2015; 93: 283–4.

17 Beall RF, Attaran A. Patent-based Analysis of the World Health Organization's 2013 Model List of Essential Medicines. 2016.

18 World Health Organization. Report of the WHO Expert Committee on the Selection and Use of Essential Medicines. 2002. http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_914.pdf (accessed March 15, 2018).

19 The Medicines Patent Pool. MedsPaL. http://www.medspal.org/ (accessed Feb 3, 2017).

20 World Health Organization. The Selection and Use of Essential Medicines: Report of the WHO Expert Committee. 2015. http://apps.who.int/iris/bitstream/10665/189763/1/9789241209946_eng.pdf?ua=1 (accessed Oct 17, 2017).

21 Shulman LN, Wagner CM, Barr R, *et al.* Proposing Essential Medicines to Treat Cancer: Methodologies, Processes, and Outcomes. *J Clin Oncol* 2016; 34: 69–75.

22 WHO EML Expert Committee. Report of the WHO Expert Committee on Selection and Use of Essential Medicines. WHO Tech. Rep. Ser. 2017.

http://www.who.int/medicines/publications/essentialmedicines/EML_2017_EC21_Unedited_Full_Report.pdf?ua=1 (accessed Sept 14, 2017).

Wirtz VJ, Hogerzeil H V., Gray AL, *et al.* Essential medicines for universal health coverage. *Lancet* 2016.
Robertson J, Barr R, Shulman LN, Forte GB, Magrini N. Essential medicines for cancer: WHO

recommendations and national priorities. Bull World Health Organ 2016; 94: 735-42.

25 UNITAID. Ensuring that essential medicines are also affordable medicines: challenges and options. 2016 https://unitaid.eu/assets/Ensuring_that_essential_medicines_are_also_affordable_medicines_challenges_and_options -1.pdf.

26 United Nations General Assembly. Political Declaration of the high-level meeting of the General Assembly on antimicrobial resistance. 2016.

http://www.un.org/ga/search/view_doc.asp?symbol=A/71/L.2&referer=/english/&Lang=E (accessed March 12, 2018).

27 The Review on Antimicrobial Resistance Chaired by Jim O'Neill. Tackling drug-resistant infections globally: final report and recommendations. 2016. https://amr-review.org/sites/default/files/160525_Final paper_with cover.pdf (accessed Feb 18, 2018).

2 Methodology

This section outlines the methodology used to explore the feasibility of expanding the MPP's mandate to work on patented essential medicines. Additional details are available in the appendix.

2.1 Identification of patented essential medicines

In order to explore the feasibility of expanding the MPP's mandate to include patented essential medicines in other therapeutic areas, the MPP first identified patented medicines included on the WHO EML. We used as our starting point recent studies published by Unitaid and the World Intellectual Property Organization (WIPO) that analysed patent protection on medicines in the EML.^{1,2} As these studies were published before the release of the most recent EML in 2017, we additionally assessed patent status for medicines added in 2017. Medicines used for the treatment of human immunodeficiency virus (HIV), hepatitis C (HCV) and tuberculosis (TB) were excluded from this analysis, as the MPP's current area of work includes these therapeutic areas.

We also reviewed the reports of the WHO Expert Committee to identify other medicines with potential for future inclusion in the EML, as discussed in the preceding chapter.

2.2 Mapping the patent landscape

The MPP identified relevant patent families for the medicines included in case studies using the FDA Orange Book and the Health Canada Patent Register.^{3,4} These databases list patents that were supplied by the originator company as relevant to patent protection. There are known limitations regarding the types of patents that are listed under both resources, for example, process patents are not included,⁵ and some of the patents listed may in practice not block generic market entry. These resources nevertheless offer the best available picture and reflect the patent holders' own assessments. This is the same methodology used for the MPP's patents and licences database MedsPaL, an established resource for the patent status of essential medicines.⁶

We assessed patent status and likely patent expiry dates in a sample of LMICs with a focus on countries with significant domestic capacity in manufacturing generic medicines. We used online patent databases, data provided by some patent offices themselves and commissioned patent lawyers to conduct searches. The jurisdictions for which patent status was assessed include the African Regional Intellectual Property Organization (ARIPO; covering 19 countries in Africa), Brazil, China, the Eurasian Patent Organization (EAPO), Guatemala, India, Indonesia, Morocco, the *Organisation Africaine de la Propriété Intellectuelle* (OAPI; covering 17 countries in Africa), Philippines, Ukraine, South Africa, Thailand, and Vietnam.

2.3 Review of disease burden and treatment landscape

We estimated the disease burden for the selected medicines using established sources for epidemiological data – the Global Burden of Disease study,^{7,8} the GLOBOCAN project

maintained by the WHO International Agency for Research on Cancer,⁹ and the Diabetes Atlas maintained by the International Diabetes Federation.¹⁰

In reviewing the landscape of treatments and diagnostics for the relevant diseases, we drew on submissions made to the WHO Expert Committee, as well as the Committee's reports, WHO publications, relevant United States and European treatment guidelines, key clinical evidence (e.g. clinical trials, meta-analyses, published real-world data), and published analyses of the availability of relevant treatments and diagnostics.

2.4 Country-level analysis

The MPP commissioned a series of national background papers from local expert clinicians to provide a perspective of the current standard of care for some of the relevant therapeutic areas in their countries. These national reports covered current diagnostic and treatment practices, current access challenges and potential opportunities for improving access to the best available treatments.

The countries covered in these national reports were:

- For cancer treatments Botswana, Haiti, Kenya, Nicaragua, Pakistan, Uzbekistan and Vietnam.
- For novel oral anticoagulants Botswana, India, Nigeria, Peru and South Africa.
- For novel treatments for type 2 diabetes Cambodia, India, Pakistan, Peru and Tanzania.

Additionally, national experts collected information on local availability, pricing, generic status and registration of the medicines.

We reviewed 25 recent national essential medicines lists (NEMLs) from LMICs to which we had access to provide a sense of the extent to which the medicines analysed in the case studies were included in NEMLs. Given the complexity of obtaining and reviewing a wide range of NEMLs, and analysing the patent status of hundreds of medicines, we did not additionally analyse medicines in NEMLs that were not already part of the case studies (see Chapter 1). However, medicines included in NEMLs but not in the WHO EML may merit further attention in the future.

2.5 Consultations with experts and stakeholders

The MPP established a Steering Group to guide the development of the feasibility study, composed of subject matter experts with extensive experience in access to medicines (see Acknowledgements).

We held a wide range of informal consultations with experts in relevant disease areas (diabetes, oncology, cardiovascular disease, and antimicrobials) and stakeholder groups. In addition to informal consultations, we conducted semi-structured interviews with civil society organisations, and representatives from originator and generics companies. We also consulted government representatives at the 2017 World Health Assembly and subsequently in other fora. We solicited peer review for individual

chapters from eminent experts in the relevant fields. A list of experts and stakeholders consulted as part of this study is included in the Acknowledgements.

2.6 Focus on new antibiotics

Numerous recent reports have analysed the issue of antimicrobial resistance and recommended MPP playing an important role as part of innovative R&D financing mechanisms..^{11–13} An earlier analysis conducted by the MPP – the TB Stewardship Report – identified ways in which the MPP could tailor its licences to contribute to addressing both access and stewardship needs for novel TB antibiotics.¹⁴

In this study, we further developed potential MPP approaches in the field of antimicrobials, drawing on the findings of the MPP's TB Stewardship Report, the report of the O'Neill Review on Antimicrobial Resistance, the Report from the Chatham House Working Group on New Antibiotic Business Models, the DRIVE-AB report, the WHO priority pathogens list (PPL), the AMR Benchmark ^{11–13,15} and consultations with leading stakeholders.

2.7 Estimation of public health and economic impact

For some medicines, we modelled quantitative estimates of the potential public health and economic impacts that could result from MPP licensing. We developed estimation models based on assumptions regarding various treatment and market factors, which are summarised in Table 1 (details in appendix).

Table 1. Assumptions/sources used for modelling potential public health and
economic impact of MPP licensing under an expanded mandate.

-	, ,
Epidemiology	Data from Global Burden of Disease study, GLOBOCAN, and IDF Atlas
Market penetration	Conservative assumptions varying by medicine, taking into account, among other factors, the proportion of the population that is undiagnosed, guideline- recommended use, and availability of alternative treatments
Efficacy	Clinical trials, meta-analyses, modelling published by the UK National Institute for Health and Care Excellence (NICE)
Cost savings	Estimated cases treated multiplied by price difference between projected generic price and current lowest originator price in India
Market dynamics	Assumed licence signed in 2019, generic market entry 1-3 years later, uptake increases linearly over 5 years*, price of MPP-enabled generic treatments decreases gradually
Territory	Countries in past MPP licences (see 2.8. Geographical scope of the analysis)
Impact duration	From time of hypothetical generic market entry to one year after expiry of relevant patents in LMICs. Impact is halved after expiry of compound patent.

2.8 Geographical scope of the analysis

The MPP's work focuses on improving health outcomes in countries designated by the World Bank as low- and middle-income economies. ^{16,17} The geographical scope of licences negotiated by the MPP varies. Since there is little precedent for access-oriented licensing in the therapeutic areas analysed, it is difficult to predict the likely

geographical scope of such licences. As a result, while in general the study looked at low- and middle-income countries (LMICs) more broadly, for the purpose of estimating public health and economic impact, we focussed on the countries that have in general been included in past MPP licences in HIV and HCV. We use the term 'countries in past MPP licences' (CPL) for this group of countries, which was defined as all low- and lowermiddle income, as defined by World Bank,¹⁷ plus all countries in sub-Saharan Africa.¹⁸

2.9 Market analysis

We collected data on pricing and availability from the Management Sciences for Health International Medical Products Price Guide,¹⁹ national databases,^{20–22} and data provided by the experts in national background papers. We assessed the availability of generic products based on data provided by the national experts, as well as by reviewing Drug Master File submissions to the US FDA, discussion with manufacturers, and generics manufacturers' websites for indications that generic versions were in development.

To complement information on access to treatments provided by national experts, we reviewed initiatives by originator companies to increase access to the selected medicines by consulting publications by the International Federation of Pharmaceutical Manufacturers and Associations and the Access to Medicine Foundation.^{23,24} We also reviewed relevant companies' corporate social responsibility reports.

Lastly, we projected potential generic prices for the medicines analysed by applying a standard generic price erosion curve to current originator prices in India,²⁵ and, separately, by calculating the cost-of-goods based on the prices of the active pharmaceutical ingredient exported from India, using previously described methods.²⁶

2.10 Analysis of opportunities and challenges

We undertook an analysis of potential opportunities and challenges for the MPP in expanding its mandate. This was based on internal evaluation of the findings in the case studies, as well as extensive consultations with diverse stakeholders, including originator and generics companies, academic experts and representatives from governments and civil society.

2.11 References

1 UNITAID. Ensuring that essential medicines are also affordable medicines: challenges and options. 2016 https://unitaid.eu/assets/Ensuring_that_essential_medicines_are_also_affordable_medicines_challenges_and_options -1.pdf.

2 Beall RF, Attaran A. Patent-based Analysis of the World Health Organization's 2013 Model List of Essential Medicines. 2016.

3 United States Food & Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm (accessed Jan 7, 2018).

4 Health Canada. Patent register. http://pr-rdb.hc-sc.gc.ca/pr-rdb/index-eng.jsp (accessed March 7, 2018).

5 The Medicines Patent Pool. Q&A on MedsPaL: How do you select the relevant patent families?

https://medicinespatentpool.org/resources/medspal/qa-on-medspal/ (accessed March 23, 2018).

6 Medicines Patent Pool. MedsPaL. http://www.medspal.org/ (accessed Feb 28, 2018).

7 Vos T, Abajobir AA, Abate KH, *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1211–59.
8 Abajobir AA, Abate KH, Abbafati C, *et al.* Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1260–344.

9 Ferlay J, Soerjomataram I, Ervik M, *et al.* GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. 2013. http://globocan.iarc.fr (accessed Feb 1, 2015).

10 International Diabetes Federation. IDF diabetes atlas 8th edition. http://www.diabetesatlas.org/ (accessed Sept 10, 2017).

11 The Review on Antimicrobial Resistance Chaired by Jim O'Neill. Tackling drug-resistant infections globally: final report and recommendations. 2016. https://amr-review.org/sites/default/files/160525_Final paper with cover.pdf (accessed Feb 18, 2018).

12 Chatham House. Towards a New Global Business Model for Antibiotics Delinking Revenues from Sales: Report from the Chatham House Working Group on New Antibiotic Business Models. 2015.

https://www.chathamhouse.org/sites/files/chathamhouse/field/field_document/20151009NewBusinessModelAnti bioticsCliftGopinathanMorelOuttersonRottingenSo.pdf (accessed Feb 15, 2018).

13 DRIVE-AB. Revitalizing the antibiotic pipeline: stimulating innovation while driving sustainable use and global access. 2018. http://drive-ab.eu/wp-content/uploads/2018/01/DRIVE-AB-Final-Report-Jan2018.pdf (accessed Feb 19, 2018).

14 The Medicines Patent Pool Foundation. TB Stewardship Report. 2016.

https://medicinespatentpool.org/uploads/2017/07/STEWARDSHIP-REPORT_FINAL-1.pdf (accessed March 8, 2018).

15 World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. http://www.who.int/medicines/publications/WHO-PPL-

Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1 (accessed March 26, 2018).

16 Medicines Patent Pool. Vision & mission. https://medicinespatentpool.org/who-we-are/vision-mission/ (accessed Jan 5, 2018).

17 The World Bank. World Bank Country and Lending Groups.

https://datahelpdesk.worldbank.org/knowledgebase/articles/906519 (accessed Jan 5, 2018).

18 The World Bank. Population, total. http://data.worldbank.org/indicator/SP.POP.TOTL (accessed May 1, 2017).

19 Management Sciences for Health. International Medical Products Price Guide.

http://mshpriceguide.org/en/home/ (accessed Oct 16, 2017).

20 South Africa Department of Health. Master Procurement Catalogue.

http://www.health.gov.za/index.php/component/phocadownload/category/196 (accessed May 12, 2017).

21 South African Medicine Price Registry. Database of Medicine Prices 22 December 2017.

http://mpr.gov.za/Publish/ViewDocument.aspx?DocumentPublicationId=4007 (accessed Feb 7, 2018).

22 CIMS. CIMS. 18 Oct 2017.

23 IFPMA. Health Partnerships Directory. http://partnerships.ifpma.org/partnerships (accessed Jan 9, 2018).

Access to Medicines Foundation. Improving access to cancer care. 2017.

https://accesstomedicinefoundation.org/media/atmf/Access-to-Medicine-Foundation_Cancer-care-

study_22May2017.pdf (accessed June 6, 2017).

Juneja S, Gupta A, Moon S, Resch S. Projected savings through public health voluntary licences of HIV drugs negotiated by the Medicines Patent Pool (MPP). *PLoS One* 2017; 12: e0177770.

Hill A, Barber MJ, Gotham D. Estimated costs of production and potential prices for the WHO Essential Medicines List. *BMJ Glob Heal* 2018; 0: e000571.

3 Patented medicines included in the EML: *Case study* on medicines for chronic myeloid leukaemia

3.1 Background

New, patented medicines have been added to the WHO EML in each of its recent revisions. Beyond HIV, HCV, and TB, other patented medicines that have recently been added to the EML have been primarily for the treatment of certain cancers, hepatitis B or for reproductive health. Two cancer medicines on the WHO EML have compound patent protection and, unless licensed to generic manufacturers, are unlikely to become available as generics in LMICs until those patents expire. In this case study, we examine the case for MPP licensing of these two medicines – dasatinib and nilotinib – which were added to the WHO EML in 2017 as second-line treatments for chronic myeloid leukaemia.^{1,2} Some other cancer medicines in the EML that still have secondary patent protection in certain countries are discussed in Chapter 8.

3.2 Burden of disease in low- and middle-income countries

Chronic myeloid leukaemia (CML) is a condition in which a type of stem cell begins to proliferate uncontrollably. This process suppresses the normal development of blood cells, leading to fatigue, anaemia and spleen enlargement. ³ Other initial symptoms of CML include fever, abdominal pain and a feeling of fullness, and pain in the bones.⁴ Before the advent of newer medicines called tyrosine kinase inhibitors (TKIs), the expected survival time for CML was five to seven years.⁵ With TKI treatment, it is estimated that survival time may now be more than 25 years.³ In 2015, there were 106,000 prevalent cases of CML in countries included in past MPP licences. There were a further 83,000 people with CML in other upper middle-income countries.⁶ We project that prevalence in countries included in past MPP licences will increase to 147,000 by 2030 and incidence will increase to 32,000 (appendix).

In 85–90% of cases, CML is caused by a mutation in chromosome structure, with the resulting altered chromosome known as the Philadelphia chromosome.⁷ This altered chromosome produces a mutated tyrosine kinase enzyme which leads to uncontrolled cell growth. Imatinib, the first drug that could selectively inhibit this mutated enzyme and thus control the disease, was developed in the 1990s,⁸ and added to the WHO EML in 2015.² Newer medicines in the same class are termed second-generation TKIs (SG-TKIs), which include dasatinib and nilotinib. These newer medicines are the focus of the analysis presented in this chapter.

In the US, the median age at presentation for CML is 55 to 65 years.⁹ In high-income countries, CML is generally diagnosed as an incidental finding before it has become symptomatic, while undertaking a blood sample analysis.⁴ Studies have suggested that the median age of presentation may be 20 years lower in Africa and Pakistan compared to high-income countries.^{10,11} However, in India, it is unusual for CML cases to be diagnosed while they are still asymptomatic – they are usually diagnosed when the disease is already more advanced.¹²⁻¹⁴ A similar pattern is reported in Nigeria.¹⁵ This

later presentation of CML in resource-poor settings is likely due to the lower rate of full blood count testing compared to high-income countries.

National background papers commissioned to inform this feasibility study suggest that the proportion of cases that are diagnosed is as low as 30% in Kenya, Haiti and Botswana, while local experts in Pakistan and Uzbekistan reported diagnosis rates may be more than 90%. Without more systematic data, these numbers need to be interpreted with caution.

3.3 Note on acute lymphocytic leukaemia

In addition to use as second-line therapy in CML, dasatinib is also indicated for acute lymphocytic leukaemia (ALL) when it displays the Philadelphia mutation (Ph+ ALL).¹⁶ There were 439,000 people living with ALL in countries included in past MPP licences in 2015,⁶ of which about 70,000 are estimated to be Philadelphia chromosome positive.

About 60% of cases of ALL occur in people less than 20 years of age,¹⁷ and about 16% of cases display the Philadelphia chromosome mutation. In broad terms, ALL manifests with symptoms similar to those in CML. However, these symptoms usually present suddenly in ALL, as opposed to slowly emerging in CML.¹⁸ In high-income countries, when optimal treatment is given, survival rates for ALL are excellent.¹⁹ A subset of ALL has a significantly worse prognosis (unless treated with TKIs), with up to 75% of those affected dying within a year.²⁰

Imatinib is approved for the first-line treatment of Ph+ ALL and dasatinib is approved for second-line treatment of Ph+ ALL. Dasatinib has been shown to be efficacious in Ph+ ALL as first- or second-line treatment, in combination with chemotherapy.²⁰ There is evidence that nilotinib is also effective in Ph+ ALL, though it is not licensed for this use.²¹ While this chapter focuses mainly on CML, the impact analysis below also considers the possible use of dasatinib for the treatment of ALL.

3.4 Outline of drugs, diagnostic methods and guidelines

Imatinib, dasatinib and nilotinib are all approved for the first-line treatment of CML.²² However, dasatinib and nilotinib were included in the EML due to their importance as second-line treatments, which therefore remains the main focus of this chapter.

While imatinib is a highly effective medicine, an estimated 23% (or 40% according to the UK National Institute for Health and Care Excellence) of patients with CML may eventually become resistant or intolerant to standard-dose imatinib.^{23,24} Treatment options for imatinib-resistant CML include high-dose imatinib (300-400mg twice daily, as opposed to the normal dose of 400mg once daily), dasatinib, or nilotinib.²²

European and US guidelines recommend all three treatments as second-line therapies.^{25,26} However, dasatinib and nilotinib may offer multiple benefits to high-dose imatinib. US guidelines consider that patients with primary resistance to imatinib are unlikely to benefit from dose escalation and a SG-TKI should be used.^{26,27} In addition,

trials have suggested that an earlier, rather than later, switch to SG-TKIs results in better patient outcomes. $^{\rm 22}$

SG-TKIs have shown greater efficacy compared to imatinib *in vitro* and have shown larger responses in proxy measures of disease activity.²⁸ So-called 'deep molecular responses' are more frequently achieved with dasatinib or nilotinib compared to high-dose imatinib. Deep molecular response is associated with better event-free survival, transformation-free survival, and failure-free survival.^{22,29-32} The risk of transformation from chronic phase to accelerated or blast phase leukaemia is decreased in patients taking dasatinib or nilotinib rather than imatinib^E.²⁴ Dasatinib and nilotinib are also considered to have favourable side effect profiles compared to imatinib.^{22,23}

Modelling exercises undertaken for the UK National Institute for Health and Care Excellence (NICE) estimated that quality adjusted life years (QALYs) and overall survival gain conferred by dasatinib and nilotinib were greater than those conferred by high-dose imatinib, and that dasatinib and nilotinib are better tolerated overall than imatinib in terms of side effects.^{23,33}

Two other TKIs have been approved for the treatment of CML: bosutinib and ponatinib.^{25,26} These medicines were not considered by the WHO Expert Committee for inclusion in the EML. We therefore do not focus on them. However, some of the conclusions may be equally applicable to bosutinib and ponatinib.

3.4.1 Diagnosis and monitoring of chronic myeloid leukaemia

Various modalities exist to diagnose and monitor CML. Cytogenetic analysis, the oldest method, requires a bone marrow sample, which is collected through a painful procedure in which a special needle is placed into the hip bone. Newer techniques can diagnose Ph+ CML using a blood sample, termed FISH and PCR^F.

In sub-Saharan Africa, significant challenges exist in diagnosing haematological malignancies due to a lack of laboratories, equipment, and skilled staff.³⁴ In India, cytogenetic analysis costs US\$8–15, FISH costs US\$31–46, and PCR costs US\$77–108, per test.¹⁴ GeneXpert machines, initially developed and distributed through health systems to diagnose multidrug-resistant TB, can be used to detect Ph+ CML. Public health experts hope the technology will make diagnosis easier and affordable in the near future.^{34–37}

National background papers commissioned to inform this feasibility study noted that in Haiti, molecular testing to diagnose Ph+ CML relies on sending bone marrow out of the country, although GeneXpert machines are being repurposed for Ph+ CML diagnosis. Diagnosis by FISH is available in Botswana. In Kenya diagnosis is performed through cytogenetic testing and/or PCR, which is partially supported by the Glivec International Patient Assistance Program (now called *CMLPath to Care*; more on this below). FISH and PCR are available in Uzbekistan.

 $^{^{\}rm E}$ In patients with non-low Sokal risk scores. 25 In a study of Indian CML patients, 79% had non-low Sokal scores. 51

^F FISH – fluorescent in situ hybridisation. PCR – reverse transcriptase polymerase chain reaction.

The major modalities of monitoring CML response to treatment are cytogenetic response, requiring bone marrow sampling, and molecular response, which uses simple blood samples. Both are proxy measures for clinical outcomes.²⁵

3.4.2 Availability and affordability of medicines

Data on access to dasatinib and nilotinib in LMICs is sparse. In India, it has been noted that in most large centers "patients who experienced treatment failure with imatinib are now back to receiving older medicines, such as hydroxyurea".¹⁴ A study in Rwanda noted that monitoring of CML patients receiving imatinib "had little practical implication given that if resistance to imatinib had developed, other treatment options were not available".³⁶ During consultations with certain governments, dasatinib and nilotinib were mentioned among the medicines for which high prices are challenging for access. In some cases, this made their inclusion in NEMLs difficult.

National background papers commissioned to inform this feasibility study showed highly varied availability between countries. There are originator access initiatives in place for imatinib and, to a lesser extent, nilotinib and dasatinib, which provide free or discounted access to these medicines for patients in some LMICs and have contributed to making them accessible (see section *3.9*). Where originator access initiatives were not in place, the drugs were either unavailable or available on the private market at high prices (Table 1). In Botswana, while generic imatinib has recently been registered, access to SG-TKIs is costly and, given the small number of patients, effective price negotiations could be challenging. In Haiti, dasatinib is theoretically available through donations. However, mutational testing for resistance to first-line agents is currently unavailable. In Pakistan there is partial support through an originator access program. In South Africa, only nilotinib appears to be available in the public sector, at US\$156 per month. On the Indian private market, nilotinib is currently priced at US\$3,742 per month,³⁸ and dasatinib at US\$2,843 per month.³⁹

Medicine	Price per month (USD)						
	Dasatinib	Nilotinib					
Botswana	Ν	No data					
Haiti	Ν	Ν					
Kenya	Originator donated through GIPAP, no generic available	\$2,260					
India	\$2,842	\$3,742					
Pakistan	\$489**	\$4,341 (partial GIPAP support)					
South Africa	\$1,650 (private), not available in public sector	\$156 (public), \$2,160 (private)					
Uzbekistan	Ν	Originator donated through GIPAP, no generic available					
Viet Nam	iet Nam N Originator donated through GIPA generic available						
N – not registered and/or unavailable. GIPAP – Glivec International Patient Access Programme, recently replaced by CMLPath to Care. **Available but not registered. Assumed dosage: imatinib 400mg/day, dasatinib 100mg/day (price for Pakistan approximated based on price for 140mg tablets), nilotinib 800mg/day.							

Table 1. Prices and availability of dasatinib and nilotinib in selected countries.

3.5 Tyrosine kinase inhibitors for CML and the WHO Expert Committee

Imatinib was first submitted for inclusion in the WHO EML in 2013 and eventually added in 2015.^{2,40} At the time imatinib was first submitted, the medicine was still under patent in several LMICs.⁴¹ In 2017, the WHO Expert Committee added dasatinib and nilotinib to the WHO EML as second-line therapies for Ph+ CML, noting that they confer "a relevant clinical benefit resulting primarily from large response rates (i.e. complete cytogenetic response) in patients with otherwise very limited treatment options".¹

3.6 Inclusion in national essential medicines lists (NEMLs)

Of the 25 recent NEMLs from LMICs that we were able to review, imatinib was included in those of Colombia, Peru, Kenya, Costa Rica, the Dominican Republic, Russia, South Africa, Panama, India and Serbia, as well as in Mexico's reimbursement list.

Dasatinib was included in the NEMLs of Peru, Thailand, Bulgaria, Croatia, Jordan, Russia and Panama.

Nilotinib was included in the NEMLs of Mexico, Thailand, Bulgaria, Jordan, Russia, South Africa, Syria, Panama and Serbia.

3.7 Patent landscape for second-generation tyrosine kinase inhibitors

While the primary patent for imatinib expired in 2013, secondary patents on imatinib are in force until 2018/21, which may delay access to generics in countries where those patents are granted. The expiry dates for the primary patent on dasatinib and nilotinib are 2020/24 (depending on the country) and 2023 respectively. Secondary patents on these medicines may provide exclusivity until 2025-2030 and could delay generic market entry in certain countries. As shown in the table below, patents have been granted in key countries of manufacture such as India, China, and South Africa, including many of the secondary patents.

Table 2. Tatent stat	us of GML	uiu	<u>gə m</u>	501	псы	1103	anu	гелр		u cz	үшу	uai	.03.		
CML	Expected date of expiry	li PO	۶A	N	P0	ΓM	z	Q	AR	API	1	łA	(R		M
		AF	BF	E	EA	5	8	N	М	<i>1</i> 0	Į	Ŧ	5	ZA	Ś
Imatinib															
Product patent	2013	•			•	•	•	•	•	•	·	•	·	•	•
β-Crystalline form of Imatinib Mesylate	2018	·	F	G	G*	·	G	R	·	·	G	G	·	G	G
Method of treating gastrointestinal stromal tumours	2021		F	G	G*	?	·		?	?	G		?	G	
Nilotinib															
Product patent	2023		G	G	G*			G			G	G		G	G
Nilotinib Monohydrochloride salt	2026	·	F	G	G*	G	F	0	G	·	G	F	·	G	·
Method of treating proliferative disorders with nilotinib.	2030	·	F	G	F*	F	G	F	G	·	G	А	·	G	·
Dasatinib															
Dasatinib product	2020/2024	·	F	F	F*	•	•	G	•	·	G	F	G	G	G
Crystalline Dasatinib monohydrate	2025	•	F	G	G*	•	·	0	•	•	F	•	·	G	G

Table 2. Patent status of CML drugs in some LMICs and expected expiry dates.

G – granted. F – filed. R – refused. * – in Russia only. Blank – not filed. ? – no data. ARIPO – African Regional Intellectual Property Organization, EAPO – Eurasian Patent Organization, OAPI – Organization Africaine de la Propriete Intellectuelle.

3.8 Relevant market analysis for generic manufacturer interest in the area

With the expiry of the primary patent on imatinib, a number of generic manufacturers have entered the Indian market and other LMICs. However, patients with CML that eventually develop resistance or intolerance to imatinib would benefit from switching to SG-TKIs such as dasatinib and nilotinib, neither of which currently have generic versions available on the market. Nine generic manufacturers have submitted data on the active pharmaceutical ingredient to the US FDA for dasatinib, and eight for nilotinib, suggesting that several companies eventually plan to apply for approval for a generic version.⁴² Some of these submissions are from manufacturers that have an established relationship with the MPP as generic partners and have been actively supplying LMICs with medicines for HIV and hepatitis C.

Market analyses estimate that about half of the high-income country market in value terms will comprise second- and third-generation CML drugs in 2020, with the other half comprising generic imatinib.⁴³ Similar projections are not available for LMICs, and will likely depend on price, generic market entry and originator access programmes. Originator nilotinib is currently priced at US\$3,742 per month on the Indian private market, and dasatinib at US\$2,843 per month. Generic prices in LMICs could vary significantly based on a number of factors, including volumes, which in the case of these medicines will remain low. In Tamil Nadu, imatinib is procured for \$8 per patient per month via state tender.⁴⁴

Medicines with lower dosage can often have a significant price advantage over generic medicines that have higher API cost requirements.⁴⁵ Dasatinib has notably lower dosage (100mg daily) than nilotinib (400mg daily) and high-dose imatinib (600-800mg daily). This may mean that generic dasatinib could eventually be less expensive, as less API is needed per tablet.

3.9 Initiatives by originators to improve access to SG-TKIs in LMICs

Novartis, the originator company for imatinib, has partnered with the Max Foundation, a non-governmental organisation, to operate a donation scheme for imatinib – previously called the Glivec International Patient Assistance Program (GIPAP), now CMLPath to Care. The programme "[makes] imatinib accessible to all medically and financially eligible patients within 80 countries on an ongoing basis as long as their physicians prescribe it and no other means of access exists".⁴⁶ In India, 55% of diagnosed patients receive imatinib through CMLPath to Care at free or a reduced price.⁴⁷ For nilotinib and dasatinib, access through this programme appears to be more limited. CMLPath to Care provides nilotinib for second-line treatment in a subset of those countries in which it provides imatinib. Many lower-middle income countries in Sub-Saharan Africa, Asia and Latin America are not covered.^{48,49} At present, the program is expected to run until 2021.⁴⁸

In Pakistan, Novartis has partnered with provincial governments. In four provinces, the agreements entail Novartis covering the cost of imatinib for nine months and of nilotinib for 11 months, with the provincial government then covering a further three months of treatment with imatinib, and one month with nilotinib. Two other provinces have a different agreement, where both Novartis and the provincial government partially cover the price of imatinib and nilotinib, but the patient must pay 20-50% of the price as well as laboratory monitoring costs. This latter programme experiences a higher rate of non-compliance, presumed to be due to higher out-of-pocket expenses.^G

Dasatinib is also donated to the Max Foundation by the originator Bristol Myers-Squibb for specified countries. The initiative is "designed to respond to spontaneous requests for treatment access on behalf of patients who are uninsured and underinsured, where product is either not available commercially, where significant access hurdles exist and where local market initiatives cannot enable access to the therapy".⁵⁰ The Max Foundation also donates GeneXpert diagnostic equipment to selected countries.⁴⁹

3.10 Estimated public health impact for MPP intervention in SG-TKIs

Potential economic and public health impacts of hypothetical MPP licences on SG-TKIs inhibitors were estimated using the methodology outlined in Chapter 2 and described in more detail in the appendix. The assumed duration of impact was five years and we modelled low-uptake and high-uptake scenarios. See the appendix for further details.

^G Details on these programmes in Pakistan are drawn from a background paper commissioned to inform this feasibility study.

Table 3. Estimated public health impact for MPP intervention in SG-TKIs in imatinib-resistant Ph+ CML.

	Dasatinib	Nilotinib
Total duration of impact	5 years	
Total patient-years of treatment	42,000–150,000	17,000-124,000
Total life-years gained (calculated only for treatment of imatinib-resistant Ph+ CML)	5,000–33,000	3,000-19,000

3.11 Estimated economic impact for MPP intervention in SG-TKIs

We estimated that total theoretical savings in countries included in past MPP licences could range between US\$0.2–1.6 billion (ranges represent low- and high-uptake scenarios). Economic savings took into account the donation programmes in place for dasatinib and nilotinib in a number of LMICs.

3.12 Conclusions

While CML is a relatively uncommon type of cancer, it can be treated with effective oral medicines to achieve nearly normal life expectancy.³ SG-TKIs such as dasatinib and nilotinib are preferable to imatinib in patients that have primary imatinib resistance, and in patients intolerant to normal-dose imatinib, and show superiority in proxy measures that are likely to translate into clinical benefits.^{22,25,26}

We estimated that an MPP licence on SG-TKIs could potentially deliver up to 150,000 patient-years of treatment in countries included in past MPP licences over a period of five years.

While the focus of this chapter has been primarily on dasatinib and nilotinib in secondline treatment, SG-TKIs may also be used in first-line treatment and may be preferable to imatinib in patients with a high risk of progression (reported to be high in a study in India⁵¹). In addition, dasatinib, and possibly nilotinib may become important first-line therapies for ALL too. We did not consider bosutinib or ponatinib, but they may also merit further analysis.

Various factors may limit the potential impact of a hypothetical MPP license on SG-TKIs. In particular, the market for SG-TKIs is small and spread thinly across LMICs, which may limit its attractiveness for generic manufacturers, until they are able to simultaneously supply more profitable markets in high-income countries. There are, however, several manufacturers that are developing these medicines and have expressed interest in supplying LMICs.

Despite these challenges, lessons can be drawn from the case of imatinib in LMICs. Despite the small market, several manufacturers developed generic versions in India many years before generics reached high-income countries, resulting in significant price reductions.⁵² The Indian state of Tamil Nadu, for example, procures imatinib for \$8 per patient per month.⁴⁴ The donation programmes established by the originator companies in partnership with the Max Foundation have played an important role in facilitating access to treatment and diagnostics for CML in certain countries and could provide a springboard for transitioning towards what could be a more sustainable access model in the future. Discussions with all parties would be important to determine opportunities and challenges.

As with imatinib, nilotinib and dasatinib are small molecules that could be manufactured at relatively low cost and several manufacturers are developing generic versions of these medicines. MPP licences could potentially provide early access in certain LMIC markets. This could enable more people to have access to two highly effective essential medicines for cancer.

3.13 References

1 WHO EML Expert Committee. Report of the WHO Expert Committee on Selection and Use of Essential Medicines. WHO Tech. Rep. Ser. 2017.

http://www.who.int/medicines/publications/essentialmedicines/EML_2017_EC21_Unedited_Full_Report.pdf?ua=1 (accessed Sept 14, 2017).

2 World Health Organization. The Selection and Use of Essential Medicines: Report of the WHO Expert Committee. 2015. http://apps.who.int/iris/bitstream/10665/189763/1/9789241209946_eng.pdf?ua=1 (accessed Oct 17, 2017).

Kantarjian H, Cortes J. Chronic Myeloid Leukemia. In: Abeloff's Clinical Oncology, 5th edn. 2014: 1944–57.
 Arber DA, Glader B, List AF, Means RT, Paraskevas F, Rodgers GM. Wintrobe's Clinical Hematology, 13th edn.

Lippincott Williams & Wilkins.

5 Apperley JF. Chronic myeloid leukaemia. *Lancet* 2015; 385: 1447–59.

6 Vos T, Allen C, Arora M, *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1545–602.

7 Demiroglu A, Joanna Steer E, Heath C, *et al.* The t(8;22) in chronic myeloid leukemia fuses BCR to FGFR1: Transforming activity and specific inhibition of FGFR1 fusion proteins. *Blood* 2001; 98: 3778–83.

8 Pray L a. Gleevec: the breakthrough in cancer treatment. *Nat Educ* 2008; 1: 37.

9 Jemal A, Siegel R, Xu J, Ward E. Cancer Statistics , 2010. *Cancer Journal, The* 2010; 60: 277–300.

10 Luow VJ. Chronic myeloid leukaemia in South Africa. *Hematology* 2012; 17: s75–8.

Aziz Z, Iqbal J, Akram M, Saeed S. Treatment of chronic myeloid leukemia in the imatinib era. *Cancer* 2007; 109: 1138–45.

12 Mishra P, Seth T, Sazawal S, Mahapatra M, Saxena R. Report of chronic myeloid leukemia from All India Institute of Medical Sciences, 1990-2010. *Indian J Med Paediatr Oncol* 2013; 34: 159–63.

13 Malhotra H, Sharma R, Singh Y, Chaturvedi H. Report of chronic myeloid leukemia SMS Medical College Hospital, Jaipur. *Indian J Med Paediatr Oncol* 2013; 34: 177.

14 Ganesan P, Kumar L. Chronic Myeloid Leukemia in India. *J Glob Oncol* 2017; 3: 64–71.

15 Korubo KI, Omunakwe HE, Nwauche CA. Chronic Myeloid Leukemia: Clinical and Laboratory Features At Presentation To a Referral Hospital In Southern Nigeria. *Blood* 2013; 122: 5174.

16 Electronic Medicines Compendium. Sprycel 20mg, 50mg, 80mg, 100mg and 140mg Film Coated Tablets. http://www.medicines.org.uk/emc/medicine/26080 (accessed Oct 23, 2017).

17 Inaba H, Greaves M, Mullighan CG. Acute lymphoblastic leukaemia. *Lancet* 2013; 381: 1943–55.

18 Larson R, Anastasi J. Acute Lymphoblastic Leukemia: Clinical Presentation, Diagnosis, and Classification. *Hematol Malig Acute Leuk* 2008; : 111.

19 Gatta G, Botta L, Rossi S, *et al.* Childhood cancer survival in Europe 1999-2007: Results of EUROCARE-5-a population-based study. *Lancet Oncol* 2014; 15: 35–47.

20 Malagola M, Papayannidis C, Baccarani M. Tyrosine kinase inhibitors in Ph+ acute lymphoblastic leukaemia: facts and perspectives. *Ann Hematol* 2016; 95: 681–93.

Huguet F. Dasatinib for acute lymphoblastic leukemia. *Expert Opin Orphan Drugs* 2015; 3: 1339–56.

22 Rosti G, Castagnetti F, Gugliotta G, Baccarani M. Tyrosine kinase inhibitors in chronic myeloid leukaemia: which, when, for whom? *Nat Rev Clin Oncol* 2016; 14: 141–54.

23 National Institute for Health and Care Excellence. Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia. 2016.

https://www.nice.org.uk/guidance/ta425/evidence (accessed Sept 19, 2017).

Hochhaus A, Larson RA, Guilhot F, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. N Engl J Med 2017; 376: 917–27.

European Society for Medical Oncology. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; 28: 41–51.

26 NCCN Guidelines Version 1.2018 Chronic Myeloid Leukemia.

27 Bixby D, Talpaz M. Seeking the causes and solutions to imatinib-resistance in chronic myeloid leukemia. *Leukemia* 2011; 25: 7–22.

28 O'Hare T, Walters DK, Stoffregen EP, *et al.* In vitro activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. *Cancer Res* 2005; 65: 4500–5.

29 Hochhaus A, Saglio G, Hughes TP, *et al.* Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: Five-year update of the randomized ENESTnd trial. *Leukemia* 2016; 30: 1044–54.

30 Hehlmann R, Müller MC, Lauseker M, *et al.* Deep molecular response is reached by the majority of patients treated with imatinib, predicts survival, and is achieved more quickly by optimized high-dose imatinib: Results from the randomized CML-Study IV. *J Clin Oncol* 2014; 32: 415–23.

Cortes JE, Saglio G, Baccarani M, *et al.* Final Study Results of the Phase 3 Dasatinib Versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Trial (DASISION, CA180-056). *Blood* 2014; 124: 152.

32 Falchi L, Kantarjian H. Significance of deeper molecular responses in patients with chronic myeloid leukemia in early chronic phase treated with tyrosine kinase inhibitors. *Am J* ... 2013.

http://onlinelibrary.wiley.com/doi/10.1002/ajh.23560/abstract.

33 Loveman E, Cooper K, Bryant J, Colquitt JL, Frampton GK, Clegg A. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: a systematic review and economic evaluation. *Health Technol Assess* 2012; 16: iii–xiii, 1-137.

Gopal S, Wood WA, Lee SJ, *et al.* Meeting the challenge of hematologic malignancies in sub-Saharan Africa. *Blood* 2012; 119: 5078–87.

Lehmann L, El-Haddad A, Barr RD. Global Approach to Hematologic Malignancies. *Hematol Oncol Clin North Am* 2016; 30: 417–32.

36 Tapela N, Nzayisenga I, Sethi R, *et al.* Treatment of Chronic Myeloid Leukemia in Rural Rwanda: Promising Early Outcomes. *J Glob Oncol* 2016; 2: 129–37.

37 López-Jorge CE, Gómez-Casares MT, Jiménez-Velasco A, *et al.* Comparative study of BCR-ABL1

quantification: Xpert assay, a feasible solution to standardization concerns. Ann Hematol 2012; 91: 1245–50.

38 1mg. http://www.1mg.com/ (accessed May 12, 2018).

39 1mg. http://www.1mg.com/ (accessed May 12, 2018).

40 World Health Organization. Report of the WHO Expert Committee on the Selection and Use of Essential Medicines. 2013. http://apps.who.int/iris/bitstream/10665/112729/1/WHO_TRS_985_eng.pdf (accessed Jan 30, 2018).

41 Beall RF, Attaran A. Patent-based Analysis of the World Health Organization's 2013 Model List of Essential Medicines. 2016.

42 U.S. Food and Drug Administration (FDA). DMF List 3Q2017.

https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/drugmasterfilesdmfs/def ault.htm (accessed Oct 24, 2017).

43 Storey S. Chronic myelogenous leukaemia market. *Nat Rev Drug Discov* 2009; published online May 8. DOI:10.1038/nrd2873.

44 Specialty 2016-17. Tamil Nadu Medical Services Corporation Limited. Available at:

http://www.tnmsc.com/tnmsc/new/user_pages/drugtender.php?drugcat=sdg2016.

45 UNITAID (2014) HIV Medicines Technology and Market Landscape. 1st Edition. Available at: http://unitaid.org/images/marketdynamics/publications/HIV-Meds-Landscape-March2014.pdf.

Garcia-Gonzalez P, Boultbee P, Epstein D. Novel Humanitarian Aid Program: The Glivec International Patient Assistance Progam—Lessons Learned from Providing Access to Breakthrough Targeted Oncology Treatment in Lowand Middle-Income Countries. *J Glob Oncol* 2015; 1: 37–45.

47 Mathews V. Generic imatinib: the real-deal or just a deal? *Leuk Lymphoma* 2014; 55: 2678–80.

48 Press release. Novartis and The Max Foundation transform pioneering cancer access program for people in lower-income countries. 2017. https://globenewswire.com/news-release/2017/09/22/1126124/0/en/Novartis-and-The-Max-Foundation-transform-pioneering-cancer-access-program-for-people-in-lower-income-countries.html (accessed Oct 23, 2017).

The Max Foundation. Our Global Reach. https://www.themaxfoundation.org/ (accessed Oct 25, 2017).
 The Max Foundation. Treatment Access Solution.

https://www.themaxfoundation.org/what/treatment/sprycel-dasatinib/ (accessed June 7, 2017).

51 Kuntegowdanahalli LC, Kanakasetty GB, Thanky AH, *et al.* Prognostic and predictive implications of Sokal, Euro and EUTOS scores in chronic myeloid leukaemia in the imatinib era—experience from a tertiary oncology centre in Southern India. *Ecancermedicalscience* 2016; 10. DOI:10.3332/ecancer.2016.679.

52 Gabble R, Kohler J. 'To patent or not to patent? the case of Novartis' cancer drug Glivec in India'. *Global Health* 2014; 10: 3.

Leoni V, Biondi A. Tyrosine kinase inhibitors in BCR-ABL positive acute lymphoblastic leukemia. *Haematologica* 2015; 100: 295–9.

4 Patented medicines that the WHO Expert Committee considered as having relevant clinical benefits but needing additional data: *Case study on novel medicines for type 2 diabetes*

4.1 Background

The WHO Expert Committee considers applications for inclusion in the EML on the basis of public health relevance, safety, efficacy and comparative cost-effectiveness. For some medicines, 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 such evidence confirms the benefits shown in earlier data. One such case can be seen in the SGLT2 inhibitors, a novel class of medicines for the treatment of type 2 diabetes.

The 2017 WHO Expert Committee considered a review of second-line treatments for type 2 diabetes and highlighted the SGLT2 inhibitors in view of their clinical benefit as second-line therapy and mortality-reducing effect in patients at high risk of cardiovascular events.¹ The Committee indicated that more clinical data were needed before this class of medicines could be reconsidered for addition to the list.

This case study will consider the current challenges with treatment of type 2 diabetes in low- and middle-income countries (LMICs) and the potential for the MPP to play a role in accelerating access to new treatments.

4.2 Burden of disease in low- and middle-income countries

Diabetes represents a major cause of illness, causing five million deaths worldwide in 2015.² The number of people living with diabetes is expected to increase from 415 million in 2015 to 642 million by 2040.² In countries included in past MPP licences, the prevalence is estimated to reach 200 million people in the next 15 years (see appendix).

Diabetes and deaths due to high blood glucose are now more common in LMICs than in high-income countries (Figure 1),³ and diabetes represents a greater disease burden globally (in terms of disease-adjusted life years) than tuberculosis or malaria.⁴

While it is estimated that about half of diabetes cases in LMICs are undiagnosed,⁵ its impact is significant. The prevalence of diabetes has quadrupled worldwide since 1980, and continues to rise particularly in LMICs (Figure 1).^{3,6,7} It is estimated that diabetes will cause more than US\$1.1 trillion economic losses in LMICs in 2030.⁸

48



Figure 1. Evolution in the proportion of the population living with diabetes, by country income category, 1980-2012. It is estimated that approximately 90% of cases are type 2 diabetes.

Figure adapted from the World Health Organization's Global report on diabetes, 2016.³ World Bank lending groups used for income categories.

The three main types of diabetes are termed type 1 diabetes (T1D), type 2 diabetes (T2D), and gestational diabetes (diabetes arising during pregnancy). T2D represents more than 90% of global diabetes and is the focus of this chapter.⁶ In all types of diabetes, the levels of blood sugar are raised, which, if uncontrolled over time, can lead to many serious and life-threatening complications.

In T2D, the body becomes resistant to insulin, secretion of insulin becomes impaired, or both.^{7,9} The development of T2D is closely associated with overweight and obesity, but there is evidence to suggest that Black, Hispanic, and Asian populations develop risk for diabetes at a lower body mass index than Caucasian populations do.^{6,7,10-13}

4.3 Complications of diabetes

The long-term clinical management of T1D and T2D is focused on preventing long-term complications, which include damage to the kidneys, eyes, nerves and cardiovascular system. Diabetes causes up to 55% of all end-stage kidney failure,³ and 7% of diabetics have damage to the retina severe enough to threaten sight.¹⁴

Cardiovascular complications are particularly important (and are the key focus of this case study). Diabetes increases the risk of cardiovascular disease,¹⁵ and cardiovascular disease is responsible for more than 70% of deaths in people with T2D.¹⁶

Compared to people living with diabetes in high-income countries, people living with diabetes in LMICs may have a higher risk of developing complications. For example,

high blood sugar is generally detected later in Africa, suggesting a higher risk of complications at the time of diagnosis.^{6,17} In addition, the onset of diabetes is generally earlier in Asians, leading to a higher long-term risk of complications.¹⁸

4.4 Outline of type 2 diabetes treatment, drug classes, diagnostic methods, and guidelines

4.4.1 Diagnosis and monitoring

T2D is diagnosed by detecting blood glucose levels that are above defined limits, using tests that measure blood glucose directly, or by measuring glycated haemoglobin (HbA1c) levels.

Blood glucose levels are ideally measured by laboratory analysis of a sample of venous blood, but point-of-care capillary blood glucose meters are more convenient and an acceptable alternative.¹⁹ However, these point-of-care devices come with their own challenges for access.²⁰ HbA1c testing is more convenient in that it does not require the individual to fast before the test. In addition, HbA1c better reflects long-term diabetes control, and point-of-care measurement devices are available. However, HbA1c measurement is more expensive than other modalities.^{19,21} A WHO survey found that blood glucose measurement was generally available in primary care settings in more than 90% of upper-middle-income countries and more than 80% of lower-middle-income countries.²²

T2D is ideally monitored through at least twice-yearly HbA1c measurements or, if not available, blood glucose measurements.¹⁹ In addition to monitoring glycaemic control, it is critical to incorporate complication surveillance, including regular monitoring of kidney function, eye and foot health, and cardiovascular risk factors.¹⁹

National background papers commissioned to inform this analysis revealed substantial variety in diagnosis and monitoring practices. In Cambodia, the majority of diabetes patients are diagnosed through random blood glucose measurement late in the disease process when complications are already severe. Similarly, in Pakistan,, the proportion of the population screened for diabetes is likely to be less than 5%, and diagnosis is normally preformed using random blood glucose measurement with a point-of-care device. In India, screening is done opportunistically, most often with a point-of-care blood glucose meter. However, in Peru blood glucose screening is part of standard cardiovascular screening done for patients more than 40 years of age.

The IDF estimates that 47% of diabetes is undiagnosed globally, with regional rates of undiagnosed diabetes ranging from a low of 30% in North America and the Caribbean to a high of 67% in Africa (Figure 5).²



Figure 5. Percentage of diabetes that is undiagnosed, by region.

Data from IDF Atlas, split by IDF region.²

4.4.2 Treatment of Type 2 Diabetes

While we focus on pharmaceutical interventions, it is important to note that interventions to promote a healthy lifestyle may be as or more important in controlling the type 2 diabetes epidemic at the population level. The WHO *Global action plan for the prevention and control of NCDs*, for example, proposes numerous policy options for member states aimed at promoting healthy eating and exercise.²³

US and European treatment guidelines advocate starting treatment with metformin as soon as T2D is diagnosed (unless contraindications are present), along with dietary changes and exercise.^{24,25}

Figure 6. Summary of pharmacological treatment guidelines for T2D (American Diabetes Association).



Current guidelines offer six classes of drugs as options for second-line treatment if and when metformin monotherapy fails (Figure 6). These six classes are sulphonylureas,

thiazolidinediones, SGLT2 inhibitors, DPP4 inhibitors, GLP1As, and insulin. Of these, the first two and insulin are therapies that have been in use for decades, while SGLT2 inhibitors, DPP4 inhibitors, and GLP1As have been brought to market in the last decade.

While in general guidelines leave the choice between the classes of second-line treatment down to patient-specific considerations,^{24,26} in patients with known cardiovascular disease, second-line agents that showed cardiovascular benefits in trials should be prioritized: the SGLT2 inhibitors canagliflozin and empagliflozin and the GLP1A liraglutide.²⁴ After second-line therapy with one of these drug classes fails, current guidelines recommend adding another of these classes as a third medication.^{24,26} US guidelines recommend that in patients who have markedly high blood glucose levels at diagnosis be treated with metformin and a second-line agent from the start.²⁴

GLP1As and insulins require subcutaneous injections and cold chain and may therefore be less suitable for large-scale use in resource-poor settings. Other challenges with insulin include the need for more regular blood glucose monitoring, a high risk of hypoglycemic events (in which blood sugar drops too low) and a weight-gain effect. Some GLP1As require injection only once weekly and have weight-reducing effects. The development of an oral GLP1A (currently in phase 3) may also contribute to making this class of antidiabetic medicines more suitable for scale-up in resource-limited settings in the future.²⁷

Thiazolidinediones have been the subject of multiple controversies surrounding potential dangers of increasing heart attacks and bladder cancer,^{28,29} although the evidence for these risks is controversial.^{7,30} Nevertheless, they confer an increased risk of bone fractures when used in women³¹ and increase the risk of developing heart failure.³² In high-income countries, thiazolidinediones are not commonly used,^{33–36} and national background papers commissioned to inform this study suggested that they are used little in LMICs, despite their low price. They are also not included in the WHO EML.

Sulphonylureas (SUs) are the only class of oral second-line medicine for type 2 diabetes currently included in the WHO EML. SUs can cause hypoglycemic events and weight gain and may contribute to beta-cell failure. However, in combination with metformin, SUs are the most widely used drug class in LMICs due to their low price and long period of clinical experience.⁷ Data on sulphonylureas' cardiovascular effects are equivocal with some studies showing increased, and some decreased, risk.^{37,38} A recent meta-analysis found that SUs conferred an increased risk of severe hypoglycemia compared to newer agents.³⁹ Aside from being unpleasant for patients and diminishing medication adherence,⁴⁰ episodes of severe hypoglycemia are linked to a significantly increased risk of cardiovascular events and mortality in patients with T2D.⁴¹

Based on the WHO Expert Committee's highlighting of SGLT2 inhibitors, we have focused on this class for the purposes of this feasibility analysis. SGLT2 inhibitors are a novel class of medicines used as second-line therapy for T2D. This class currently includes empagliflozin, canagliflozin and dapagliflozin.

In general, the benefits of SGLT2 inhibitors compared to other oral second-line T2D drug classes are their weight-reducing effect, and mortality-reducing effects for patients

with high cardiovascular risk profiles,⁴² notably described in the EMPA-REG trial for empagliflozin⁴³ and in the CANVAS trial for canagliflozin^H.⁴⁴ These benefits for patients with cardiovascular risks were highlighted by the WHO EML Committee, and are also reflected in the recently updated guidelines of the American Diabetes Association, which recommend that second-line therapy in patients with known cardiovascular disease should be treated with SGTL2 inhibitors or liraglutide (a GLP-1 agonist).²⁴

The SGLT2 inhibitors' main side-effects are associated with their mechanism of action (increased excretion of glucose in the urine), a higher rate of urogenital infections, and a risk of dehydration due to increased passage of urine (osmotic diuresis). ⁴²,⁴⁵ There are concerns that canagliflozin (but not empagliflozin or dapagliflozin) confers an increased risk of amputation, although the exact causal link is unclear.⁴⁶ Assessments by the UK National Institute for Health and Care Excellence (NICE) found that overall, SGLT2 inhibitors were superior to the SUs, thiazolidinediones, and DPP4 inhibitors in terms of quality-adjusted life years gained through treatment, although inferior to GLP1As (which are currently limited to injectable formulations).⁴⁷⁻⁴⁹

DPP4 inhibitors and GLP1As, with drugs in both classes under patent protection (see section 6), could also potentially be candidates for MPP licensing, and parts of the impact analysis described later in this chapter may also apply to those classes.

4.4.3 Availability and affordability of medicines for diabetes.

In a 2015 WHO survey, the standard first-line medicine for T2D, metformin, was reported to be generally available in the public sector in approximately 40% of low-income countries and more than 70% of lower-middle-income countries. The availability of SUs, the most commonly used second-line drug class, was lower. It was generally available in the public sector in only 15% of low-income countries and 67% of lower-middle-income countries.⁵⁰ A survey by the International Diabetes Federation found that T2D medicines were available for purchase in approximately half of low-income countries and 48–89% of middle-income countries (depending on the drug class), but that full government provision of T2D medicines was very low.⁵¹

A survey of 30 countries undertaken by Health Action International (HAI) assessed affordability of treatments and found that metformin and sulphonylureas were both available and affordable in 28% of cases in low-income countries and 23% of cases in middle-income countries^{1,52} Although the prices offered for metformin and sulphonylureas are in general low,⁵³ mark-ups within the supply chain and other supply chain problems contribute substantially to a lack of availability and affordability.^{6,52}

National background papers commissioned as part of this analysis identified a number of illustrative examples in relation to the new T2D medicines, namely the DPP4 inhibitors, SGLT2 inhibitors, and GLP1As:

^H A trial on the cardiovascular and renal effects of dapagliflozin (DECLARE-TIMI58) is ongoing,⁵⁶ and a real-world analysis that has found cardiovascular benefit for dapagliflozin is described below. ^I Medicines were considered available and affordable when they were available 80% of the time or more, and a monthly supply cost no more than the equivalent of one day's wages for the lowest-paid government worker or were available for free in the public sector.

- In Pakistan, SGLT2 inhibitors are not registered and not available and GLP1As are registered but expensive. An estimated 10% of patients eligible for triple therapy with DPP4 inhibitors receive it, and less than 5% of those eligible for triple therapy with GLP1As receive the treatment.
- In India, teneligliptin, a DPP4 inhibitor that was one of the earlier DPP4 inhibitors to go off patent, has become widely used, as other DPP4 inhibitors were less affordable. Teneligliptin is little-known outside of India and Japan. While SGLT2 inhibitors are becoming more popular due to their weight loss effect, DPP4 inhibitors entered the market earlier and are thus still more commonly prescribed and are more affordable. However, the significant majority of Indians pay for medicines out-of-pocket.⁵⁴ GLP1 agonists are used only in a few specialist centres due to their high price.
- In Cambodia, less than 1% of those that could benefit from SGLT2 inhibitors or DPP4 inhibitors receive them, and GLP1As are not available.
- In Tanzania, some SGLT2 inhibitors and DPP4 inhibitors were available, but only in the private sector, and at a high price.

In summary, while data are limited, available information suggests that newer secondline medicines are generally not widely available in LMICs (DPP4 inhibitors being an exception in a few countries). Second-line medicines may be accessible in the private market in some countries, but their prices can be prohibitive for many.

Table 1. Prices and registration status for medicines for type 2 diabetes, as reported in national background papers.

Medicine	Lowest available price per unit (USD)						
	Cambodia	Pakistan	Peru	Tanzania			
Metformin 500mg*	\$0.02†	\$0.01†	\$0.13 [†]	\$0.004†			
Metformin 850mg*	N	\$0.01†	\$0.02†	N			
Sulphonylureas							
Glibenclamide 5mg	\$0.02†	\$0.01†	\$0.02†	\$0.003†			
Gliclazide 30mg*	\$0.15†	\$0.03 ⁺	\$0.70**	N			
Pioglitazone 15mg	N	\$0.01 ⁺	\$1.45 [†]	N			
SGLT2 Inhibitors							
Canagliflozin 100mg	Ν	N \$2.05					
Empagliflozin 10mg	Limited donations by originator	Ν	\$2.38	Ν			
Dapagliflozin 5mg	Limited donations by originator	Ν	N \$1.81				
DPP4 Inhibitors							
Saxagliptin 2.5mg	Ν	N	\$1.63	N			
Sitagliptin 50mg	Ν	\$0.09 ⁺	\$2.68	\$0.80			
Linagliptin 5mg	N	N	\$1.40	Ν			
Vildagliptin 50mg	N	\$0.14†	\$0.77	\$0.69			
GLP1 agonists							
Liraglutide 18mg in 3mL vial	N	N	\$109.50	N			
*Standard-release formulation. **extended-release formulation. † – generic. N: – not registered or not available. Assumed 1 Pakistani rupee = 0.0095 US dollars, 1 Tanzanian shilling = 0.000445 US dollars. For Tanzania, maximum retail price for dispensaries and health centers used, as reported by the Medical Stores Department 55							

4.5 T2D medicines and the WHO Expert Committee.

In 2017, the WHO Expert Committee reviewed all second-line T2DM treatment classes for potential inclusion in the EML. 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 [more] data are needed to confirm this finding".¹ While the Committee did not add any new antidiabetic medicines to the EML, the favorable conclusion with regard to SGLT2 inhibitors in particular suggests the potential for inclusion in future EMLs if and when further data become available.

Further data on the cardiovascular effects of SGLT2 inhibitors in trials and real-world settings will become available over the next two to three years. Multiple large trials are underway to further elucidate the effect of SGLT2 inhibitor therapy on cardiovascular and renal disease. These trials are expected to be completed in the next three years, and include the DECLARE-TIMI58, Dapa-HF, and Dapa-CKD trials for dapagliflozin, the CREDENCE trial for canagliflozin, and the EMPEROR trials for empagliflozin.^{56–61} In addition, real-world data are beginning to emerge: the EASEL study, published in November 2017, retrospectively analysed a cohort of over 25,000 patients using SGLT2

inhibitors,⁶² finding reductions in the rate of cardiovascular events and all-cause mortality comparable to those seen in Phase III trials.

4.6 Inclusion in national essential medicines lists (NEMLs).

A 2014 study found that second-line medicines for T2D, with the exception of sulfonylureas, were included in NEMLs of only about a tenth or less of LMICs surveyed.⁶³ We did not find SGLT2 inhibitors included in any of the NEMLs we were able to review. Government representatives, in discussions with the MPP, identified high costs as one of the reasons these treatments may not have been included. One health technology assessment mentioned by one government consulted concluded that at currently available prices they were not considered cost-effective.

4.7 Patent landscape for SGLT2 inhibitors

The main product patents on SGLT2 inhibitors expire between 2023 and 2025 and have been filed or granted in many of the LMICs for which it was possible to collect information, including those with significant manufacturing capacity such as India, China, South Africa, Brazil, and Thailand. Several secondary patents may also delay further competition for these products in countries in which patents have been granted. Table 4 also includes patent data for the DPP4 inhibitors and the GLP1As showing a similar pattern. It should be noted, however, that for DPP4 inhibitors a number of generics have already entered the market in some countries (e.g. India, Pakistan) and there has been significant patent litigation around the DPP4 inhibitors sitagliptin, saxagliptin, and vildagliptin in India.⁶⁴⁻⁶⁶

Type 2 diabetes	Expected date of expiry	IPO	A.	N	PO	M	z	6	Ä	ΓIJ	1	[A	g		M
		AR	BR	CH	EA	5	Ē	Z	M	OA	ΗH	H	UK	ZA	N
	SGL2	inhi	bito	rs											
Canagliflozin															
Canagliflozin product	2024		F	F	G		G	G			G	G	G	G	G
Crystalline form of canagliflozin hemihydrate	2027		F	G	G	G	G	0			G	G	G	G	G
Method of treatment with SGLT inhibitor and a DPP4 inhibitor	2029		F	G		•	G	0	•		G	G			
Dapagliflozin															
Dapagliflozin product	2020/2023		F	G	G		G	G			G	G	G	G	G
Pharmaceutical formulation of dapagliflozin propanediol monohydrate	2027		F	G	G	·	G	0			G	G		G	
Crystalline dapagliflozin propanediol	2027		F	G	G		G	0			G	G	G	G	
Empagliflozin															
Empagliflozin product	2025		F	G	G		G	G			G	F	G	G	G
Crystalline form of empagliflozin	2026		F	G	G		G	0			G	G	G	G	G
Combination of empagliflozin and linagliptin.	2028		F	G	G		G	0	G		G	G	G	G	G
	DPP4	inhi	bito	rs	_										
Alogliptin															
Alogliptin product patent.	2024		F	F	G		G	0	G		G	F	G	G	G
Method of treating Type II diabetes using	2026	ŀ	F	G	G	ŀ	G	R/A	G	G	G	F	G	G	F
alogliptin and pioglitazone						_									
Linagliptin	2022		_	6	-		0	0			0		6		
Product	2023		F	G	G		G	G			G	F	G	G	G

Table 4. Patent status of type 2 diabetes drugs in select LMICs and expected expi	iry
dates.	

Method of treating type 2 diabetes with combination	2027		F	F	F	·	F	F	·	·	F	F	G	ŀ	·
Intermediate and process for preparation	2025		F	G	G*			F			G	F		G	F
Saxagliptin		<u> </u>		-	-			-	,	ľ.	-		ĺ.	<u> </u>	
Product or salt	2021		G	G			G	G			G	G		G	
Coated tablet	2025		F	G			G	G			G	G	G	G	G
Sitagliptin															
Sitagliptin product	2022		G	G	G		G	G	G		G	G	G	G	G
Sitagliptin phosphate and its hydrates	2024		F	G	G		G		F		G	G	G	F	G
GLP-1 agonists															
Dulaglutide															
Dulaglutide product	2024		G	G	G			G					G		
Exenatide															
Injectable composition	2021		F	G											
Method of lowering plasma glucagon with exendin	2020	·	G	G	·	·	·	·		·		·	·	ŀ	
Composition for sustained-release of exendin	2025		F	G	G			G							
Liraglutide															
Liraglutide Product	2017														
Liraglutide Formulation	2025		F	G				0							
Composition of Insulin Degludec	2028		F	F				G						G	
Albiglutide															
Albiglutide product specifically.	2025/2026		F	G			G	G	G		G			F	G
Method for enhancing GLP-1 activity	2027		F	F	G		F	F	G		G	F	G	G	F
Semaglutide (pipeline medicine)															
Product and composition	2026		F	G				G						G	

G – granted. F – filed. R – refused. *Patent terminated in AM, AZ, BY, KG, KZ, MD, TJ and TM. Blank – not filed. ? – no data. ARIPO – African Regional Intellectual Property Organization, EAPO – Eurasian Patent Organization, OAPI – Organization Africaine de la Propriete Intellectuelle.

4.8 Relevant market analysis

Currently, the originators of empagliflozin and dapagliflozin both have distribution agreements with generic companies in India.^{67,68} To our knowledge, no distribution agreements exist for canagliflozin to supply LMICs. At least two generics manufacturers disclose that they have SGLT2 inhibitor products in development on their websites.^{69,70}

The global market for T2D medicines is expected to double between 2015 and 2025,⁷¹ and market analysis has identified diabetes as the top therapeutic area in terms of expected growth in emerging markets in the medium term.⁷² Originator SGLT2 inhibitors are currently priced at US\$19-23 per month on the Indian private market.⁷³ This stands in contrast to median prices for the oral antidiabetic drugs currently on the WHO EML: gliclazide at \$1.33 per month and metformin at \$1.94 per month (Table 5).

Dapagliflozin and empagliflozin have significantly lower dosages (10mg and 10-25mg daily, respectively) compared to canagliflozin (100-300mg daily). This suggests that, if manufactured at scale, generic dapagliflozin and empagliflozin may be less expensive to produce.

8 1						
Description	Buyer median price per month					
Gliclazide*	\$1.33					
Metformin slow-release	\$7.13					
Metformin immediate-release using 500mg tablets*	\$1.94					
Metformin immediate-release using 850mg tablets	\$1.04					
Data from the International Medical Products Price Guide published by Management Sciences for Health. ⁵³						
Prices given for representative daily dose in US dollars Blank – no data *Included in the 2017 WHO Model						

Table 5. Current global monthly prices for type 2 diabetes medicines (USD).

Data from the International Medical Products Price Guide published by Management Sciences for Health.⁵³ Prices given for representative daily dose in US dollars. Blank – no data. *Included in the 2017 WHO Model List of Essential Medicines.

4.9 Estimated public health impact

Potential economic and public health impacts of hypothetical MPP licences on SGLT2 inhibitors were estimated using the methodology outlined in Chapter 2 and described in more detail in the appendix. While the estimates outlined in this section apply specifically to the SGLT2 inhibitors, some of the findings may also apply to other new classes of T2D medicines.

The number of patients in countries in past MPP licences that could potentially receive treatment with MPP-enabled generic SGLT2 inhibitors was calculated to reach 1.1–3.3 million, delivering 7–19 million patient-years of treatment, over the seven years leading up to expiry of patent protection.

Based on available data on the impact of SGLT2 inhibitors on mortality among people with high cardiovascular risk,^{43,44} we estimated that early access to SGLT2 inhibitors could potentially avert 31,000–126,000 major adverse cardiovascular events (MACE), depending on the scenario (Table 6). This assumed that SGLT2 inhibitors would be used preferentially in T2D patients with higher cardiovascular risk. These estimates are for canagliflozin and empagliflozin only, as there are as yet no published trial data on the impact of dapagliflozin on MACE and mortality (though trials are ongoing). It was also estimated that early access could confer a total of 68,000–275,000 additional QALYs, compared to sulphonylureas, for people living with T2D.

In addition to the potential for wider use as a second-line treatment, SGLT2 inhibitors could be of use as a third-line treatment. Most patients need a new line of treatment added every few years until they are eventually switched to insulin therapy.

These impacts in MACE events and QALYs were found with conservative assumptions regarding rates of diagnosis and market uptake in low, medium and high uptake scenarios (see appendix for details).

		SGLT2 inhibitors
Assumed duration of impact	7 years	
Number of patients treated with MPP-	Low	up to 1.1 million
enabled product	Med	up to 2.2 million
	High	up to 3.3 million
Total major adverse cardiovascular	Low	31,000-43,000
events averted	Med	59,000-83,000
	High	89,000-126,000
Total QALYs gained	Low	68,000-94,000
	Med	132,000-181,000
	High	199,000 – 226,000

Table 6. Estimated public health impact of MPP licensing of SGLT2 inhibitors.

QALY – quality-adjusted life year.

4.10 Estimated economic impact

The economic impact calculation estimated the theoretical savings possible through the purchase of more affordable quality-assured generic versions of the medicines instead of procurement of the same quantity of originator product. The assumed quantity purchased, per year, was based on projected disease burden and assumptions regarding rate of diagnosis, access to healthcare, and market penetration. Estimated savings were US\$0.9–3.1 billion, depending on the uptake scenario and medicine.

4.11 Conclusions

The global burden of T2D is considerable and prevalence in countries in past MPP licences is estimated to reach 200 million people in the next 15 years. In addition to representing a significant health burden, diabetes causes substantial economic losses in LMICs, and financial burden for patients. For example, in India, people with T2D and low incomes spend between a quarter and a third of their income on diabetes care.⁷⁴

Metformin is the recommended treatment for first-line treatment. The only oral secondline treatment currently included in the EML is associated with weight gain, a risk of severe hypoglycemic events,³⁹ and possibly an increased risk of stroke.³⁸ Newer types of antidiabetic medicines have potential benefits. Among these benefits, and depending on the class, are the weight-reducing effect, the lower rate of severe hypoglycaemia, and the cardiovascular mortality benefit demonstrated by SGLT2-inhibitors, which was highlighted by the WHO's Expert Committee.¹

From discussions with diabetes clinicians and national background papers commissioned by the MPP, it is clear that, with few exceptions, these medicines are generally not being used in LMICs because they are altogether unavailable or affordable only to few patients who pay for them out-of-pocket. Without licences, it is unlikely that generic competitors will be able to enter markets in many countries before patents expires. However, when generic market entry becomes possible, prices of SGLT2 inhibitors could become more affordable and this may facilitate their inclusion in national reimbursement schemes, at least for patients at high risk of cardiovascular events. Our modelling suggested that MPP licensing of SGLT2 inhibitors could extend access to 1.1–3.3 million people, delivering 7–19 million patient-years of treatment. Treatment at these levels would avert an estimated 31,000–126,000 cases of major adverse cardiovascular events, confer 68,000–275,000 additional QALYs. It should be noted, however, that these figures would be highly sensitive to the rate of market uptake for MPP-enabled generics and the number of countries covered by licences.

In terms of public health impact, we focussed on cardiovascular complications and QALYs. However, multiple other potential effects of affordable SGLT2 inhibitors were not captured in this analysis, including benefits gained through delaying or avoiding complications such as visual impairment, kidney disease, and diabetic foot disease. As insulin use brings a slew of challenges for patients and is associated with its own access challenges in poor countries,⁷⁵ delaying the need for insulin could be another important benefit of SGLT2Is. The economic impact estimated in this analysis derives only from savings on the cost of medicines and did not consider other benefits to the patient and indirect wider benefits to economies.

Aside from SGLT2Is, GLP1As and DPP4 inhibitors are gaining popularity in high-income country contexts and are under patent protection. DPP4 inhibitors appear to be available as generics in a few countries and some are currently the subject of patent disputes in India. GLP1As would likely become more attractive as an option for LMICs if and when the oral GLP1A in development is approved.

Optimal management of diabetes in the long term requires well-organised multidisciplinary care. Broader access to novel medicines would only be one piece in a package of strategies in LMICs. Interventions to promote healthier diets and exercise are likely to be particularly important and are considered cost-effective.⁷⁶

Multiple factors pose challenges for treating diabetes in LMICs. T2D is typically insidious in its development. Without screening, it can present at a stage where serious complications are already present. Diagnostic modalities, though significantly more affordable than in some other diseases, can nevertheless be unaffordable or unavailable for other reasons.²⁰ Without improvements in diagnosis and access to diabetes care more generally, any newly available diabetes medicine will have limited impact at the population level. Current treatment access even to the first-line therapy (metformin) remains low in certain countries and increased efforts are needed to diagnose people with T2D early and connect link them to effective treatment.

The WHO Expert Committee's assessment highlighted the clinical benefits of the SGLT2 inhibitors but recommended that additional data were needed to confirm their effects in decreasing cardiovascular mortality. These data are likely to become available soon, through a number of ongoing trials and observational data from real-world cohorts.^{56–62} If data were to confirm the findings, concerns around availability and affordability in LMICs would likely arise, and licensing through the MPP could contribute to making these medicines more widely available at affordable prices through a collaborative accesss mechanism.

4.12 References

1 WHO EML Expert Committee. Report of the WHO Expert Committee on Selection and Use of Essential Medicines. WHO Tech. Rep. Ser. 2017.

http://www.who.int/medicines/publications/essentialmedicines/EML_2017_EC21_Unedited_Full_Report.pdf?ua=1 (accessed Sept 14, 2017).

2 International Diabetes Federation. IDF diabetes atlas 8th edition. http://www.diabetesatlas.org/ (accessed Sept 10, 2017).

3 World Health Organization. Global report on diabetes. 2016.

http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf?ua=1 (accessed Oct 3, 2017). 4 Abajobir AA, Abate KH, Abbafati C, *et al.* Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1260–344.

5 Beagley J, Guariguata L, Weil C, Motala A. Global estimates of undiagnosed diabetes in adults. *Diabetes Res Clin ...* 2014. http://www.sciencedirect.com/science/article/pii/S0168822713003847.

6 Atun R, Davies JI, Gale EAM, *et al.* Diabetes in sub-Saharan Africa: from clinical care to health policy. *Lancet* Diabetes Endocrinol 2017; 5: 622–67.

7 DeFronzo RA, Ferrannini E, Groop L, *et al*. Type 2 diabetes mellitus. *Nat Rev Dis Prim* 2015; : 15019.

8 Bommer C, Sagalova V, Heesemann E, *et al.* Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030. *Diabetes Care* 2018; : dc171962.

9 Narayan KMV. Type 2 Diabetes: Why We Are Winning the Battle but Losing the War? 2015 Kelly West Award Lecture. *Diabetes Care* 2016; 39: 653–63.

10 Mbanya JCN, Motala AA, Sobngwi E, Assah FK, Enoru ST. Diabetes in sub-Saharan Africa. *Lancet (London, England)* 2010; 375: 2254–66.

11 Kengne AP, Echouffo-Tcheugui J-B, Sobngwi E, Mbanya J-C. New insights on diabetes mellitus and obesity in Africa-part 1: prevalence, pathogenesis and comorbidities. *Heart* 2013; 99: 979–83.

12 O'Hara EG, Nuche-Berenguer B, Kirui NK, *et al.* Diabetes in rural Africa: what can Kenya show us? *Lancet Diabetes Endocrinol* 2016; 4: 807–9.

13 Hu FB. Globalization of diabetes: The role of diet, lifestyle, and genes. *Diabetes Care* 2011; 34: 1249–57.

14 Yau JWY, Rogers SL, Kawasaki R, *et al.* Global Prevalence and Major Risk Factors of Diabetic Retinopathy. *Diabetes Care* 2012; 35: 556–64.

15 The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; 375: 2215–22.

16 Laakso M. Cardiovascular Disease in Type 2 Diabetes from Population to Man to Mechanisms. *Diabetes Care* 2010; : 442–9.

17 Levitt NS. Diabetes in Africa: epidemiology, management and healthcare challenges. *Heart* 2008; 94: 1376–82.

18 Ramachandran A, Wan Ma RC, Snehalatha C. Diabetes in Asia. *Lancet* 2010; 375: 408–18.

19 World Health Organization. Global Report on Diabetes. 2016.

20 Beran D, Yudkin JS. Looking beyond the issue of access to insulin: What is needed for proper diabetes care in resource poor settings. *Diabetes Res Clin Pract* 2010; 88: 217–21.

21 Gomez-Perez FJ, Aguilar-Salinas CA, Almeda-Valdes P, Cuevas-Ramos D, Lerman Garber I, Rull JA. HbA1c for the Diagnosis of Diabetes Mellitus in a Developing Country. A Position Article. *Arch Med Res* 2010; 41: 302–8.

22 World Health Organization. Global Report on Diabetes. Geneva, Switzerland: World Health Organization, 2016 DOI:ISBN 978 92 4 156525 7.

23 World Health Organization. Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2020. 2013. http://apps.who.int/iris/bitstream/10665/94384/1/9789241506236_eng.pdf (accessed March 4, 2018).

American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care* 2018; 41.

Inzucchi SE, Bergenstal RM, Buse JB, *et al.* Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2015; 58: 429–42.

26 International Diabetes Federation. IDF Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care. 2017. https://www.idf.org/component/attachments/attachments.html?id=1270&task=download (accessed Sept 28, 2017).

27 DiabetesInControl.com. New Oral GLP-1 Promising for Type 2 Diabetes. 2016.

http://www.diabetesincontrol.com/new-oral-semaglutide-promising-for-type-2-diabetes/ (accessed Oct 16, 2017). 28 Consoli A, Formoso G. Do thiazolidinediones still have a role in treatment of type 2 diabetes mellitus? *Diabetes Obes Metab* 2013; 15: 967–77.

²⁹ Tuccori M, Filion KB, Yin H, Yu OH, Platt RW, Azoulay L. Pioglitazone use and risk of bladder cancer: population based cohort study. *BMJ* 2016; : i1541.

30 Soccio RE, Chen ER, Lazar MA. Thiazolidinediones and the Promise of Insulin Sensitization in Type 2 Diabetes. *Cell Metab* 2014; 20: 573–91.

31 Zhu Z-N, Jiang Y-F, Ding T. Risk of fracture with thiazolidinediones: An updated meta-analysis of randomized clinical trials. *Bone* 2014; 68: 115–23.

Hernandez A V., Usmani A, Rajamanickam A, Moheet A. Thiazolidinediones and Risk of Heart Failure in Patients with or at High Risk of Type 2 Diabetes Mellitus. *Am J Cardiovasc Drugs* 2011; 11: 115–28.

33 Clemens KK, Shariff S, Liu K, *et al.* Trends in Antihyperglycemic Medication Prescriptions and Hypoglycemia in Older Adults: 2002-2013. *PLoS One* 2015; 10: e0137596.

Hampp C, Borders-Hemphill V, Moeny DG, Wysowski DK. Use of Antidiabetic Drugs in the U.S., 2003–2012. *Diabetes Care* 2014; 37: 1367–74.

35 Sharma M, Nazareth I, Petersen I. Trends in incidence , prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care : a retrospective cohort study. 2016. DOI:10.1136/bmjopen-2015-010210.

Christensen DH, Rungby J, Thomsen RW. Nationwide trends in glucose-lowering drug use, Denmark, 1999–2014. *Clin Epidemiol* 2016; Volume 8: 381–7.

37 Castilla-Guerra L, Fernandez-Moreno M del C, Leon-Jimenez D, Carmona-Nimo E. Antidiabetic drugs and stroke risk. Current evidence. *Eur J Intern Med* 2017; published online Sept. DOI:10.1016/j.ejim.2017.09.019.

Liu R, Wang H, Xu B, *et al.* Cerebrovascular Safety of Sulfonylureas: The Role of K ATP Channels in Neuroprotection and the Risk of Stroke in Patients With Type 2 Diabetes. *Diabetes* 2016; 65: 2795–809.

39 Methods and Applications Group for Indirect Treatment Comparisons. Application for the revision of second line treatments of type II diabetes. 2017.

http://www.who.int/selection_medicines/committees/expert/21/applications/s18_T2D_antidiabetics_rev.pdf?ua=1 (accessed Sept 14, 2017).

40 Polonsky W, Henry R. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence* 2016; Volume 10: 1299–307.

41 Hanefeld M, Frier BM, Pistrosch F. Hypoglycemia and Cardiovascular Risk: Is There a Major Link? *Diabetes Care* 2016; 39: S205–9.

42 Canadian Agency for Drugs and Technologies in Health. New Drugs for Type 2 Diabetes: Second-Line Therapy — Recommendations Report. 2017.

https://www.cadth.ca/sites/default/files/pdf/TR0012_T2DM_Final_Recommendations.pdf (accessed Sept 14, 2017). 43 Zinman B, Wanner C, Lachin JM, *et al.* Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; 373: 2117–28.

Neal B, Perkovic V, Mahaffey KW, *et al.* Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017; 377: 644–57.

Liu J, Li L, Li S, *et al.* Effects of SGLT2 inhibitors on UTIs and genital infections in type 2 diabetes mellitus: a systematic review and meta-analysis. *Sci Rep* 2017; 7: 2824.

46 Fadini GP, Avogaro A. SGTL2 inhibitors and amputations in the US FDA Adverse Event Reporting System. *Lancet Diabetes Endocrinol* 2017; 5: 680–1.

47 Shyangdan D, Jacob RP, Connock M, Johnston R, Cummins E, Waugh N. Empagliflozin for the treatment of type 2 diabetes: a single technology assessment. 2014.

https://www.nice.org.uk/guidance/ta336/documents/diabetes-type-2-empagliflozin-id641-evaluation-report2. 48 Copley V, Pickett K, Shepherd J, Loveman E, Jones J. Canagliflozin in combination therapy for treating type 2 diabetes. https://www.nice.org.uk/guidance/ta315/evidence.

49 Dapagliflozin STA: ERG comments on economics of manufacturer ACD submission.

https://www.nice.org.uk/guidance/ta288/documents/diabetes-type-2-dapagliflozin-evaluation-report2 (accessed June 9, 2017).

50 World Health Organization. Assessing national capacity for the prevention and control of noncommunicable diseases. 2016. http://apps.who.int/iris/bitstream/10665/246223/1/9789241565363-eng.pdf (accessed Oct 5, 2017).

51 International Diabetes Federation. Access to Medicines and Supplies for People with Diabetes: a global survey on patients' and health professionals' perspective. 2016.

52 Ewen M, Zweekhorst M, Regeer B, Laing R. Baseline assessment of WHO's target for both availability and affordability of essential medicines to treat non-communicable diseases. *PLoS One* 2017; 12: e0171284.

53 Management Sciences for Health. International Medical Products Price Guide. 2015.

http://mshpriceguide.org/ (accessed Oct 6, 2017).

54 van Doorslaer E, O'Donnell O, Rannan-Eliya RP, *et al.* Effect of payments for health care on poverty estimates in 11 countries in Asia: an analysis of household survey data. *Lancet* 2006; 368: 1357–64.

MSD price catalogue 2017-2018. http://www.msd.go.tz/index.php/msd-price-catalogue (accessed Jan 22, 2018).

56 ClinicalTrials.gov. Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58).

https://www.clinicaltrials.gov/ct2/show/NCT01730534?term=TIMI+declare&rank=1 (accessed Sept 10, 2017). 57 ClinicalTrials.gov. Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (Dapa-HF).

https://clinicaltrials.gov/ct2/show/NCT03036124?term=dapa-hf&rank=1 (accessed Jan 5, 2018).

58 ClinicalTrials.gov. A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (Dapa-CKD).

https://clinicaltrials.gov/ct2/show/NCT03036150?term=dapa-ckd&rank=1 (accessed Jan 5, 2018).

59 ClinicalTrials.gov. Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE).

https://clinicaltrials.gov/ct2/show/NCT02065791?term=credence&rank=2 (accessed Jan 5, 2018).

60 ClinicalTrials.gov. EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved).

https://clinicaltrials.gov/ct2/show/NCT03057951?term=emperor&rank=2 (accessed Jan 5, 2018).

61 ClinicalTrials.gov. EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced). https://clinicaltrials.gov/ct2/show/NCT03057977?term=emperor&rank=1 (accessed Jan 5, 2018).

62 Udell JA, Yuan Z, Rush T, Sicignano NM, Galitz M, Rosenthal N. Cardiovascular Outcomes and Risks After Initiation of a Sodium Glucose Co-Transporter 2 Inhibitor: Results From the EASEL Population-Based Cohort Study. *Circulation* 2017; : CIRCULATIONAHA.117.031227.

Bazargani YT, de Boer A, Leufkens HGM, Mantel-Teeuwisse AK. Selection of Essential Medicines for Diabetes
 in Low and Middle Income Countries: A Survey of 32 National Essential Medicines Lists. *PLoS One* 2014; 9: e106072.
 SpicyIP. Compulsory Licence Application filed over AstraZeneca's Saxagliptin.

https://spicyip.com/2015/07/compulsory-licence-application-filed-over-astrazenecas-saxagliptin.html (accessed Jan 28, 2018).

65 SpicyIP. Novartis sues Biocon over anti-diabetes drug vildagliptin: Bitter pill?

https://spicyip.com/2014/04/novartis-sues-biocon-over-anti-diabetes-drug-vildagliptin-bitter-pill-2.html (accessed Jan 28, 2018).

66 SpicyIP. Questionable Witnesses and Unquestionable Reasoning: Observations on Merck v. Glenmark. https://spicyip.com/2015/10/questionable-witnesses-and-unquestionable-reasoning-observations-on-merck-v-glenmark.html (accessed Jan 28, 2018).

67 Press release. Sun Pharma and AstraZeneca India enter partnership in Type 2 diabetes. 2016. https://www.astrazeneca.com/content/dam/az/Country-Sites/India/AstraZeneca_Press release 23 March 2016.pdf (accessed Sept 14, 2017).

68 Press release. Type 2 Diabetes: Boehringer Ingelheim India and Lupin Announce Strategic Co-marketing Agreement. 2016. http://www.lupin.com/boehringer-ingelheim-india-and-lupin-announce-strategic-co-marketing-agreement.php (accessed Sept 13, 2017).

69 Aurobindo. Product list. http://www.aurobindo.com/our-business-units/api/product-list (accessed March 21, 2018).

70 Lupin. Product catalogue. http://lupin.com/product-catalogue.php (accessed March 21, 2018).

71 Global Type 2 Diabetes Market Set to Almost Double to \$58.7 Billion. *Drug Dev Deliv* 2016; published online Aug. http://www.drug-dev.com/Main/Back-Issues/Global-Type-2-Diabetes-Market-Set-to-Almost-Double-1140.aspx (accessed Oct 9, 2017).

72 Strategy&. Pharma emerging markets 2.0: How emerging markets are driving the transformation of the pharmaceutical industry. 2013. https://www.strategyand.pwc.com/media/file/Strategyand_Pharma-Emerging-Markets-2.0.pdf (accessed 0ct 9, 2017).

73 1mg. http://www.1mg.com/ (accessed May 7, 2017).

Ramachandran A, Snehalatha C, Shetty AS, Nanditha A. Trends in prevalence of diabetes in Asian countries. *World J Diabetes* 2012; 3: 110.

75 Beran D, Ewen M, Laing R. Constraints and challenges in access to insulin: a global perspective. *Lancet Diabetes Endocrinol* 2016; 4: 275–85.

World Health Organization. Global action plan for the prevention and control of non-communicable diseases 2013–2020. 2013 http://apps.who.int/iris/bitstream/10665/94384/1/9789241506236_eng.pdf?ua=1.

5 Patented medicines that have clinical benefits but did not meet the EML Expert Review committee's comparative cost-effectiveness criterion: *Case study on novel oral anticoagulants*

5.1 Background

One of the criteria used by the WHO EML Expert Committee is that of comparative costeffectiveness.¹ Comparative cost-effectiveness is assessed when multiple treatments are available for the same indication. In some cases, the WHO Expert Committee has identified medicines as offering relevant public health benefits over the next best treatment but considered that they were not cost-effective compared to treatments that are already on the EML at current prices. For these medicines, availability at lower costs would change the cost-effectiveness balance, potentially tipping it in favour of addition to the EML in the future.

In this case study, we review a class of medicines termed novel oral anticoagulants (NOACs)^J, which are used in preventing blood clots. In 2015, the WHO Expert Committee reviewed an application for the inclusion of NOACs in the EML and considered 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".² While NOACs offer advantages over the next best therapy (warfarin), and are the guideline-recommended first-line treatment in the US and Europe, they are rarely used in LMICs. The advantages of using NOACs include that they do not require regular monitoring, have fewer drug and food interactions, and emerging evidence suggests that they are safer than warfarin.

In the context of the MPP's role in contributing to reducing the prices of medicines in LMICs, this case study seeks to understand the public health need for NOACs in LMICs, the potential for their introduction and what the public health and economic impact could be if the MPP secured licences on NOACs to facilitate affordable access in LMICs.

More generally, the case study seeks to understand whether there could be a role for the MPP in relation to medicines, such as the NOACs, assessed by the EML Expert Committee as offering clinical benefits but not meeting the comparative costeffectiveness criterion at current prices.

NOACs have two approved uses that are discussed in this analysis: they are used prophylactically in patients with a heart rhythm disturbance termed non-valvular atrial fibrillation (NVAF), to prevent the common complications of stroke and other blood clots (stroke and systemic embolism; SSE), and in patients who have had a blood clot in a vein (venous thromboembolism (VTE)) to treat the acute phase of the disease and to prevent another one from occurring. A third use, for the prevention of blood clots in patients that have had hip or knee surgery, is not discussed in this chapter.

^J Also referred to as non-vitamin K antagonist oral anticoagulants or direct-acting oral anticoagulants.

5.2 Burden of Disease in Low- and Middle-Income Countries

5.2.1 The global burden of atrial fibrillation, stroke, and systemic embolism.

Atrial fibrillation (AF) is the most common type of rhythm disturbance of the heart: in Europeans over the age of forty, the lifetime risk for developing AF is one in four.^{3,4} Acutely, AF is usually asymptomatic or causes only mild symptoms. However, chronically, it confers significant risk of blood clots in the brain, causing stroke, or elsewhere in the circulation, causing injury to tissue or organs.

By 2020, it is estimated that there will be 17.8 million people with non-valvular AF in LMICs (Figure 1).⁵ AF causes significant long-term morbidity and mortality, increasing, among other things, the risk of heart failure by a factor of two-three and stroke by a factor of four-five.³ In addition, stroke has been observed to be more closely associated with AF as a risk factor in LMICs than in high-income countries.^{6,7}

Figure 1. Projected prevalence of non-valvular atrial fibrillation by country income category (appendix for details)



Linear projections based on GBD data.⁵

Stroke is a significant cause of death in LMICs. The proportion of deaths that are caused by stroke is in decline in high-income countries, but increasing in most other world regions.⁸ Stroke is associated with a significantly higher fatality rate in LMICs, with, for example, 41% of stroke patients in Kolkata, India, and 57% of stroke patients in the Gambia, dying within 30 days.⁹⁻¹¹ In survivors, stroke is associated with significant disability, with 50% experiencing one-sided weakness, 46% experiencing cognitive deficits, 35% experiencing depression, 31% unable to walk without assistance, 22% incontinent of urine, 20% losing vision on one side, and 19% losing the ability to converse.¹²

This disability is particularly catastrophic in developing countries. In a recent WHO survey of 177 countries, the majority of low- and lower-middle-income countries reported that provisions for the treatment of acute stroke and stroke rehabilitation were available in less than a quarter of public healthcare facilities.¹³ It was reported that in China, 37% of households that suffered a stroke were pushed below the poverty line.¹⁴ Studies found that only 17% of stroke survivors in Nigeria returned to work,¹⁵ and 65% of survivors in Tanzania permanently retired.¹⁶

Anticoagulation therapy is a crucial tool for the prevention of stroke, reducing incidents in patients with risk factors by approximately 66%.¹⁷

Limited data are available on the annual risk of stroke conferred by AF outside of North America and Europe.¹⁸ In a recent analysis of 15,400 patients presenting to emergency departments in 47 countries with a primary or secondary diagnosis of AF, a stroke occurred within one year in 4% of all patients, 1% of patients in India, 3% in the Middle East, 7% in South-East Asia, and 8% in Africa.¹⁹

5.2.2 The global burden of venous thromboembolism.

Venous thromboembolism is an event in which a blood clot forms in veins. The main locations where this occurs are in the lower limbs, termed a deep venous thrombosis (DVT), and in the lungs, termed a pulmonary embolism (PE). Pulmonary embolisms carry a high risk of death, with about 40% of those affected dying within a year.²⁰ DVTs in most cases do not result in lasting damage to the leg. However, the clot in the leg can travel to the lungs, causing a PE, which poses a significant risk to life.

In addition to the high risk of death, VTE also causes substantial disability.²¹ For example, following DVT, 10-20% of patients develop severe post-thrombotic syndrome, which affects the ability to walk.²²

While there are limited data on the global epidemiology of VTE, the broadest available study estimated the annual incidence of VTE in low- and middle-income countries at 6 million, among hospital inpatients alone. Based on this study, we estimated the annual incidence of VTE in countries previously included in MPP licences to be 3.6 million (appendix).^{22,23} As projections for future trends in VTE burden are not, to our knowledge, available, we assume that this incidence would remain constant over the next few years for the purposes of estimating MPP impact. This is likely to be a conservative assumption as VTE burden is expected to rise.²² In addition, this captures only VTEs in hospital inpatients.

5.3 Outline of drugs, drug classes, diagnostic methods, and guidelines.

5.3.1 Diagnosis and management of AF.

AF is relatively simple to diagnose even in resource-limited settings. It can be detected by a clinician by simply taking a patient's pulse and is suspected if the pulse is found to be irregular. The diagnosis is confirmed by electrocardiography. After diagnosis, the clinician must balance the likely benefits and risks of starting anticoagulation as primary prevention of SSE. To decide on appropriate therapy, guidelines recommend the use of predictive scoring systems that are simple and can be calculated based on medical history alone. In general, no laboratory tests are required before initiating anticoagulation.

National background papers contributed by national experts in Botswana, Nigeria, South Africa and Peru^K to collect information for this study confirmed that such diagnostic techniques are regularly used in primary care and hospitals and the locally available infrastructure is sufficient for effective AF diagnosis. In India, electrocardiography was reported as often unavailable outside of large urban centres and, while clinical diagnosis is reliable, it has lower sensitivity and many cases are likely missed.

If the scoring system predicts moderate or high risk, a NOAC is the preferred first-line treatment for prevention of SSE in high-income countries. ²⁴ Treatment is continued life-long unless intolerable or dangerous side effects emerge, or a contraindication develops (for example, end-stage kidney disease).

Besides anticoagulation, other medications are commonly used in AF to control the heartrate and, in some cases, to control the heart rhythm.²⁴ These medicines, such as calcium channel blockers and beta blockers, are generic. A recent WHO survey with results from 177 countries found that calcium channel blockers were generally available in the public health sector in 31%, 64%, and 81% of low-income, lower-middle income and upper-middle income countries, and beta blockers in 38%, 67%, and 86% respectively.¹³

5.3.2 Diagnosis and management of VTE.

DVT is relatively easy to detect clinically, as it presents as acute one-sided leg swelling. PE is more challenging to diagnose as it commonly presents with vague symptoms. A risk-stratification scoring system (Wells score) is available to estimate the likelihood of DVT and PE before the need for laboratory tests or imaging. A relatively simple and affordable blood test exists to further narrow the probability.²⁵ The diagnosis of DVT is confirmed with an ultrasound of the leg, which can be performed at the bedside. Ultrasound devices are becoming more compact and affordable and availability in LMICs is increasing.²⁶ They are a priority diagnostic instrument for any hospital, as they are used in many different areas of medicine. National background papers contributed by national experts indicated that ultrasound is routinely used to confirm DVT in Botswana, Nigeria, Peru, South Africa, and large metropolitan centres in India.

In PE, the gold standard diagnostic test uses computer-assisted tomography (CT scan), which is often not available in resource-limited settings.²⁷ National background papers indicated that CT is routinely used in Botswana, Peru, and large metropolitan centres in India, while in Nigeria, South Africa, and rural India most cases are diagnosed on clinical grounds. However, a combination of the Wells score and the D-dimer blood test can correctly exclude more than 95% of non-cases.²⁸

^k National experts contributing background papers for this Chapter were: Professor Marc Blockman (University of Cape Town/Groote Schuur Hospital, South Africa), Dr Prabhakar Dorairaj (Public Health Foundation India, India), Dr German Malaga (Hospital Cayetano Heredia, Peru), and Dr Anthony Oyekunle (University of Botswana, Botswana).

In both DVT and PE, guidelines in high-income countries recommend therapy with a NOAC generally for 3-6 months^L, and treatment without admission to hospital, or discharge from hospital as early as possible unless the patient is considered high-risk.²⁹ Guidelines note that the use of some NOACs (apixaban or rivaroxaban) enables treatment without admission or early discharge, as they do not require pre-treatment with heparin, which is needed if using other NOACs or warfarin.²⁹

5.3.3 Warfarin.

Warfarin is the most commonly used medicine in the vitamin K antagonist (VKA) class and the most widely used anti-coagulant in LMICs, according to national background papers undertaken by national experts to inform this study. Aspirin and other antiplatelet medications are also widely used in LMICs to prevent stroke in patients with AF, despite being significantly inferior to anticoagulants (VKAs and NOACs) and exclusion from modern guidelines recommendations.^{24,29,30} Warfarin is taken orally in tablet form and has been in clinical use as an anticoagulant for decades.³¹ When using warfarin in acute VTE, heparin, which is an injectable blood thinner, must be added to the treatment for the first 10 days.³²

The pharmacokinetics of warfarin are highly variable between patients, and potentially affected by a number of factors such as other medicines and foods. ³³⁻³⁵ As warfarin has a narrow therapeutic window (i.e. a narrow range of blood concentration within which it is safe and effective), the dose of warfarin must be carefully tailored and monitored for each patient. If the levels of warfarin in the blood are too low, the drug will not be effective. If it is too high, there is a substantial risk of bleeding and death.

Warfarin therapy is monitored using a blood test known as an international normalized ratio (INR) test. Though numerous protocols exist for the initiation of warfarin therapy, in general, multiple INR tests must be done in the first few weeks of warfarin treatment, and thereafter every 1-3 months. Warfarin levels in the blood must be within a certain range at least 65% of the time in order for warfarin to have a significant benefit over other treatments.³⁶

Little data have been published on the availability of, and adherence to, INR monitoring in resource-limited settings. A study in South Africa found that four out of five patients on warfarin failed to maintain an average time in therapeutic range that meets the 65% target.³⁷ In Ethiopia, it was found that 70% of patients on warfarin therapy did not have effective and safe blood levels of warfarin.³⁸ Small studies undertaken in hospital inpatients in Nigeria and Botswana found that only 39% and 20% of INR tests were in therapeutic range, respectively.^{39,40}

Background papers undertaken to inform this analysis in Botswana, India, Nigeria, Peru and South Africa concluded that the convenience of NOACs, reduced need for testing, and reduced drug and food interactions presented major advantages in these countries. Prices of NOACs appeared to be the main barrier to treatments adoption. A national expert in South Africa noted that access to NOACs "in the public sector would be

^L Unless the patient has cancer, in which case LMWH is preferred over VKA or NOACs.

essential due to lack of INR clinics close to many of our patients, especially the rural areas" (appendix).

Expert analyses of stroke management in LMICs have suggested that in many settings the burden of INR monitoring makes physicians reluctant to prescribe warfarin to patients.⁴¹⁻⁴³ In addition, INR monitoring comprises a substantial part of the total cost to health systems and patients of using warfarin as an anticoagulant. For example, a study in Mexico found that the cost of warfarin itself represented less than 2% of the total costs of warfarin therapy.⁴⁴ Added to these costs is the inconvenience of having to travel to a health facility to undertake monitoring and any dose adjustments.⁴³

With all anticoagulants, the risk of bleeding increases, and in situations of acute bleeding the anti-coagulation may need to be 'reversed'. For example, if a patient taking warfarin suffers trauma, they are likely to bleed more than someone who is not taking warfarin, and their bleeding is likely to be harder to stop. Another scenario in which warfarin may need to be reversed is if emergency surgery is needed in order to minimise the likelihood of excessive blood loss during surgery. In the context of emergencies like these, warfarin can be reversed by using prothrombin complex concentrate (a product that is extracted from donated blood) and/or vitamin K.⁴⁵ However, full reversal can take more than 24 hours.⁴⁶

5.3.4 Novel oral anticoagulants.

Novel oral anticoagulants (NOACs) are also known as non-vitamin K antagonist oral anticoagulants. There are four medicines in this class: dabigatran, rivaroxaban, apixaban, and edoxaban. Though NOACs became available less than a decade ago, they are now the most commonly prescribed antithrombotic treatment in Europe and US, prescribed more often than warfarin by a wide margin, in line with guidelines.⁴⁷

NOACs is indicated for non-valvular AF and not for valvular AF, such as rheumatic heart disease – a syndrome in which an autoimmune reaction to a bacterial throat infection causes damage to the heart.^{18,48} Rheumatic heart disease causes a significant proportion of AF in LMICs.¹⁸ In such cases, warfarin can still be used. An ongoing clinical trial is investigating the use of rivaroxaban in patients with rheumatic heart disease.⁴⁹

The major advantages of NOACs compared to warfarin are:

- No requirement for monitoring due to significantly more consistent and predictable pharmacokinetics. This may be particularly important in LMICs where access to INR monitoring is may be limited.
- Significantly lesser restrictions on foods and interactions with other medications.
- A meta-analysis found that NOACs were safer and more effective in Asians and significantly reduced the risk of SSE and major bleeding compared to warfarin.⁵⁰
- For rivaroxaban and apixaban, no requirement for lead-in coadministration of an injectable anticoagulant (heparin) in acute VTE treatment.²⁹
- Some meta-analyses have found that NOACs have superior efficacy to warfarin.^{51,52}

Real-world evidence is also emerging to show that some NOACs may have additional benefits over VKAs than those described above. A study of 61,678 patients in a Danish database found a lower risk of bleeding and death with apixaban and dabigatran compared to warfarin.⁵³ A study of 15,390–32,350 patients in the US mirrored this, finding that apixaban and dabigatran conferred a lower risk of major bleeding than warfarin.⁵⁴ Meta-analyses of the main randomised controlled trials for NOACs found that NOACs as a class conferred significantly greater reduction in strokes, all-cause mortality, and intracranial haemorrhage compared to warfarin, but increased the risk of gastrointestinal bleeding.^{51,52} Other meta-analyses, however, have not confirmed the significance of these findings for individual NOACs.^{55,56}

The main disadvantage of NOACs compared to warfarin is the absence of reversal agents for all but one NOAC. While warfarin can be reversed relatively easily, the only NOAC for which a reversal agent exists is dabigatran, for which a biological reversal agent has been developed (idarucizumab). Reversal agents for the others are in development and may enter the market in 2018,⁵⁷ but in most cases of bleeding, discontinuation and supportive care are likely to be sufficient, in large part owing to the NOACs' short half-lives.^{58,59}

NOACs are in general well-tolerated. Among the side effects, dabigatran is associated with significantly increased rates of dyspepsia (indigestion), with 5–10% of patients experiencing this side effect.^{60,61} Use of dabigatran is also contraindicated in renal impairment. NOACs are contraindicated in pregnancy. Analyses from the US suggest that adherence to rivaroxaban and apixaban is higher than for dabigatran or warfarin^M.^{62–65}

5.3.5 Relative differences between individual NOACs

Significant differences in efficacy between the different NOACs are yet to be conclusively demonstrated.^{55,66,67} However, there appear to be important differences in safety and practical terms.

Recent meta-analyses have found that apixaban appears to be safer, in terms of bleeding risk, than warfarin and the other NOACs.^{66,67} Both apixaban and rivaroxaban are associated with a lower rate of side effects and discontinuations compared to dabigatran.^{62,63,68,69} In addition, in the treatment of VTE, dabigatran and edoxaban require at least five days (average 10 days)³⁵ of lead-in treatment with another injectable anticoagulant (heparin), requiring an extended hospital stay, while apixaban and rivaroxaban do not have this requirement.²⁹ This would add costs and inconvenience to the patient. A 10-day treatment course with heparin, needed as a lead-in overlapping treatment if using warfarin, dabigatran and edoxaban, costs US\$26–69 at lowest available prices (see appendix), plus the costs of longer hospitalisation.

In the US, recent data show that apixaban is now the most widely prescribed NOAC, with rivaroxaban as a close second. Dabigatran use is significantly lower, and edoxaban use is negligible.⁷⁰

 $^{^{\}rm M}$ Edoxaban had not become available within the timeframe of the cited studies.

In addition, generic apixaban, rivaroxaban, and edoxaban have the potential for being cheaper than dabigatran in view of their considerably lower dosage and active pharmaceutical ingredient (API) requirement (Table 1). The cost of API can be a central determinant of generic prices, accounting for 65–90% of the price of antiretroviral medicines in competitive generic markets, and medicines with lower dosage can often have a significant price advantage over generic medicines that have higher API cost requirements.⁷¹ Therefore, the significantly lower dosing of apixaban (10mg daily), rivaroxaban (20mg daily) and edoxaban (60mg daily) compared to dabigatran (300mg daily) may mean potential for lower generic prices in the long term.

Tuble 1. Dosuge and treatment protocorjor Nones.								
Medicine	NVAF treatment	VTE treatment						
Dabigatran	150mg twice daily	150mg twice daily following treatment with a parenteral anticoagulant for at least 5 days						
Rivaroxaban	20mg once daily	15mg twice daily for the first three weeks, then 20 mg once daily						
Apixaban	5mg twice daily	10mg twice daily for first week, then 5mg twice daily						
Edoxaban	60mg once daily	60mg once daily following treatment with a parenteral anticoagulant for at least 5 days						

Table 1. Dosage and treatment protocol for NOACs.

5.3.6 Availability and affordability of medicines for anticoagulation in AF and VTE.

Before the emergence of NOACs, the preferred first-line medicines used in primary prevention of stroke in AF were warfarin, aspirin, and clopidogrel, with warfarin being, , the most effective medicine out of the three by a significant margin..³⁰ Although there is a lack of published data on the availability and affordability of these medicines, background papers on Botswana, India, Nigeria, Peru, and South Africa undertaken to inform this feasibility study uniformly noted that warfarin and aspirin are widely available at low cost. A recent study of 45 hospitals and 100 private pharmacies in Uganda found 65% availability of warfarin.⁷²

An analysis of 15,400 patients presenting to emergency departments in 46 countries found that, among patients for whom oral anticoagulants were clinically indicated, the percentage of patients that were on oral anticoagulants was less than 40% in Southeast Asia and South America, less than 30% in India, less than 20% in Africa, and only slightly above 10% in China (Figure 2).⁷³ These figures may be overestimates of the proportion of people for whom oral anticoagulants are guideline-indicated that actually receives these medicines (appendix).^{30,55,73}



Figure 2. Percentage of clinically eligible patients receiving oral anticoaugulants, by country/region.

Data from Oldgren et al.⁷³ OACs – oral anticoagulants. Graph shows OAC use among patients who had non-rheumatic AF and a CHADS2 score of 2 or above.

There is little information available on NOAC registration, availability, or use in LMICs, although the costs of NOACs have been noted as prohibitive in sub-Saharan Africa,⁷⁴ India,⁷⁵ Asia,⁷⁶ and South America.⁷⁷ Background papers confirmed that NOACs have very limited availability, with lack of reimbursement by healthcare systems and price being some of the barriers to wider use. In South Africa, access to NOACs is essentially confined to a small proportion of patients in the private sector. In Botswana, "[m]ost experts point to the cost of the NOACs as being the major stumbling block to unfettered prescription and use of the NOACs." In Nigeria, the experts consulted identified two significant barriers, namely the comparatively higher cost of NOACs and the lack of awareness of NOACs locally and reluctance of most physicians to prescribe them. In India, physicians often do not prescribe warfarin because INR monitoring is poor, making the treatment ineffective. In Peru, NOACs are not in the formularies of the public healthcare system, and their availability is limited to the private system or a minimal proportion of patients from the public system that can support costs.

5.4 Anticoagulants and the EML Expert Committee.

NOACs were submitted for inclusion in the WHO EML in 2015. The Expert Committee's report noted the favourable overall clinical benefits of NOACs and some of the advantages over warfarin in terms of monitoring and dietary requirements. It also noted, however, that "the prices of novel oral anticoagulants (NOACs) in most countries are still several times higher than those of older oral anticoagulants such as warfarin, even taking into account of the cost of monitoring warfarin dose and response" and that "the large difference in costs between NOACs and warfarin was disproportional to the observed incremental benefit".
The EML committee therefore considered that "despite some cost-effectiveness analyses suggesting that the NOACs are "cost-effective", replacing warfarin with a NOAC will require significant investment of a country's healthcare funds, which might be better spent on alternative treatments for other diseases or healthcare facilities."

The failure in the comparative cost-effectiveness criterion appears to have been a significant factor in the Expert Committee's rejection, along with concerns about the lack of the NOACs' reversibility and of data supporting improved outcomes. In recent years, some evidence suggested that NOACs may be superior to warfarin in efficacy and safety, both in meta-analyses of the trials and in real-world settings (see *5.3.4. and 5.3.5.*, above). The concern over lack of reversal agents may also be overcome in the near future, through new reversal agents (adexanet alpha and ciraparantag) that are currently in late stae development. In addition, the concern about reversibility may not be as significant, as bleeding in patients taking NOACs can usually be managed without a reversal agent (see *5.3.4.*, above).

5.5 Inclusion in national essential medicines lists (NEMLs).

We found that NOACs were included in seven of the 25 LMIC NEMLs that we were able to review. One or more NOACs were included in the NEML of Romania, Russia, Serbia, Jamaica, and Panama, and the reimbursement list of Mexico. In the context of consultations with a select number of governments, high prices for NOACs were noted as one of the reasons for non-inclusion in national EMLs.

5.6 Patent landscape for NOACs.

The primary patent for dabigatran has expired in LMICs in 2018, although there are secondary patents until 2024/5 that may delay access to generics in countries where those patents are granted. The expiry dates for the primary patent of the other NOACs in LMICs are 2020, 2022, and 2023 for rivaroxaban, apixaban, and edoxaban respectively. There are also secondary patents on these medicines that may provide exclusivity until 2026-2031 and could potentially play a role in keeping generics out of the market. As shown in Table 2 below, there are patents filed or granted in key countries of generic manufacture such as India, China, and South Africa.

With the expiry of the primary patent on dabigatran, it is likely that generic manufacturers may be able to sell the treatment in countries without blocking secondary patents. Nevertheless, even if a generic version of dabigatran were to become available in some LMICs, there could be significant benefit in enabling generic entry of other NOACs, both from a clinical perspective as well as in terms of price. These were described above.

The need for access to more affordable generic medications was highlighted in the World Heart Federation's 2017 'Roadmap for Nonvalvular Atrial Fibrillation', which noted 'strategies for improving the affordability of [cardiovascular] medications', including '[promoting] the use of high-quality, safe, and efficacious generic medications by overcoming legal barriers relating to patents and licenses in LMICs'.⁴³

73

NOACS	Expected date of expiry	ARIPO	BRA	CHN	EAPO	GTM	NQI	QNI	MAR	OAPI	PHL	ТНА	UKR	ZA	NNM
Apixaban															
Apixaban product generically	2019		F	G	G			G			G			G	
Apixaban product	2022		G	G			G	G			G	F	G	G	G
Crystalline apixaban composition	2031		F	F				F						G	G
Dabigatran															
Dabigatran product and its etexilate	2018		G	G	G		G	G			G	G	G	G	G
Blister packaging for Dabigatran formulation	2025		G	R	G**		G	G			G		G	G	G
Polymorphic Modification II of Dabigatran Etexilate Mesylate	2024		F	G	G**		G	G			G	F		G	G
Rivaroxaban															
Rivaroxaban Product	2020		G	G		G	G	G	G		G	F	G	G	
Process of preparing tablets	2024		G	G	G*	G	G	G	G		G	G	G	G	•
Method of treating a thromboembolic disorder	2026		F	R			G	А	G		G		G	G	
Edoxaban															
Edoxaban and its salts	2022		G	G	.*		G	G			G	G		G	
For III crystals of edoxaban	2031		F	G				G							
Edoxaban tablet composition	2028		G	G	.*		G	G			G			G	G

Table 2. Patent status of NOACs in selected LMICs

* Patent granted in RU. ** Patent terminated in AM, AZ, KZ, KG, KZ, MD, TJ and TM. ARIPO – African Regional Intellectual Property Organization, EAPO – Eurasian Patent Organization, OAPI – Organization Africaine de la Propriete Intellectuelle

5.7 Estimated public health impact.

We estimated that MPP licence could facilitate 0.5–1.6 million additional patient-years of treatment for patients with NVAF, preventing 10,000–31,000 cases of SSE across countries in sub-Saharan Africa, low-income countries, and lower-middle-income countries. For the VTE indication, we estimated that 234,000–702,000 additional patients could be treated, preventing 94,000–281,000 VTE events (further details in the appendix).

Table 2. Estimated public health impact for NVAF/SEE

Assumed duration of MPP impact	4 years
Absolute risk reduction for SSE, per year	2%
Cumulative number of patient-years treated to prevent SSE in NVAF	522,000-1,566,000
Cumulative cases of SSE averted	10,000-31,000

Table 3. Estimated public health impact for VTE

Assumed duration of MPP impact	4 years
Absolute risk reduction for VTE per year	40%
Cumulative number of patients treated for VTE	234,000–702,000
Cumulative cases of VTE averted	94,000–281,000

5.8 Estimated economic impact.

We estimated the potential economic impact of MPP licensing of NOACs in terms of combined savings for SSE and VTE indications, taking into account the potential cost advantages of NOACs for which there are no generics currently on the market. The assumed quantity purchased, per year, was based on projected disease burden and conservative assumptions regarding rate of diagnosis, access to healthcare, and market penetration.

We estimated that MPP licensing could enable savings of US\$82–332 million, depending on the medicine licensed and market penetration. We were unable to find pricing information for edoxaban in India (used as the reference country in our analysis).

5.9 Relevant market analysis.

The global market for anticoagulants is expected to grow by 44% in value between 2016 and 2021.⁷⁸ Originator NOACs are currently priced US\$69–70 per month in the Indian private market. As noted earlier, several generic versions of dabigatran entered the Indian private market in early 2018, with the lowest priced version costing US\$26 per month.⁷⁹ Cost of production modelling, based on the current market price of raw materials, suggested that NOACs could be profitably manufactured at fairly low cost and could become available at lower prices as volumes increase and the market expands (see appendix). The lowest available price for warfarin is around \$1 per month, but there are significant healthcare system costs linked to its use, particularly in connection to the monitoring requirements.⁸⁰ Over time, it is expected that total costs of using generic NOACs would be lower than warfarin therapy.

5.10 Conclusions.

There is a substantial burden of atrial fibrillation and venous thromboembolism in LMICs. It is estimated that there will be 17.9 million people NVAF in LMICs by 2020, each with a 1-8% yearly risk of stroke.¹⁹ In addition, there are at least 6 million cases of VTE annually in LMICs.²¹ Compounding this significant burden, LMICs are faced with multiple challenges in treating and preventing stroke and VTE, such as limited facilities to treat and rehabilitate those with stroke.¹³

The recommended first-line therapy for these indications in high-income countries is with NOACs,^{3,29,60} owing to disadvantages of the next best therapy – warfarin – such as the need for monitoring, and food and drug interactions. In resource-poor settings, attending regular clinic appointments for warfarin monitoring can be challenging for patients and health systems, and physicians in resource-poor settings are often reluctant to prescribe warfarin to patients for this reason. NOACs, however, are unavailable to most patients in LMICs. The recent entry of generic versions of dabigatran to the Indian market can be expected to lead to increased access. ⁸¹

There may be certain economic and clinical advantages for using other NOACs instead of dabigatran. These include possible superior safety of apixaban, the advantage of not needing to coadminister an injectable anticoagulant in the treatment of VTE when using apixaban or rivaroxaban, and the likely lower generic prices that could be achieved for other NOACs, owing to their significantly lower dosages compared to dabigatran.

We estimated that MPP licensing could facilitate up to 1.9 million patient-years of treatment for both NVAF and VTE. Licensing could also lead to savings for developing county health systems. The economic impact was estimated only for savings in direct expenditure on medicines; other aspects potentially conferring economic gains such as reduction in disability were not included. Similarly, we did not include potential savings from averting additional costs associated with warfarin use, such as monitoring and time spent in hospital.

In view of the limited current use of NOACs in many LMICs and the limited commercial originator markets in such countries, there may be opportunities for win-win agreements that could benefit all stakeholders, through appropriate royalties.

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 to more people in LMICs, where otherwise their use remains limited. Given the lower monitoring requirements of NOACs over alternatives, this could enable more people to access anticoagulation therapy, therefore reducing the risk of strokes and other sometimes fatal complications in LMICs.

5.11 References.

1 World Health Organization. Revised procedure for updating WHO's Model List of Essential Drugs. 2001. http://apps.who.int/medicinedocs/documents/s22165en/s22165en.pdf (accessed March 8, 2018).

2 World Health Organization. The Selection and Use of Essential Medicines: Report of the WHO Expert Committee. 2015. http://apps.who.int/iris/bitstream/10665/189763/1/9789241209946_eng.pdf?ua=1 (accessed Oct 17, 2017).

3 Lip GYH, Fauchier L, Freedman SB, *et al.* Atrial fibrillation. *Nat Rev Dis Prim* 2016; 2: 16016.

4 Lloyd-Jones D, Wang T, Leip E, Al. E. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004; 110: 1042–6.

5 Vos T, Abajobir AA, Abate KH, *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1211–59.

6 Nguyen TN, Hilmer SN, Cumming RG. Review of epidemiology and management of atrial fibrillation in developing countries. 2013; 167: 2412–20.

7 Bista D, Chalmers L, Bereznicki L, Peterson G. Potential use of NOACs in developing countries: Pros and cons. *Eur J Clin Pharmacol* 2014; 70: 817–28.

8 Institute for Health Metrics and Evaluation. GBD Results Tool. http://ghdx.healthdata.org/gbd-results-tool (accessed April 13, 2017).

9 Lloyd-Sherlock P. Stroke in Developing Countries: Epidemiology, Impact and Policy Implications. *Dev Policy Rev* 2010; 28: 693–709.

Pandian JD, Srikanth V, Read SJ, Thrift AG. Poverty and stroke in India: a time to act. *Stroke* 2007; 38: 3063–9.

11 Walker RW, Rolfe M, Kelly PJ, George MO, James OFW. Mortality and recovery after stroke in The Gambia. *Stroke* 2003; 34: 1604–9.

12 Kelly-Hayes M, Beiser A, Kase CS, Scaramucci A, D'Agostino RB, Wolf PA. The influence of gender and age on disability following ischemic stroke: the Framingham study. *J Stroke Cerebrovasc Dis* 2003; 12: 119–26.

13 World Health Organization. Assessing national capacity for the prevention and control of noncommunicable diseases. 2016. http://apps.who.int/iris/bitstream/10665/246223/1/9789241565363-eng.pdf (accessed Oct 5, 2017).

14 Heeley E, Anderson CS, Huang Y, *et al.* Role of health insurance in averting economic hardship in families after acute stroke in China. *Stroke* 2009; 40: 2149–56.

15 Akinpelu AO, Gbiri CA. Quality of life of stroke survivors and apparently healthy individuals in southwestern Nigeria. *Physiother Theory Pract* 2009; 25: 14–20.

16 Howitt SC, Jones MP, Jusabani A, *et al.* A cross-sectional study of quality of life in incident stroke survivors in rural northern Tanzania. 2011; : 1422–30.

17 You JJ, Singer DE, Howard P, Lane DA, Eckman MH. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST J* 2012; 141: e531S-e575S.

18 Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol* 2014; 11: 639–
54.

Healey JS, Oldgren J, Ezekowitz M, *et al.* Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *Lancet* 2016; 388: 1161–9.

20 Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton III LJ. Predictors of Survival After Deep Vein Thrombosis and Pulmonary Embolism: A Population-Based, Cohort Study. *Arch Intern Med* 1999; 159: 445–53.

²¹ Jha AK, Larizgoitia I, Audera-Lopez C, Prasopa-Plaizier N, Waters H, Bates DW. The global burden of unsafe medical care: analytic modelling of observational studies. *BMJ Qual Saf* 2013; 22: 809–15.

22 Raskob GE, Angchaisuksiri P, Blanco AN, *et al.* Thrombosis: A major contributor to global disease burden. *Thromb Res* 2014; 134: 931–8.

Jha a K, Larizgoitia I, Audera-Lopez C, Prasopa-Plaizier N, Waters H, Bates DW. The global burden of unsafe medical care: analytic modelling of observational studies. *BMJ Qual Saf* 2013; 22: 809–15.

24 Kirchhof P, Benussi S, Kotecha D, *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; 37: 2893–962.

25 Badhal SS, Sharma S, Saraya A, Mukhopadhyay AK. Prognostic significance of D-dimer, natural anticoagulants and routine coagulation parameters in acute pancreatitis. *Trop Gastroenterol*; 33: 193–9.

26 Shah S, Bellows BA, Adedipe AA, Totten JE, Backlund BH, Sajed D. Perceived barriers in the use of ultrasound in developing countries. *Crit Ultrasound J* 2015; 7: 11.

World Health Organization. Global forum to improve developing country access to medical devices. http://www.who.int/mediacentre/news/notes/2010/medical_devices_20100908/en/ (accessed Oct 14, 2017).

28 Geersing G-J, Erkens PMG, Lucassen WAM, *et al.* Safe exclusion of pulmonary embolism using the Wells rule and qualitative D-dimer testing in primary care: prospective cohort study. *BMJ* 2012; 345: e6564–e6564.

Kearon C, Akl EA, Ornelas J, *et al.* Antithrombotic Therapy for VTE Disease. *Chest* 2016; 149: 315–52.
 Hart RC, Pearce LA, Aguilar MI. Meta-analysis : Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation. *Ann Intern Med* 2007; 146: 857–67.

Hellemons BSP, Langenberg M, Lodder J, *et al.* Primary prevention of arterial thromboembolism in nonrheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin. *Bmj* 1999; 319: 958–64.

32 Electronic Medicines Compendium. Clexane Forte Syringes.

http://www.medicines.org.uk/emc/medicine/10054#POSOLOGY (accessed Oct 10, 2017).

33 Sweetman S. Martindale: The Complete Drug Reference, 36th edn. Pharmaceutical Press, 2009.

National Institutes of Health Clinical Center Drug-Nutrient Interaction Task Force. Important Drug and Food
 Information. https://www.cc.nih.gov/ccc/patient_education/drug_nutrient/coumadin1.pdf (accessed Jan 9, 2018).
 D'Souza R, Ostro J, Shah PS, *et al.* Anticoagulation for pregnant women with mechanical heart valves: a
 systematic review and meta-analysis. *Eur Heart J* 2017; 38: 1509–16.

Connolly SJ, Pogue J, Eikelboom J, *et al.* Benefit of Oral Anticoagulant Over Antiplatelet Therapy in Atrial Fibrillation Depends on the Quality of International Normalized Ratio Control Achieved by Centers and Countries as Measured by Time in Therapeutic Range. *Circulation* 2008; 118: 2029–37.

Ebrahim I. A Retrospective Cohort Review of Time in the Therapeutic Range (TTR) for Patients on Warfarin at a Dedicated Tertiary and District Level INR Clinic in South Africa. *Pharmacoepidemiol Drug Saf* 2017; 26: 3–636.
Fenta TG, Assefa T, Alemayehu B. Quality of anticoagulation management with warfarin among outpatients in a tertiary hospital in Addis Ababa, Ethiopia: a retrospective cross-sectional study. *BMC Health Serv Res* 2017; 17: 389.

39 Mwita JC. Quality of Anticoagulation with Warfarin at a Tertiary Hospital in Botswana. In: Third Training Workshop and Symposium MURIA Group. Windhoek, Namibia, 2017.

40 Anakwue RC, Ocheni S, Madu AJ. Utilization of oral anticoagulation in a teaching hospital in Nigeria. *Ann Med Health Sci Res* 2014; 4: 286.

41 Pandian JD, William AG, Kate MP, *et al.* Strategies to Improve Stroke Care Services in Low- and Middle-Income Countries: A Systematic Review. *Neuroepidemiology* 2017; 49: 45–61.

Bryer A. New antithrombotic drugs : a revolution in stroke management. *Cardiovasc J Afr* 2012; 23: 61–2.
 Murphy A, Banerjee A, Breithardt G, *et al.* The Word Heart Federation Roadmap for Nonvalvular Atrial Fibrillation. *Glob Heart* 2017. DOI:10.1016/j.gheart.2017.01.015.

⁴⁴Briere JB, Bowrin K, Wood R, Holbrook T, Roberts J. The cost of warfarin treatment for stroke prevention in patients with non-valvular atrial fibrillation in Mexico from a collective perspective. *J Med Econ* 2017; 20: 266–72.

Keeling D, Baglin T, Tait C, *et al.* Guidelines on oral anticoagulation with warfarin - fourth edition. *Br J Haematol* 2011; 154: 311–24.

Garcia DA, Crowther MA. Reversal of Warfarin: Case-Based Practice Recommendations. *Circulation* 2012; 125: 2944–7.

47 Huisman M V, Rothman KJ, Paquette M, *et al.* The Changing Landscape for Stroke Prevention in AF: Findings From the GLORIA-AF Registry Phase 2. *J Am Coll Cardiol* 2017; 69: 777–85.

48 Seckeler MD, Hoke TR. The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. *Clin Epidemiol* 2011; 3: 67–84.

49 Population Health Research Institute. InvestIgation of rheumatic AF treatment using vitamin K antagonists,
 rivaroxaban or aspirin studies. 2018. http://www.phri.ca/research-study/invictus/ (accessed March 20, 2018).
 50 Wang K-L, Lip GYH, Lin S-J, Chiang C-E. Non–Vitamin K Antagonist Oral Anticoagulants for Stroke

Prevention in Asian Patients With Nonvalvular Atrial Fibrillation. Stroke 2015; 46: 2555-61.

Ruff CT, Giugliano RP, Braunwald E, *et al.* Comparison of the efficacy and safety of new oral anticoagulants
 with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014; 383: 955–62.
 Hicks T, Stewart F, Eisinga A. NOACs versus warfarin for stroke prevention in patients with AF: a systematic

review and meta-analysis. *Open Hear* 2016; 3: e000279.

53 Larsen TB, Skjøth F, Nielsen PB, Kjældgaard JN, Lip GYH. Comparative effectiveness and safety of nonvitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ* 2016; : i3189.

54 Yao X, Abraham NS, Sangaralingham LR, *et al.* Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation. *J Am Heart Assoc* 2016; 5: e003725.

55 Tereshchenko LG, Henrikson CA, Cigarroa J, Steinberg JS. Comparative Effectiveness of Interventions for Stroke Prevention in Atrial Fibrillation: A Network Meta-Analysis. *J Am Heart Assoc* 2016; 5: e003206.

56 Wells GA, Kelly S, Elliott J, *et al.* Direct oral anticoagulants for the treatment of venous thromboembolic events: a systematic review and network meta-analysis. 2016.

https://www.ottawaheart.ca/sites/default/files/uploads/documents/Researchers/gwells-doac-vte-scientific-report-2015-2016.pdf (accessed Jan 20, 2018).

57 BioPharma Dive. Take two: Portola's reversal agent secures FDA review. 2017.

http://www.biopharmadive.com/news/portola-andexxa-bla-approval-review/449368/ (accessed Oct 19, 2017).
Burnett A, Siegal D, Crowther M. Specific antidotes for bleeding associated with direct oral anticoagulants. *BMJ* 2017; : j2216.

59 Proietti M, Lip GY. Antidotes to non-vitamin K oral anticoagulants: necessary or not? *Expert Opin Pharmacother* 2015; 16: 1573–6.

60 Heidbuchel H, Verhamme P, Alings M, *et al.* Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2015; 17: 1467–507.

61 Connolly SJ, Ezekowitz MD, Yusuf S, *et al.* Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2009; 361: 1139–51.

62 Pan X, Kachroo S, Liu X, Kawabata H, Phatak H. Real world discontinuation among early users of apixaban, dabigatran, rivaroxaban or warfarin among atrial fibrillation patients newly initiated on anticoagulation therapy: tell of first 200 days. In: ESC Congress. 2014.

63 Katz A. Which NOAC for Which Patient? In: ICI Meeting. 2015. http://2015.icimeeting.com/wp-content/uploads/2016/01/1446-Katz-Hall-J-tue.pdf.

Brown JD, Shewale AR, Talbert JC. Adherence to Rivaroxaban, Dabigatran, and Apixaban for Stroke
 Prevention in Incident, Treatment-Naïve Nonvalvular Atrial Fibrillation. *J Manag Care Spec Pharm* 2016; 22: 1319–29.
 Borne RT, O'Donnell C, Turakhia MP, *et al.* Adherence and outcomes to direct oral anticoagulants among patients with atrial fibrillation: findings from the veterans health administration. *BMC Cardiovasc Disord* 2017; 17: 236.

66 Proietti M, Romanazzi I, Romiti GF, Farcomeni A, Lip GYH. Real-World Use of Apixaban for Stroke Prevention in Atrial Fibrillation. *Stroke* 2018; 49: 98–106.

67 Cohen AT, Hamilton M, Mitchell SA, *et al.* Comparison of the novel oral anticoagulants apixaban, dabigatran, edoxaban, and rivaroxaban in the initial and long-term treatment and prevention of venous thromboembolism: Systematic review and network meta-analysis. *PLoS One* 2015; 10: e0144856.

Monaco L, Biagi C, Conti V, *et al.* Safety profile of the direct oral anticoagulants: an analysis of the WHO database of adverse drug reactions. *Br J Clin Pharmacol* 2017; 83: 1532–43.

69 Vedovati MC, Verdecchia P, Giustozzi M, *et al.* Permanent discontinuation of non vitamin K oral anticoagulants in real life patients with non-valvular atrial fibrillation. *Int J Cardiol* 2017; 236: 363–9.

70 Patrick M. Bristol-Myers Squibb's Profitability: Can Eliquis Do the Job in 2017? Mark. Realis. 2017. https://marketrealist.com/2017/01/oral-anticoagulant-eliquis-may-boost-bristol-myers-squibbs-profitability-2017/ (accessed March 20, 2018).

van de Ven N, Fortunak J, Simmons B, *et al.* Minimum target prices for production of direct-acting antivirals and associated diagnostics to combat hepatitis C virus. *Hepatology* 2015; 61: 1174–82.

72 Kibirige D, Atuhe D, Kampiire L, *et al.* Access to medicines and diagnostic tests integral in the management of diabetes mellitus and cardiovascular diseases in Uganda: insights from the ACCODAD study. *Int J Equity Health* 2017; 16: 154.

Oldgren J, Healey JS, Ezekowitz M, *et al.* Variations in Cause and Management of Atrial Fibrillation in a Prospective Registry of 15 400 Emergency Department Patients in 46 Countries: The RE-LY Atrial Fibrillation Registry. *Circulation* 2014; 129: 1568–76.

54 Stambler B, Ngunga L. Atrial fibrillation in Sub-Saharan Africa: epidemiology, unmet needs, and treatment options. *Int J Gen Med* 2015; : 231.

Dalal JJ, Dhall A, Bhave A. Current perspective on use of NOAC in clinical practice in India. *J Assoc Physicians India* 2016; 64: 56–65.

76 Lee LH. DOACs – advances and limitations in real world. *Thromb J* 2016; 14: 17.

77 Massaro AR, Lip GYH. Stroke Prevention in Atrial Fibrillation: Focus on Latin America. *Arq Bras Cardiol* 2016. DOI:10.5935/abc.20160116.

78 BCC Research. Antithrombotic/Anticoagulant Drugs: Technologies and Global Markets. 2016. https://www.bccresearch.com/market-research/pharmaceuticals/antithrombotic-anticoagulant-drugs-markets-

report-phm119b.html (accessed Oct 18, 2017).

791mg. http://www.1mg.com/ (accessed May 7, 2017).

80 Management Sciences for Health. International Medical Products Price Guide.

http://mshpriceguide.org/en/home/ (accessed Oct 16, 2017).

81 Labour Law Reporter. Minimum Wages – Delhi. 2017. https://www.labourlawreporter.com/min-wages-delhi/ (accessed March 18, 2018).

82 Mozaffarian D, Benjamin EJ, Go AS, *et al.* Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation* 2016; 133: e38-60.

6 Patented medicines for which the WHO Expert Committee recommended a therapeutic area review by a separate working group: *Case studies on lung cancer, prostate cancer, multiple myeloma and breast cancer*

6.1 Background

In this section, we consider cancer medicines submitted to the WHO Expert Committee for inclusion in the EML in 2017 and for which 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."¹ The report of the Committee indicates that "the working group should support WHO in establishing some guiding principles in relation to the potential inclusion of second line treatments, clarifying what constitutes a clinically relevant therapeutic effect that is sufficient to grant to a cancer medicine the status of essential medicine."¹ These medicines will, therefore, be reconsidered in 2019:

- Erlotinib, afatinib, gefitinib, and crizotinib for lung cancer
- Enzalutamide and abiraterone for prostate cancer, and
- Trastuzumab emtansine (T-DM1), pertuzumab, and lapatinib for breast cancer.

Trastuzumab, which was added to the WHO EML in 2015,² is also included in the analysis of breast cancer medicines for completeness.

Figure 1. Mortality from selected cancers in low income, lower-middle income countries, and Sub-Saharan Africa.



NHL – non-Hodgkin lymphoma. Data from the GLOBOCAN 2012 online analysis tool.³

In addition, the WHO Expert Committee indicated that "the Cancer Working group should consider other important oncology conditions for review that were not part of the previous update, including (but not limited to) multiple myeloma, renal and brain cancers".¹ In that context, we also considered one medicine for multiple myeloma, lenalidomide, as a possible candidate that was highlighted by a number of stakeholders during our consultations.

Figure 1 provides an overview of the mortality projections of different cancers in countries included in past MPP licences for reference throughout this chapter.

6.2 Lung cancer

In this section, we briefly outline the potential for facilitating broader access to tyrosine kinase inhibitors (TKIs) erlotinib, afatinib, crizotinib, and gefitinib, in treating lung cancer in LMICs. All four drugs are approved for the treatment of advanced non-small cell lung cancer (NSCLC) that displays specific mutations – the EGFR mutation for erlotinib, afatinib, and gefitinib, and the ALK or ROS1 mutations for crizotinib. We refer to these medicines collectively as lung cancer TKIs.

6.2.1 Epidemiology of lung cancer in LMICs

In developing countries, lung cancer is the leading oncological cause of death in men, and the second leading cause after breast cancer in women.⁴ There were 1.2 million new cases of lung cancer in LMICs in 2015.⁵ The mortality for lung cancer is projected to rise more rapidly than other cancer types (Figure 1), with a 57% increase in mortality projected between 2015 and 2030.⁶

Erlotinib, afatinib, and gefitinib are approved for first-line use in advanced NSCLC that displays a mutated EGFR gene, and are considered interchangeable for this indication in US and European guidelines.^{7,8} NSCLC represents 85-90% of lung cancer cases,⁹ and about 15% to a third of NSCLC cases display a mutated EGFR gene. Studies have suggested that the rate of EGFR mutations is higher in Asians.^{8,10-14} Erlotinib and afatinib each have other indications, in which they are not interchangeable: erlotinib is additionally indicated for use in metastatic pancreatic cancer without testing for EGFR positivity, and afatinib is additionally indicated for use in advanced squamous-cell lung cancer after progression on chemotherapy, even if EGFR mutations have not been detected. These additional indications are included in the estimated size of disease burden that would be eligible for treatment with erlotinib or afatinib (Table 1), but are not discussed further in this analysis as they represent cases in which lung cancer TKIs are relatively less important compared to existing therapies.

Crizotinib is approved for first-line use in advanced NSCLC that displays mutations in the ALK and/or ROS1 genes. The ALK mutation is seen in 3-5% of NSCLC, and the ROS1 mutation is seen in 1-2% of lung cancers.¹⁵

We estimated that when cancer subtype, mutation status, and stage at presentation are taken into account, between 11,000 and 91,000 new people in countries included in

past MPP licences could benefit from these medicines each year (Table 1; details on estimation in the appendix). The numbers increase significantly if additional upper-middle-income countries are included. While the numbers may be limited the disability-adjusted life years lost (DALYs) is significant.

Table 1. Estimated size of disease burden in countries included in past MPP licences potentially eligible for treatment with erlotinib, afatinib, crizotinib, and gefitinib.

	0		0)				
Medicine	Incidence	DALYs lost	Prevalence				
Erlotinib	90,000	2,263,000	86,000				
Afatinib	91,000	2,220,000	123,000				
Crizotinib	11,000	274,000	15,000				
Gefitinib	30,000	729,000	40,000				

DALY - disability-adjusted life year.

6.2.2 Diagnosis of lung cancer and mutation testing

Data from the US suggests that most lung cancer cases present at an advanced stage.¹⁶ Case studies undertaken to inform this study suggested the same scenario in LMICs. The first investigation of choice is usually imaging by X-ray, which will successfully identify the disease in most cases.¹⁷ If resources allow, the next investigation should be a CT (computer-assisted tomography) scan. Compared to simple radiography, CT scanning equipment is far more expensive and requires expert staff.

After imaging, obtaining a tissue or cell sample allows confirmation of the diagnosis. Biopsies in general require highly trained staff and expensive equipment such as bronchoscopes and a CT scanner. Sputum cytology involves collection of a sample of sputum coughed up by the patient and analysing the sputum under a microscope to look for cancer cells. While it is not preferred in high-income guidelines,¹⁸ some argue that is a viable alternative to biopsy in resource-poor settings, being far cheaper, non-invasive, and technically simpler.¹⁹

Testing to establish the presence of the relevant mutation (EGFR, ALK, or ROS-1 as applicable) is a prerequisite to using the medicines discussed in this section. This can be done either by analysing biopsy samples with techniques such as immunohistochemistry, or by analysis of sputum samples with PCR-based methods. Though sputum PCR has a lower sensitivity than more invasive methods, it is more affordable,^{19,20} and is gaining support as a viable test for determining EGFR mutation status when more invasive biopsy is not possible.^{21,22} Diagnosis by sputum PCR, to our knowledge, has not yet been described for ROS-1 or ALK mutations.

Background papers undertaken to inform this feasibility study suggested that diagnostics for EGFR, ALK, and ROS-1 mutations have limited availability in several LMICs. Currently, EGFR and ALK testing is available in some pathology centres in Vietnam, though patients have to pay out-of-pocket for the test. EGFR, ALK, and ROS-1 testing are expected to become available at government laboratories in Uzbekistan in the next year. In Kenya, EGFR testing is performed in top urban hospitals for one subtype of NSCLC and ALK testing is done on special request. Mutation testing for NSCLC is not available in Botswana or Haiti.

6.2.3 Efficacy and tolerability of lung cancer TKIs

Landmark TKI trials for afatinib, erlotinib and gefitinib showed improvements in progression-free survival and quality of life compared to standard chemotherapy but did not demonstrate benefits in overall survival.^{23–25} Once the disease has progressed, a switch to chemotherapy is in general recommended.^{7,8}

Lung cancer TKIs cause less toxicity than conventional (cytotoxic) chemotherapy,^{26–30} and, importantly, far lower rates of adverse events such as immune suppression, anaemia, and increased risk of bleeding (thrombocytopenia). Managing these complications usually requires hospital admission and specialised facilities, which poses a significant challenge for using cytotoxic chemotherapy in resource-limited settings.¹² The absence of these requirements represents a significant potential advantage to using lung cancer TKIs in these settings.

6.2.4 Availability of medicines

Table 2 summarises availability and pricing data collected in background papers undertaken to inform this feasibility study (except data for South Africa and India, which have been collected from public sources³¹⁻³³).

Country	Lowest available prio	ce per patient per montl	n (USD)	
	Erlotinib	Afatinib	Gefitinib	Crizotinib
Uzbekistan	\$2,100	N	Ν	N
Kenya	\$480*	Ν	\$145*	Ν
Haiti	Ν	N	Ν	N
Nicaragua	\$2,600	Ν	\$1,920	\$8,450
Vietnam	\$630*	Ν	\$600*	Ν
Pakistan	\$333*†	\$1,067*†	\$66*†	\$15,000†
South Africa	\$2,081	N	N	N
India	\$408*	Ν	\$91*	\$1,492

Table 2. Availability and prices of lung TKIs in selected LMICs.

N – not registered and/or unavailable. *Generic.†Available but not registered. For erlotinib in Pakistan, a higher priced originator product exists, and is registered. The price shown is for the lower priced, unregistered, generic product. No registration data for India. Viet Nam prices are for procurement in public hospitals. Month = 30 days. Exchange rates of 31 Oct 2017.

From the national background papers,^N gefitinib and erlotinib appear to be more widely available than afatinib and crizotinib and generics seem to be available in several countries. This is likely due to the earlier launch of gefitinib and erlotinib. Considering they are small molecule oral medicines, all four drugs have affordability challenges in LMICs. Even the lowest observed price – \$66 per month for gefitinib in the private market in Pakistan – is likely to be unaffordable for the majority of the population. Similarly, even with numerous manufacturers, generic erlotinib has a relatively high price in India, where it has been the subject of patent litigation.³⁴ This may be partially

National experts contributing background papers for this Chapter were: Nicholas Anthony Othieno Abinya (University of Nairobi, Kenya), Professor Zeba Aziz (Hameed Latif Hospital, Pakistan), Dilshod Egamberdiev (National Cancer Center of Uzbekistan), Temidayo Fadelu (Dana-Farber Cancer Institute, USA), Yehoda Martei (University of Pennsylvania, USA), Orlando Benito Martínez-Granera, (Fundación Movicancer Nicaragua, Nicaragua), and Tuan Anh Pham (National Cancer Hospital, Vietnam).

due to the limited market size and thus limited sales volumes. Crizotinib is the only one for which there appear to be no generics on the market today. Though afatinib, gefitinib, and crizotinib do not yet appear to be marketed in South Africa, applications for their registration have been submitted as they have been listed in the Schedules to the Medicines and Related Substances Act.³⁵ They also are not yet procured by the public sector.

6.2.5 EML Expert Committee

In their 2017 review cycle, the Expert Committee considered that "[e]rlotinib, gefitinib and afatinib are associated with a more favourable tolerability profile and comparable efficacy to cytotoxic chemotherapy, and crizotinib has been associated with greater efficacy in terms of [progression-free survival] and [overall survival] compared with chemotherapy. However, the need to screen patients to determine suitability for treatment must be taken into account by health systems. The availability, affordability, and quality of diagnostic screening of patients for EGFR mutations and ALK gene rearrangements will be an important factor requiring consideration by the Working Group in prioritizing cancer therapies for future EML applications."¹

6.2.6 National essential medicines lists

Of the 25 LMIC NEMLs reviewed, erlotinib is included in the NEMLs of Mexico, Bulgaria, Cote d'Ivoire, Jordan, Moldova, the Russian Federation, Trinidad and Tobago, Ukraine, Panama, Serbia. Gefitinib is included in most of the NEMLs that include erlotinib. Afatinib is included in Serbia's NEML, and crizotinib is included in Panama's NEML. This overview is not exhaustive.

In consultations with certain LMIC governments during the preparation of this feasibility study, high prices for certain cancer medicines was indicated as a reason for not including them in national EMLs in certain countries.

6.2.7 Patent landscape

A patent search revealed that primary patents for erlotinib and gefitinib have expired, but secondary patents have been granted in many LMICs, with expected expiry in 2020 and 2023, respectively, which may delay competitive supply in some countries. Afatinib appears to have primary patents and secondary patents in many LMICs and are in force until 2021 and 2024, respectively. Crizotinib is protected by primary patents in many LMICs until 2025.

Lung Cancer	Expected date of expiry	lPO	۲A	Z	PO	M	z	D	AR	II	II.	IA	(R	ц	M
	слрпу	AF	BF	CE	EA	5	9	N	Ŵ	0	ΡF	Ē	5	ZA	5
Erlotinib															
Erlotinib product	2016				G*										
Crystalline Erlotinib hydrochloride form B	2020	G	F	G	G		G	G	G		G		G	G	G
Afatinib															
Afatinib product generically	2018		F	R	G*									G	
Crystalline Afatinib dimaleate Form A	2024		F	G	G**		G	G			G	F	G	G	G
Afatinib product	2021	·	F	G	G** *		G	G	•	•	G	G	G	G	G
Gefitinib															
Gefitinib product	2016														
Crystalline DMSO solvate of Form 3 of Gefitinib	2023		F	G	G*		G	G			G	G	G	G	
Crizotinib															
Crizotinib product generically	2024	G	F	G	G		G	G	G	G	G		G	G	G
Method of treating abnormal cell growth with Crizotinib	2026	•	F	G	•		•	•		•	•	•	•	G	•
Crizotinib Product Specific	2025	G	F	G	G	G	G	G	G	G	G	G	G	G	G
Crystalline form 1 of Crizotinib	2026		F	G	G*			R/A						G	

Table 3. Patent landscape for lung TKIs.

. – patent not found. F – filed. G – granted. R/A – rejected, under appeal. * RU only, ** KZ and RU only, *** BY and RU only, **** BY KZ RU only.

6.2.8 Conclusions

Erlotinib, gefitinib, afatinib, and crizotinib – oral small-molecule cancer medicines – offer benefits in tolerability, progression-free survival,^{23–25} and possibly overall survival,^{36,37} for a proportion of lung cancer cases.

These medicines have challenging diagnostic requirements. In general, the use of these medicines would necessitate biopsy, which is demanding in terms of requiring technically skilled staff, and resource-intensive equipment. After biopsy, special diagnostics are required to identify cases that display the mutations that these medicines target. These diagnostics are either unavailable or very costly in some LMICs, and the limited market size may prevent them from becoming widely available and affordable in the near future.

On the other hand, these medicines offer some distinct advantages for use in lowresource settings, including significantly lower toxicity than cytotoxic chemotherapy, and low requirements for monitoring or facilities.¹² In addition, if these oral medicines were affordable, despite the added requirement of mutation detection, they may reduce overall costs to LMIC healthcare systems by reducing the costs associated with the regular visits needed for cytotoxic chemotherapy, and the costs associated with managing the toxicities of cytotoxic chemotherapy.

The primary patents for erlotinib and gefitinib have expired in most LMICs and generics have entered the market, but challenges may remain in relation to secondary patents in certain jurisdictions where generics are still not available (e.g. South Africa). For afatinib, patent protection will expire in 2021 in most jurisdictions with additional patents in certain jurisdictions until 2024. Patent protection for crizotinib is likely to be

in place until at least 2025, but the number of lung cancer cases that may benefit from crizotinib is significantly smaller (11,000 new cases annually in countries previously included in MPP licences), making the market for both the medicine and the relevant mutation tests very limited.

In summary, the potential role for the MPP in relation to the medicines for lung cancer reviewed here is likely to be limited due to small market size (particularly for crizotinib), challenging diagnostic requirements, and availability of generic versions of erlotinib and gefitinib in some countries. Nevertheless, access to affordable treatments can be an important driver for the development of diagnostic capacity, and national background papers suggest that several countries are increasing such capacity at least in certain tertiary care centres. The MPP may be able to play a role in increasing access to some of these medicines, for example, through targeted licences for specific countries in which secondary patents are in place. Licences could contribute to enabling earlier generic market entry in such countries.

6.3 Prostate cancer

In this section, we outline the potential for the MPP to facilitate access to abiraterone and enzalutamide for the treatment of prostate cancer in LMICs.

6.3.1 Epidemiology of prostate cancer in LMICs

Prostate cancer is the fifth highest oncological cause of death in men in developing countries,⁴ with over three million people with prostate cancer in LMICs.⁵ The mortality from prostate cancer is projected to increase by 68% from 2015 to 2030 (Figure 1).⁶ In Africa and Asia, screening for prostate cancer is not common, and it is likely that a large proportion of prostate cancer patients present at a late stage.^{38,39} The mortality rate for prostate cancer in Africa and the Caribbean is more than twice the world average.³

Abiraterone and enzalutamide are approved for the treatment of metastatic prostate cancer that is resistant to first-line hormonal therapies. Abiraterone is additionally approved for the treatment of high-risk metastatic prostate cancer that is not yet resistant to first-line therapy, giving it a wider range of use than enzalutamide. We estimated that 168,000 people in countries in past MPP licences are guideline-eligible for treatment with enzalutamide, and 311,000 people are eligible for treatment with abiraterone (Table 4, details on estimation in the appendix).

botentiany engible for treatment with enzalutamide of abriaterone.											
Medicine	Incidence	DALYs	Prevalence								
Abiraterone	47,000	454,000	311,000								
Enzalutamide	25,000	245,000	168,000								

Table 4. Estimated number of prostate cancer cases in countries in past MPP licences potentially eligible for treatment with enzalutamide or abiraterone.

6.3.2 Diagnosis of prostate cancer

In high-income settings, prostate cancer is diagnosed through a combination of clinical history and risk factor assessment, clinical examination, serial blood testing for prostate-specific antigen (PSA), imaging, and biopsy.⁴⁰

An analysis of prostate cancer treatment in Nigeria considers PSA expensive and notes the difficulties in diagnosing prostate cancer due to a lack of trained urologists and ultrasound-guided biopsy.⁴¹ The overall rate of prostate biopsy in sub-Saharan Africa is low,⁴² and diagnosis is typically made when the cancer is already advanced, and regularly made on clinical grounds alone.⁴³ On the other hand, according to national background papers undertaken to inform this feasibility study, guided biopsies and PSA measurement are widely available in Nicaragua and Uzbekistan.

6.3.3 WHO Expert Committee

An application was submitted to include enzalutamide in the 2017 update of the WHO EML. No application was submitted for abiraterone. The Expert Committee's report "recommended that enzalutamide should not be added to the EML at this time, but should be considered as part of a comprehensive review encompassing additional medicines (e.g. abiraterone) at its next meeting."¹

6.3.4 Treatment of prostate cancer

Surgery and radio therapy with curative intent are in general not recommended in metastatic prostate ${\rm cancer^{0.44}}$

The first-line pharmaceutical treatment in metastatic prostate cancer is androgen deprivation therapy (ADT) with abiraterone, which can include surgical removal of the testes and/or treatment with medicines.^{44,45} The first medicines for ADT – bicalutamide and leuprorelin – were added to the WHO EML in 2015 following a review of cancer medicines by the Union for International Cancer Control (UICC).^{46,47}

Abiraterone is recommended in the first-line treatment for metastatic prostate cancer, given together with ADT.⁴⁸ Enzalutamide and abiraterone are both recommended as treatments for metastatic prostate cancer that has become resistant to ADT.⁴⁴ Both abiraterone and enzalutamide confer benefits in overall survival.^{48,49} Concurrent steroid therapy (prednisone or prednisolone – generic oral medicines) is required for abiraterone but not for enzalutamide.⁵⁰

Cytotoxic chemotherapy has a high rate of adverse events such as immunosuppression, which require specialised facilities and in most cases hospital admission. In many LMICs, chemotherapy is limited by the availability of appropriate facilities and the cost of chemotherapy. Abiraterone and enzalutamide have been shown to confer similar or greater survival benefits compared to cytotoxic chemotherapy (docetaxel) and may thus be considered a therapeutic alternative to cytotoxic chemotherapy (trials to determine whether abiraterone or enzalutamide should be used *with* rather than *before* cytotoxic chemotherapy are ongoing).^{44,45,48,51} Thus, at present, both abiraterone and enzalutamide may represent important treatment options for patients for whom chemotherapy is undesirable, or in settings where chemotherapy is difficult to administer.^{50,52}

⁰ Though surgery and/or radiotherapy may be used in managing complications (such as spinal cord compression) or as part of palliation.

With evidence to support the benefit of using abiraterone earlier in the disease process (i.e. before resistance to ADT develops), and no equivalent evidence for enzalutamide, abiraterone may be more important from a public health perspective in LMICs at present.

6.3.5 Availability of medicines

Table 5 summarises availability and pricing data for enzalutamide and abiraterone, collected in background papers undertaken to inform this feasibility study (except data for South Africa and India, which have been collected from public sources³¹⁻³³).^P

Country	Lowest available price per patient p	er month (USD)
	Enzalutamide	Abiraterone
Uzbekistan	Ν	N
Kenya	\$3,305	\$627*
Haiti	N	N
Nicaragua	\$4,950	N
Vietnam	N	\$1,920
Pakistan	\$6,580 ⁺	\$380*†
India	\$4,807	\$598*
South Africa	\$2,567	\$2,370

Table 5. Availability and prices of enzalutamide and abiraterone in selected LMICs.

N – not registered and/or unavailable. *Generic. †Available but not registered. No registration data for India.

Background papers undertaken to inform this feasibility study suggested that enzalutamide and abiraterone are not widely used in LMICs. Generic abiraterone appears to be available in Kenya, Pakistan, and India, but prices are still high, although significantly more affordable than enzalutamide. This may be due to abiraterone only recently becoming favoured in guidelines and generics new entry into the market.

The preferred treatment in many parts of Africa is bilateral orchidectomy – surgical removal of both testes in order to decrease testosterone levels.^{38,41} This is partially due to the higher costs of reducing testosterone levels with pharmaceuticals.⁴¹ A background paper on cancer care in Haiti, undertaken to inform this feasibility study, identified a similar trend. In some countries in Asia, an older medicine, ketoconazole (primarily used as an antifungal) is used instead of newer anti-androgens due to their high price, despite ketoconazole having significantly greater adverse effects.^{44,50}

6.3.6 National essential medicines lists

Of the 25 NEMLs from LMICs that we were able to collect, enzalutamide was present only in the NEML of Serbia, though our search overview was not exhaustive.

In consultations with certain LMIC country governments during the preparation of this feasibility study, high prices for certain cancer medicines were indicated as a reason for not including them in national EMLs in certain countries.

^P See footnote above, in section 6.2., for a list of experts that provided national background papers for this Chapter.

6.3.7 Patent landscape

Enzalutamide is under compound patent protection in some LMICs. In the US, Europe, and Australia, generic versions of abiraterone may be blocked by a method-of-use patent until 2027,⁵³ but this patent appears not to have been filed or granted in most LMICs for which data was gathered (table below). While other reports have highlighted other patents on abiraterone, this analysis focuses on those listed in the USFDA Orange Book and the equivalent national patents in LMICs.

	Expected date of expiry	ARIPO	BRA	CHN	EAPO	GTM	IDN	QNI	MAR	0API	THd	ТНА	UKR	ZAF	NNM
Enzalutamide															
Product	2026/202 7	•	F	G	G*	•	G	R/ A	•				•	G	
Abiraterone															
Method of treatment with abiraterone and prednisone	2027		·	F		?	·		?	?	•	·	?		·

Table 6. Patent landscape for enzalutamide and abiraterone.

. – patent not found. F – filed. G – granted. R/A – rejected, under appeal. * RU only, ** KZ and RU only, *** BY and RU only, *** BY KZ RU only.

6.3.8 Conclusions for prostate cancer

The burden of prostate cancer in LMICs is substantial, with mortality rates in many LMICs higher than in high-income countries.

Abiraterone or enzalutamide, if available at more affordable prices, could offer significant benefits to people with prostate cancer in LMICs. At present, abiraterone appears to be more promising from a public health perspective in LMICs as evidence supports its use earlier in the disease. One potential drawback for abiraterone could be its need for concurrent treatment with an oral steroid (not required for enzalutamide), which would add to the price and may not be well-tolerated by some. Both drugs offer an alternative to chemotherapy that is effective, have substantially lower side effects, and do not require specialised facilities for administration. These advantages are especially significant in resource-poor settings.

Based on our analysis, while there are some secondary patents, these do not appear to be blocking generic market entry for abiraterone in most LMICs for which we were able to collect data, and generic versions are already available in some countries. It is therefore unclear what, if any, role the MPP could play in facilitating broader access to abiraterone, unless the MPP could contribute to the transfer of technology to manufacturers and/or partner with other stakeholders to facilitate market entry and uptake. Enzalutamide has primary patent protection until 2026/2027 in some LMICs and could potentially be a candidate for MPP licensing, pending future recommendations by the EML cancer working group and the WHO Expert Committee.

6.4 Multiple myeloma

This section looks at the potential for MPP to play a role in enhancing access to lenalidomide for the treatment of multiple myeloma in LMICs. Multiple myeloma is a cancer of the blood. Presenting symptoms typically include anaemia, bone pain, kidney failure, and high blood calcium levels (causing symptoms such as constipation).⁵⁴

6.4.1 Epidemiology of multiple myeloma in LMICs

Multiple myeloma represents about 1% of all cancer cases and 10% of blood cancer cases.⁵⁵ In 2016, there were 134,195 people living with multiple myeloma in LMICs. In Europe, the median age at diagnosis is 72.⁵⁵ We estimated that 64,000 people in countries included in past MPP licences are clinically eligible for treatment with lenalidomide (Table 7).

Table 7. Estimated number of multiple myeloma cases in countries in past MPP licences potentially eligible for treatment with lenalidomide.

Incidence	DALYs	Prevalence
29,000	704,000	64,000

6.4.2 Diagnosis of multiple myeloma

Multiple myeloma is diagnosed on the basis of clinical symptoms and confirmed using, at minimum, urine and blood electrophoresis and a bone marrow sample. Background papers commissioned to the feasibility study noted that these tests are available in Botswana, Nicaragua, Pakistan, Uzbekistan, Vietnam, as well as in urban centres in Kenya.^Q

6.4.3 WHO Expert Committee

Lenalidomide has not specifically been submitted to the WHO Expert Committee for addition to the WHO EML. However, in 2017, the WHO Expert Committee called for the established of a "Cancer Working group [that] should consider other important oncology conditions for review that were not part of the previous update, including (but not limited to) multiple myeloma, renal and brain cancers".¹ Lenalidomide was mentioned by multiple stakeholders as an important medicine for multiple myeloma for which there are access issues in some LMICs.

6.4.4 Treatment of multiple myeloma

Lenalidomide is an oral, once-daily medicine. Lenalidomide with dexamethasone (a generically available steroid) is the only guideline-preferred fully oral first-line combination treatment.^{55,56} Treatment generally lasts for at least one year. Five -year survival in multiple myeloma was previously about 30-40% before newer medicines, but is now around 50% with the use of lenalidomide and dexamethasone.^{57,58}

^Q See footnote above, in section 6.2., for a list of experts that provided national background papers for this Chapter.

Lenalidomide was developed as a derivative of thalidomide, a long-generic medicine whose efficacy in treating multiple myeloma was discovered in the early 2000s.⁵⁹ Lenalidomide has been shown to be superior to thalidomide in its side effects profile, though superiority in overall survival has not yet been demonstrated.^{59,60} In terms of side effects, lenalidomide is associated with significantly less neuropathy (nerve damage) than thalidomide – about a third of patients taking thalidomide experience some nerve damage. Additionally, lenalidomide is associated with an increased risk of venous thromboembolism, and therefore prophylaxis with aspirin or a different anticoagulant such as a NOAC is recommended for patients being treated with lenalidomide.

The addition of bortezomib to lenalidomide/dexamethasone offers an 11 month increase in median overall survival,⁶¹ and bortezomib may thus also be a promising candidate in the future both for addition to the EML and for MPP licensing. Bortezomib is an injectable medicine which has substance patent protection in the US expiring in 2022, though patents may not be widely in force in most LMICs.

6.4.5 Availability of medicines

Country	Lowest available price per patient per month (USD)
Haiti	N
Nicaragua	\$9,333
Vietnam	\$280*
Botswana	Ν
Pakistan	\$142*
India	\$63*
South Africa	\$7,224

Table 8. Availability and prices of lenalidomide in selected LMICs.

N – not registered and/or unavailable. No registration data for India. 10mg per day dose assumed. *Generic

Multiple generic versions are available in India, though the current generic monthly price is likely to be unaffordable for the majority of the population. Generics are also available in Vietnam and Pakistan, which appear to be imported from India. Generics are not currently available in South Africa or Nicaragua, where prices are significantly higher.

6.4.6 National essential medicines lists

Of the 25 NEMLs from LMICs that we reviewed, lenalidomide was included in the NEML of Guatemala, Mexico, Russia, and Serbia.

6.4.7 Patent landscape

The patent landscape for lenalidomide is shown in Table 9. The primary (compound) patent is not in force in most LMIC jurisdictions. A patent on crystalline form of lenalidomide, however, has been widely granted in LMICs and is expected to expire in 2027. In India, this patent was refused, which may explain the availability of multiple generic versions.

Table 9. Patent landscape for lenalidomide.

	Expected date of expiry	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	THI	ТНА	UKR	ZA	MNV
Product patent	2019	•	•	G	G*	•		•	•	•			•	•	•
Method of treating myelodysplastic syndrome with lenalidomide	2023	·	G	G	·	·			·					G	
Crystalline form B	2027	G	R/A	G	G**		G	R	G	G	G		G	G	G
Method of treating multiple myeloma and non-Hodgkin's lymphoma	2023		G	G	F*			R			G		G	G	
Method of treating mantle cell lymphoma	2028			G	G*										•

. – not filed/withdrawn/abandoned. G – granted. F – filed. R – refused. R/A – refused and under appeal. *RU only **patent ceased in RU

6.4.8 Conclusions

Multiple myeloma affects an estimated 134,000 people in LMICs. We estimated that 64,000 people live in countries included in past MPP licences and would be clinically eligible for treatment with lenalidomide. The burden of disease associated with multiple myeloma in the countries is substantial, representing 704,000 DALYs. While the primary patent is not in force in most LMICs, a secondary patent on a crystalline form of lenalidomide may delay generic market entry in some LMICs. Prices of lenalidomide appear to be high across LMICs, particularly where there is a single supplier.

The requirement of bone marrow aspiration may pose a challenge to wider treatment of multiple myeloma. However, expert clinicians who provided background papers for this study reported that the required diagnostics are available in many LMICs.

The combination bortezomib-lenalidomide-dexamethasone appears to currently be the best treatment for patients with multiple myeloma^R.^{55,56} If bortezomib is not available, lenalidomide-dexamethasone is still a guideline-recommended all-oral first line regimen.

In conclusion, following any decisions by the EML cancer working group on recommended treatments for multiple myeloma, MPP licensing could contribute to accelerating access to lenalidomide in LMICs where generic market entry may not be possible yet, enabling broader access to treatment for people with multiple myeloma.

6.5 Breast cancer

In this section, we consider treatments for HER2-positive breast cancer that have been recently highlighted by the WHO EML Expert Committee as candidates for future review: trastuzumab emtansine (T-DM1), pertuzumab, and lapatinib. In addition, we note the case of trastuzumab, which was added to the WHO EML 2015. Of these five drugs, lapatinib is the only one that is not a biologic – it is a small molecule tyrosine

^R For patients who will not receive autologous stem cell transplantation.

kinase inhibitor. Palbociclib, a breast cancer medicine for HER2-negative breast cancer, is discussed separately, in Chapter 8.

We use the term similar biotherapeutic product (SBP) to describe biologic medicines that are similar to an originator biologic medicine in quality, safety, and efficacy. This term is in most cases synonymous with 'biosimilar'.

6.5.1 Epidemiology of breast cancer in LMICs

Breast cancer is the leading oncological cause of death in women in developing countries,⁴ with 1.4 million new cases in LMICs in 2015.⁵ While the incidence rates for breast cancer are highest in North America and Europe, the mortality rates are highest in Western Africa and Northern Africa.³

Data from the US suggest that about 40% of breast cancer cases present at an advanced stage.¹⁶ The proportion of patients presenting with metastatic disease is higher in LMICs in Asia and Africa, and median age at presentation is lower.^{62–64} For example, while 48% of breast cancer is diagnosed at Stage I (i.e. an early stage) in the US,⁶⁵ this number has been reported at only 4% and 23% in centres in India and Malaysia, respectively,⁶² and 77% of breast cancers present at an advanced stage in Sub-Saharan Africa.⁶⁴ Median age at diagnosis is 60 years in the US,⁶⁵ but the average age in China is 45-55 years,⁶³ and a systematic review of 83 studies spanning 17 sub-Saharan African countries found that most patients in Africa were aged 35-49 years.⁶⁴

In around 15-20% of breast cancer cases,⁶⁶ tumour cells overexpress a specific receptor, termed HER2, which in these cancer cells is the central driver for the disease process. HER2 positivity is associated with more aggressive disease (in the absence of HER2-targeted treatment).⁶⁷ All of the medicines considered in this section are HER2-targeted treatments.

We estimated that, when cancer subtype, mutation status, and stage at presentation are taken into account, between 535,000 and 1,112,000 people in countries in past MPP licences could benefit from trastuzumab, T-DM1, pertuzumab, and lapatinib (Table 10, details on estimation in the appendix).

Medicine	Incidence (cases per year)	DALYs	Prevalence		
Trastuzumab	147,000	1,285,000	1,112,000		
Any one of: trastuzumab emtansine (T-DM1), pertuzumab, and lapatinib	65,000	499,000	535,000		

Table 10. Estimated size of disease burden in countries in past MPP licences potentially eligible for treatment with trastuzumab, pertuzumab, T-DM1, and lapatinib.^s

^S Trastuzumab is indicated first-line for all HER2+ breast cancers (i.e. both early and advanced cancers). Pertuzumab is indicated in metastatic HER2+ breast cancer. Lapatinib and T-DM1 are indicated in metastatic HER2+ breast cancer after failure of trastuzumab. For the purposes of these estimates, we assumed that all patients with metastatic breast cancer treated with trastuzumab would eventually become resistant and would therefore become eligible for T-DM1 and/or lapatinib. It should be noted, however, that this is likely an overestimation ⁹⁶.

6.5.2 Diagnosis of breast cancer

Screening of breast cancer is not common in resource-poor settings due to multiple factors.⁶² Mammography equipment, which is widely used as the first-line diagnostic technique in high-income countries and many middle-income countries, is unavailable in some LMIC. ⁶⁸

In order to use HER2-targeted therapy, a biopsy has to be obtained once the tumour is identified, and molecular testing used to assess the mutation status of the tumour. Both obtaining the biopsy and molecular testing of the sample require specialised facilities, equipment, and highly-trained staff.

National background papers undertaken to inform this feasibility study suggest that HER2 mutation diagnostics have mixed availability in LMICs.^T Currently, HER2 testing is available in some pathology centres in Vietnam, though patients have to pay out-of-pocket for the test. HER2 testing is expected to become available at government laboratories in Uzbekistan in the next year. HER2 testing is normally not done in Haiti due to lack of laboratory capacity. HER2 testing is available and covered in the public sector in Botswana. In Kenya, HER2 testing is available at the main hospital in Nairobi. It should be noted, however, that limited access to treatment has been a key barrier to broader scaling up of HER2 testing (interviews with key stakeholders). This may change as access to trastuzumab increases in LMICs.

6.5.3 Treatment of breast cancer

The stages of breast cancer divide, generally, into early (localised), locally-advanced, and metastatic. In general, surgery and radiotherapy are recommended first-line treatments in early breast cancer, but not in metastatic breast cancer, where treatment with medicines is preferred.^{69,70} In locally-advanced breast cancer, some tumours may be operable, and some tumours initially considered inoperable may become operable after treatment with radiotherapy and/or systemic therapy.^{71,72} Despite the fact that the great majority of breast cancer present at an advanced stage in sub-Saharan Africa,⁶⁴ mastectomy (total removal of the breast(s)) is the most common treatment for breast cancer in the region.⁷³ A 2010 survey found that less than half of African countries had an external-beam radiotherapy machine.⁷⁴ While mastectomies can be performed in most hospitals with surgical facilities,⁷⁵ but access to surgery can be a major challenge in many low-income and lower-middle-income countries.⁷⁶ The high proportion of cases that present with advanced disease and the low availability of radiotherapy and surgery suggest that a large proportion of breast cancer patients would benefit from superior outcomes if gold-standard medical therapy become available.

Trastuzumab is the only anti-HER2 therapy recommended for early breast cancer in current European guidelines.⁷⁰ The preferred therapy in advanced HER2-positive breast

^T See footnote above, in section 6.2., for a list of experts that provided national background papers for this Chapter.

cancer is cytotoxic chemotherapy combined with trastuzumab and pertuzumab^U. After disease progression on this regimen, the recommended second-line treatment is with T-DM1 (preferred over lapatinib).⁶⁹

6.5.4 Availability of medicines

Table 11 summarises availability and pricing data for HER2-targeted medicines, collected from national background papers undertaken to inform this feasibility study (except data for South Africa and India, which have been collected from public sources^{31,33}).

Country	Price per month (USD)					
	Trastuzumab	T-DM1	Pertuzumab	Lapatinib		
Uzbekistan	\$873*	Ν	\$4,667	N		
Kenya	\$789*	Ν	N	N		
Haiti	Ν	Ν	N	N		
Nicaragua	\$1,640	\$8,496	\$5,267	N		
Vietnam	\$1,676*	N	N	N		
Pakistan	\$1,256	\$11,958 [†]	\$4,647 †	\$2,304		
India	\$970*	Ν	N	\$1,149		
South Africa	\$7,214	N	N	\$1,585		
N – not registered and/or unavailable. *Generic/similar biotherapeutic product. †Available but not registered. No registration data for India. Assumed dosage regimens (body weight assumed 60kg): trastuzumab – 6mg/kg body weight every 3 weeks, pertuzumab – 420mg every 3 weeks, T-DM1 – 3.6mg/kg body weight every 3 weeks, lapatinib – 1500mg daily. Month = 28 days. Perfect vial sharing assumed.						

Table 11. Availability and prices of HER2-targeted medicines in selected LMICs.

According to the background papers, trastuzumab SBP is available in Uzbekistan from BIOCAD, is available in Kenya from Mylan and Galaxy, is available from Mylan in Vietnam, and is available in India from Emcure and Biocon.

Of the four medicines included in this section, trastuzumab was mostly widely available. Despite the availability of SBPs for trastuzumab in many countries, the monthly prices of trastuzumab are still high, and several countries still have a single supplier. This may be partly explained by the relatively recent market entry of SBPs and by the high development and manufacture costs for SBPs. The background papers estimated that 10%, 7%, 5% and 5% of patients who could benefit from trastuzumab actually have access in Vietnam, Pakistan, Uzbekistan and Kenya, respectively. One informed stakeholder provided a higher estimate of about 29% of patients needing trastuzumab receiving it in a representative sample of developing countries. Estimates for pertuzumab, T-DM1, and lapatinib were generally much lower in those four countries.

There are multiple reasons for limited access to treatments for HER2-positive breast cancer, including challenges in diagnosis, limited access to specialized facilities and expert medical staff, price, and lack of public reimbursement for treatment. The list is by no means exhaustive. Significant access programs from originator companies were reported for the diagnosis and treatment of breast cancer in certain countries in Asia, Latin America and North Africa. Examples include screening and diagnostic services,

^U The cytotoxic chemotherapy preferred in this regimen is any one of: docetaxel, paclitaxel, nab-paclitaxel, vinorelbine, and capecitabine.⁶⁹ Of these, all but nab-paclitaxel are included in the WHO EML.

awareness campaigns, training of pathologists, tiered prices for treatment in public sector, establishment of "women consulting rooms" and patient assistance programs.

There are at least 17 trastuzumab SBPs being developed by various companies, at various stages of development.⁷⁷ In South Africa and India, Roche (the originator pharmaceutical company for trastuzumab) markets two versions of trastuzumab – Herceptin, and Herclon. Herclon is sold exclusively to the public sector in South Africa, and on the private market in India at a price approximately 50% lower than Herceptin. SBPs of trastuzumab are priced lower than Herclon in India, but are not available in South Africa.⁷⁸ In India, Roche holds an agreement with Emcure, under which Emcure manufactures and markets trastuzumab (marketed as Biceltis) locally, using Roche's technology.⁷⁹

6.5.5 Patent landscape

There are a number of patents on trastuzumab that are still in force until 2018 to 2026.⁸⁰ However, as SBPs are now available in many LMICs, those patents may not be considered to be blocking. Patents on pertuzumab and T-DM1 have been granted in many LMIC jurisdictions, with protection potentially lasting until 2025 and 2029, respectively (Table 12). For lapatinib, the primary patent expires in 2019, and secondary patents expire in 2026.

Breast cancer	Expected date of expiry	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	DHL	ТНА	UKR	ZAF	VNM
T-DM1															
MOT tumor comprising identifying said with overexpression of ErbB2 receptor	2020		AP	G										G	
MOT cancer expressing human epidermal growth factor receptor 2 protein by administering combination of Transtuzumab emtansine with chemotherapeutic agent selected from GDC-0941 and GNE-390, as a combined formulation or by alternation.	2029		F	G	F			A	G		G	F	G	G	G
Lyophilized composition of a conjugate comprising a humanized antibody that binds to DM1,	2024		F	F	G			G						G	·
Pertuzumab															
MOT for cancer expressing HER2 antibody 2C4	2020		F	G	G*									G	
MOT for HER2 expressing cancer with fixed dose of pertuzumab	2025		F	R	G*		R	R	G		G	F	G	G	G
composition of HER2 antibody	2025		F	G	G****	F	G	G	G		G	F	G	G	G
Pertuzumab formulation	2025		F	G	G****	F	G	G	G		G	F	G	G	G
Lapatinib															
Lapatinib product specifically	2019	G	G	G	G		G	G	F	G	F	F	G	G	
Lapatinib Ditosylate Salt	2021		F	G				R			G			G	
Lapatinib Ditosylate monohydrate film coated tablet Composition and preparation	2026		F	G				F						G	

Table 12. Patent landscape for HER2-targeted medicines.

. – patent not found. F – filed. G – granted. * RU only, ** KZ and RU only, *** BY and RU only, **** BY KZ RU only.

6.5.6 WHO Expert Committee

An application was made to include T-DM1 in the 2017 update of the WHO EML. No applications were made for pertuzumab or lapatinib. Trastuzumab is on the WHO EML, having been added in 2015.

The 2017 WHO Expert Committee recommended "that trastuzumab emtansine [T-DM1] should not be added to the EML at this time but should be considered as part of a comprehensive review encompassing additional medicines (e.g. pertuzumab, lapatinib, bevacizumab) at its next meeting."¹

6.5.7 Conclusions

Trastuzumab, pertuzumab, and T-DM1 have demonstrated improvements in overall survival in HER2-positive metastatic breast cancer and are the recommended first-line (trastuzumab and pertuzumab) and second-line (T-DM1) treatments for HER-positive advanced breast cancer, in European guidelines. In LMICs, many cases present at an advanced stage, and the availability of radiotherapy and surgery is limited. In this context, effective systemic therapies could be especially valuable.

There are multiple challenging factors that may limit the extent to which these medicines could be used in resource-limited settings. The use of these medicines would rely on successful diagnosis of HER2-positive metastatic breast cancer, and the ability of patients to attend 3-weekly treatment sessions at a specialised facility. HER2-positivity must be assessed before using these medicines, and facilities to enable HER2 testing (including biopsy) may be unavailable in several LMICs, though background papers illustrated a trend of increasing availability.

Aside from lapatinib, the HER2-targeted therapies outlined in this section are biologics. Biologics pose multiple challenges. Their use requires a cold chain, which may pose a major challenge in some settings. Price reductions with SBPs appear to be smaller than the price reductions seen in generic competition for small molecules (i.e. nonbiologics).⁸¹ There are numerous factors that add additional costs to the manufacture process that small molecules do not have, such as higher development costs, costs associated with manufacture, and added regulatory requirements (additional clinical trials that prospective SBP manufacturers must undertake). Nevertheless, recent experience shows that significant price decreases are possible with SBPs, even when SBP markets are still in their infancy,⁸² and numerous SBPs were identified as available in national background papers.

Trastuzumab has a larger demand volume than the other three medicines due to its indication in early breast cancer, as well as its earlier market entry. Similarly, pertuzumab may attract a larger demand volume than T-DM1 or lapatinib as it is indicated earlier in the disease, which may translate to a larger potential patient pool. However, for all three, the availability of trastuzumab is a prerequisite for their use (as

recommended in guidelines), and access to trastuzumab remains a challenge, though access has been increasing and SBPs are increasingly available in many LMICs.

In terms of specific challenges for the MPP entering the biologic space, there are questions regarding whether LMICs included in an MPP licence would represent a sufficient market to incentivise investment in developing an SBP if manufacturers were limited to selling to this market. While lapatinib is a small molecule, and development of generic versions may therefore be easier, faster, and may achieve lower monthly prices in LMIC markets, it is considered less effective than T-DM1 in guidelines.⁶⁹ Moreover, with the primary patent on lapatinib expiring in 2019, the scope for MPP may be rather limited.

In summary, there are distinct challenges for MPP working on trastuzumab, pertuzumab, T-DM1, and lapatinib. However, background papers from a select number of LMICs suggest that the availability of and access to relevant diagnostics is increasing. In addition, access to affordable treatments can be an important driver for further development of diagnostic capacity, and for national initiatives to expand care. Following the review by the EML cancer working group and the WHO Expert Committee in 2019, the MPP could explore concrete opportunities for licensing breast cancer medicines that are highlighted. In the case of biologics, this may also require strong provisions for technology transfer.

6.6 Similar biotherapeutic product (SBP) manufacture in LMICs

In reviewing a number of the new cancer medicines, in particular those for breast cancer, discussions around the challenges for the development and registration of SBPs were raised by multiple stakeholders. This section provides a brief overview of some challenges and recent developments, and the potential role that the MPP could play in relation to SBPs if it decided to expand its mandate to include these medicines. The WHO defines an SBP as a "biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product".⁸³

6.6.1 SBP development in LMICs

Though SBPs are still a relatively new phenomenon, estimates for the number of SBPs currently in the pipeline range from 600 to more than 900.^{84,85} While it was initially expected that SBPs would achieve price reductions of only around 30%,⁸⁶ reductions in the neighbourhood of 70% have been achieved in recent years.⁸²

Probably the largest challenge for SBP development is that manufacturers are in general required to undertake larger (Phase III) clinical trials to show comparable efficacy and safety to the reference (originator) product. In addition, some countries require that clinical trials for SBPs be conducted locally – or that a certain proportion of patients are from the local population.⁸⁷ In the US and EU, there are regulatory processes in place that can support manufacturers developing SBP products throughout development with advice to help compilation of an application dossier. In LMICs, such support may not be available.⁸⁸ Lastly, manufacturers entering the SBP space will need to build new manufacturing plants, which often have to be very large in order to lower production costs to competitive levels.⁸⁹

The WHO has developed guidelines for SBP regulatory review,⁸³ and has recently announced a pilot programme for the prequalification of two SBPs (rituximab and trastuzumab).⁹⁰ National guidelines for SBP approval, often a crucial first step in enabling SBP markets, have also been developed in numerous LMICs, including Malaysia, Turkey, Taiwan, Thailand, Brazil, Saudi Arabia, South Africa, Argentina, Cuba, India, Iran, Mexico, Peru, China, and Russia.⁹¹⁻⁹³ In the absence of national guidelines, regulators in many cases rely on WHO, FDA, or EMA guidelines.^{91,92} In Brazil, the government has established public-private partnerships to kick-start local SBP production capacity. The partnerships are additionally supported by guarantees of government advance market commitments.⁹⁴ Turkey and Russia have similar governmental initiatives aimed at boosting domestic SBP production capacity.⁸⁷

In summary, while there are significant challenges for SBP development in LMICs, the WHO and some LMIC governments are making efforts to encourage the development of domestic production capacity, and the pipeline of SBPs is rapidly expanding.

6.6.2 Considerations regarding potential MPP work in SBPs

MPP licensing for SBPs could potentially improve access in LMICs, as has been the case for small molecules.

A specific concern for the MPP entering the biologic space raised by some stakeholders, was whether LMICs included in an MPP licence would represent a sufficient market to incentivise investment in developing an SBP, given the high costs of development.

It is therefore possible that for the MPP to play a role in biologics, the technology transfer aspect of MPP licensing agreements would be of greater importance than it is for small-molecule medicines. Transfer of originator materials such as cell lines and details on manufacturing process, which are otherwise protected as trade secrets, could significantly lower barriers to SBP market entry and reduce costs. In effect, such licensing agreements could draw from the experience of the agreements that some originator companies have already made with LMIC SBP manufacturers to supply local/regional markets (e.g. for rituximab and trastuzumab in India).⁷⁹ This is an area that would require further analysis and further discussion with pharmaceutical companies.

6.7 References

1 WHO EML Expert Committee. Report of the WHO Expert Committeeon Selection and Use of Essential Medicines. WHO Tech. Rep. Ser. 2017.

http://www.who.int/medicines/publications/essentialmedicines/EML_2017_EC21_Unedited_Full_Report.pdf?ua=1 (accessed Sept 14, 2017).

2 WHO Model List of Essential Medicines - 19th List (April 2015)(Amended November 2015).

http://www.who.int/medicines/publications/essentialmedicines/EML_2015_FINAL_amended_NOV2015.pdf?ua=1. 3 International Agency for Research on Cancer. Online analysis. 2012.

http://globocan.iarc.fr/Pages/online.aspx (accessed Nov 2, 2017).

4 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65: 87–108.

5 Vos T, Allen C, Arora M, *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1545–602.

6 Ferlay J, Soerjomataram I, Ervik M, *et al.* GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. 2013. http://globocan.iarc.fr (accessed Feb 1, 2015).

7 National Comprehensive Cancer Network. Non-Small Cell Lung Cancer. 2017.

https://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf (accessed Nov 7, 2017).

8 Novello S, Barlesi F, Califano R, *et al.* Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 2016; 27: v1–27.

9 Devesa SS, Bray F, Vizcaino AP, Parkin DM. International lung cancer trends by histologic type: Male:female differences diminishing and adenocarcinoma rates rising. *Int J Cancer* 2005; 117: 294–9.

10 Werutsky G, Debiasi M, Sampaio FH, *et al.* P1.08: Updated Analysis of Global Epidemiology of EGFR Mutation in Advanced Non-Small Cell Lung Cancer. *J Thorac Oncol* 2016; 11: S184–5.

11 Shi Y, Li J, Zhang S, *et al.* Molecular Epidemiology of EGFR Mutations in Asian Patients with Advanced Non-Small-Cell Lung Cancer of Adenocarcinoma Histology – Mainland China Subset Analysis of the PIONEER study. *PLoS One* 2015; 10: e0143515.

12 Soo RA, Anderson BO, Cho BC, *et al.* First-line systemic treatment of advanced stage non-small-cell lung cancer in Asia: consensus statement from the Asian Oncology Summit 2009. *Lancet Oncol* 2009; 10: 1102–10.

13 Shigematsu H, Lin L, Takahashi T, *et al.* Clinical and Biological Features Associated With Epidermal Growth Factor Receptor Gene Mutations in Lung Cancers. *JNCI J Natl Cancer Inst* 2005; 97: 339–46.

Dearden S, Stevens J, Wu Y-L, Blowers D. Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). *Ann Oncol* 2013; 24: 2371–6.

15 Korpanty GJ, Graham DM, Vincent MD, Leighl NB. Biomarkers That Currently Affect Clinical Practice in Lung Cancer: EGFR, ALK, MET, ROS-1, and KRAS. *Front Oncol* 2014; 4. DOI:10.3389/fonc.2014.00204.

Siegel R, DeSantis C, Virgo K, *et al.* Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin* 2012; 62: 220–41.

17 Gridelli C, Rossi A, Carbone DP, *et al.* Non-small-cell lung cancer. *Nat Rev Dis Prim* 2015; : 15009.

18 National Institute for Health and Care Excellence. Lung cancer: diagnosis and management. 2011.

https://www.nice.org.uk/guidance/cg121/chapter/1-Guidance (accessed Feb 8, 2018).

19 Ammanagi A, Miskin A, Sangolli S, Dombale V, Dandagi G. Sputum cytology in suspected cases of carcinoma of lung (Sputum cytology a poor man's bronchoscopy!). *Lung India* 2012; 29: 19.

20 Hubers AJ, Prinsen CFM, Sozzi G, Witte BI, Thunnissen E. Molecular sputum analysis for the diagnosis of lung cancer. *Br J Cancer* 2013; 109: 530–7.

21 Ellison G, Zhu G, Moulis A, Dearden S, Speake G, McCormack R. EGFR mutation testing in lung cancer: a review of available methods and their use for analysis of tumour tissue and cytology samples. *J Clin Pathol* 2013; 66: 79–89.

Hubers AJ, Heideman DAM, Yatabe Y, *et al.* EGFR mutation analysis in sputum of lung cancer patients: A multitechnique study. *Lung Cancer* 2013; 82: 38–43.

23 Greenhalgh J, Dwan K, Boland A, *et al.* First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. In: Green JA, ed. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd, 2016. DOI:10.1002/14651858.CD010383.pub2.

24 Shaw AT, Kim D-W, Nakagawa K, *et al.* Crizotinib versus Chemotherapy in Advanced ALK -Positive Lung Cancer. *N Engl J Med* 2013; 368: 2385–94.

25 Lee J-K, Hahn S, Kim D-W, *et al.* Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors vs Conventional Chemotherapy in Non–Small Cell Lung Cancer Harboring Wild-Type Epidermal Growth Factor Receptor. *JAMA* 2014; 311: 1430.

Wu Y-L, Zhou C, Liam C-K, *et al.* First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. *Ann Oncol* 2015; 26: 1883–9.

27 Zhou C, Wu YL, Chen G, *et al.* Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; 12: 735–42.

Maruyama R, Nishiwaki Y, Tamura T, Yamamoto N, Tsuboi M, Nakagawa K. Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. 2008; 26: 4244–52.
Kim ES, Hirsh V, Mok T, *et al.* Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet* 2008; 372: 1809–18.

30 Yang JC-H, Wu Y-L, Schuler M, *et al.* Afatinib versus cisplatin-based chemotherapy for EGFR mutationpositive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 2015; 16: 141–51.

31 South Africa Department of Health. Master Procurement Catalogue.

http://www.health.gov.za/index.php/component/phocadownload/category/196 (accessed May 12, 2017).

32 South African Medicine Price Registry. Database Of Medicine Prices 22 December 2017.

http://mpr.gov.za/Publish/ViewDocument.aspx?DocumentPublicationId=4007 (accessed Feb 7, 2018). 33 CIMS. CIMS. 18 Oct 2017.

LiveLaw.in. Patent Battle Over Lung Cancer Drug: SC Disposes Of Cipla's Appeal Against Roche As Withdrawn. 2017. www.livelaw.in/patent-battle-lung-cancer-drug-sc-disposes-ciplas-appeal-roche-withdrawn/ (accessed Feb 9, 2018).

South Africa Department of Health. Medicines and related substances act, 1965 (act 101 of 1965): schedules.

http://www.mccza.com/documents/f6bf8a532016_Consolidatedschedules2008200920112012201320142015Marc h_May2016(includingprescribers).pdf (accessed March 23, 2018).

36 Zhao D, Chen X, Qin N, *et al.* The prognostic role of EGFR-TKIs for patients with advanced non-small cell lung cancer. *Sci Rep* 2017; 7: 40374.

37 Shaw AT, Yeap BY, Solomon BJ, *et al.* Effect of crizotinib on overall survival in patients with advanced nonsmall-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. *Lancet Oncol* 2011; 12: 1004– 12.

Adeloye D, David RA, Aderemi AV, *et al.* An Estimate of the Incidence of Prostate Cancer in Africa: A Systematic Review and Meta-Analysis. *PLoS One* 2016; 11: e0153496.

 Chen R, Ren S, Yiu MK, *et al.* Prostate cancer in Asia: A collaborative report. *Asian J Urol* 2014; 1: 15–29.
 James N. Clinical Features and Diagnosis of Prostate Cancer. In: Primer on Prostate Cancer. Tarporley: Springer Healthcare Ltd., 2014: 5–15.

Bowa K. An overview of the diagnosis and management of prostate cancer in Nigeria: Experience from a north-central state of Nigeria. *Ann Afr Med* 2010; 9: 111.

42 Harvey N, Adeyoju A, Brough R. Prostate Cancer in Sub-Saharan Africa: Diagnosis and Management. In: Cancer in Sub-Saharan Africa. Cham: Springer International Publishing, 2017: 95–107.

43 Jalloh M, Friebel TM, Sira Thiam F, *et al.* Evaluation of 4,672 routine prostate biopsies performed in six African countries. *J Africain du Cancer / African J Cancer* 2013; 5: 144–54.

44 Parker C, Gillessen S, Heidenreich A, Horwich A. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; 26: v69–77.

James ND, de Bono JS, Spears MR, *et al.* Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. *N Engl J Med* 2017; : NEJMoa1702900.

46 Union for International Cancer Control. Metastatic prostate cancer. 2014.

http://www.who.int/selection_medicines/committees/expert/20/applications/MetastaticProstate.pdf?ua=1 (accessed Nov 2, 2017).

47 World Health Organization. The Selection and Use of Essential Medicines: Report of the WHO Expert Committee. 2015. http://apps.who.int/iris/bitstream/10665/189763/1/9789241209946_eng.pdf?ua=1 (accessed Oct 17, 2017).

48 European Society for Medical Oncology. eUpdate – Cancer of the Prostate Treatment Recommendations. 2017. http://www.esmo.org/Guidelines/Genitourinary-Cancers/Cancer-of-the-Prostate/eUpdate-Treatment-Recommendation (accessed Feb 7, 2018).

49 Beer TM, Armstrong AJ, Rathkopf DE, *et al.* Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. *N Engl J Med* 2014; 371: 424–33.

50 Williams S, Chiong E, Lojanapiwat B, Umbas R, Akaza H. Management of prostate cancer in Asia: resourcestratified guidelines from the Asian Oncology Summit 2013. *Lancet Oncol* 2013; 14: e524–34.

51 ClinicalTrials.gov. A Trial of Androgen Deprivation, Docetaxel, and Enzalutamide for Metastatic Prostate Cancer. https://clinicaltrials.gov/ct2/show/NCT03246347 (accessed April 5, 2018).

52 Morhason-Bello IO, Odedina F, Rebbeck TR, *et al.* Challenges and opportunities in cancer control in Africa: a perspective from the African Organisation for Research and Training in Cancer. *Lancet Oncol* 2013; 14: e142–51.

53 Drug In Focus: Abiraterone. 2016; published online Oct.

54 Kumar SK, Rajkumar V, Kyle RA, *et al.* Multiple myeloma. *Nat Rev Dis Prim* 2017; 3: 17046.

55 Moreau P, San Miguel J, Sonneveld P, *et al.* Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 2017; 28: iv52-iv61.

56 Kumar SK, Callander NS, Alsina M, *et al.* NCCN Guidelines Insights: Multiple Myeloma, Version 3.2018. *J Natl Compr Cancer Netw* 2018; 16: 11–20.

57 Facon T, Dimopoulos MA, Dispenzieri A, *et al.* Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. *Blood* 2018; 131: 301–10.

⁵⁸ Pulte D, Redaniel MT, Brenner H, Jansen L, Jeffreys M. Recent improvement in survival of patients with multiple myeloma: variation by ethnicity. *Leuk Lymphoma* 2014; 55: 1083–9.

59 Luo J, Gagne JJ, Landon J, Avorn J, Kesselheim AS. Comparative effectiveness and safety of thalidomide and lenalidomide in patients with multiple myeloma in the United States of America: A population-based cohort study. *Eur J Cancer* 2017; 70: 22–33.

60 Dimopoulos MA, Terpos E, Niesvizky R. How lenalidomide is changing the treatment of patients with multiple myeloma. *Crit Rev Oncol Hematol* 2013; 88: S23–35.

Durie BGM, Hoering A, Abidi MH, *et al.* Bortezomib with lenalidomide and dexamethasone versus
 lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate
 autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet* 2017; 389: 519–27.
 Agarwal G, Pradeep P V., Aggarwal V, Yip CH, Cheung PSY. Spectrum of breast cancer in Asian women. *World J Surg* 2007; 31: 1031–40.

Fan L, Strasser-Weippl K, Li J-J, et al. Breast cancer in China. Lancet Oncol 2014; 15: e279–89.

Jedy-Agba E, McCormack V, Adebamowo C, Dos-Santos-Silva I. Stage at diagnosis of breast cancer in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Glob Heal* 2016; 4: e923–35.

Iqbal J, Ginsburg O, Rochon PA, Sun P, Narod SA. Differences in Breast Cancer Stage at Diagnosis and Cancer-Specific Survival by Race and Ethnicity in the United States. *JAMA* 2015; 313: 165.

66 Loibl S, Gianni L. HER2-positive breast cancer. *Lancet* 2017; 389: 2415–29.

67 Slamon DJ, Clark GM, Wong SG, Levin WJ., Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science (80-)* 1987; 235: 177–82.

Vieira R, Biller G, Uemura G, Ruiz C, Curado M. Breast cancer screening in developing countries. *Clinics* 2017; 72: 244–53.

69 Cardoso F, Costa A, Senkus E, *et al.* 3rd ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). *Ann Oncol* 2016; : mdw544.

70 Senkus E, Kyriakides S, Ohno S, *et al.* Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; 26: v8–30.

Yip CH, Anderson B. The Breast Health Global Initiative: clinical practice guidelines for management of breast cancer in low- and middle-income countries. *Expert Rev Anticancer Ther* 2007; 7: 1095–104.

72 Cardoso F, Costa a., Norton L, *et al.* ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Ann Oncol* 2014; 25: 1871–88.

73 Kingham TP, Vanderpuye V, Casper C, *et al.* Treatment of cancer in sub-Saharan Africa. *Lancet Oncol* 2013; 14: 158–67.

Abdel-Wahab M, Bourque JM, Pynda Y, *et al.* Status of radiotherapy resources in Africa: An International Atomic Energy Agency analysis. *Lancet Oncol* 2013; 14. DOI:10.1016/S1470-2045(12)70532-6.

75 Gelband H, Jha P, Sankaranarayanan R, Horton S, editors. Disease Control Priorities, Third Edition (Volume 3): Cancer. The World Bank, 2015 DOI:10.1596/978-1-4648-0349-9.

76 Meara JG, Leather AJM, Hagander L, *et al.* Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. *Lancet* 2015; 386: 569–624.

77 Generics and Biosimilars Initiative. Biosimilars of trastuzumab. 2017.

http://www.gabionline.net/Biosimilars/General/Biosimilars-of-trastuzumab (accessed Feb 21, 2018).

Fix the Patent Laws Campaign. Patent barriers to medicine access in South Africa: A case for patent law reform. 2016. http://www.fixthepatentlaws.org/wp-content/uploads/2016/09/MSF-FTPL-report-FINAL-VERSION.pdf (accessed Feb 21, 2018).

79 Press bureau. Emcure to make, market Roche products. Hindu Bus. Line. ; published online Sept.

https://www.thehindubusinessline.com/companies/Emcure-to-make-market-Roche-products/article20497435.ece. 80 Medicines Patent Pool. MedsPaL. http://www.medspal.org/ (accessed Feb 28, 2018).

81 Blackstone EA, Fuhr JP. The Economics of Biosimilars. *Am Heal Drug Benefits* 2013; 6: 469–78.

82 Chopra R, Lopes G. Improving Access to Cancer Treatments: The Role of Biosimilars. *J Glob Oncol* 2017; 3: 596–610.

83 World Health Organization. Guidelines on evaluation of similar biotherapeutic products (SBPs). http://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf (accessed Feb 21, 2018).

Rader RA. Biosimilars Pipeline Analysis: Many Products, More Competition Coming. Bioprocess Online. 2016. https://www.bioprocessonline.com/doc/biosimilars-pipeline-analysis-many-products-more-competition-coming-0001 (accessed Feb 21, 2018).

Pulakkat H. Make in India: Can India be a hub for the \$200 billion worth biosimilars opportunity. Econ. Times. 2016; published online Feb 18.

https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/make-in-india-can-india-be-a-hub-for-the-200-billion-worth-biosimilars-opportunity/articleshow/51032054.cms.

86 RAND Corporation. The Cost Savings Potential of Biosimilar Drugs in the United States. 2014. https://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf (accessed Sept 25, 2017).

Pharmaceutical Product Development LLC. Developing Biosimilars in Emerging Markets: Regulatory and
 Clinical Considerations. 2013. http://healthtrustpg.com/biosimilars/pdf/ppd.pdf (accessed Feb 21, 2018).
 Welch AR, 6 Tips For Navigating Emerging Market Biosimilar Regulations. Biosimilar Dev. 2016.

88 Welch AR. 6 Tips For Navigating Emerging Market Biosimilar Regulations. Biosimilar Dev. 2016. https://www.biosimilardevelopment.com/doc/tips-for-navigating-emerging-market-biosimilar-regulations-0001 (accessed Feb 21, 2018).

89 Rader RA. Biosimilar Markets and Regulation: Which Countries Are Going All In? Bioprocess Int. 2017. http://www.bioprocessintl.com/manufacturing/biosimilars/biosimilar-markets-regulation-countries-going/ (accessed Feb 21, 2018).

90 World Health Organization. WHO to begin pilot prequalification of biosimilars for cancer treatment. 2017.

91 Hurley P, Boren J, Congiatu C. Challenges in Global Biosimilar Development: A Regulatory Perspective. *Contract Pharma* 2015; published online June.

92 Welch AR. What To Know About Emerging Market Biosimilar Pathways. Biosimilar Dev. 2016.

https://www.biosimilardevelopment.com/doc/what-to-know-about-emerging-market-biosimilar-pathways-0001 (accessed Feb 21, 2018).

93 Welch AR. The Thai FDA's Approach To Biologics And Biosimilars. 2017.

https://www.biosimilardevelopment.com/doc/the-thai-fda-s-approach-to-biologics-and-biosimilars-0001 (accessed Feb 21, 2018).

94 Welch AR. A Deep Dive Into Brazil's Biosimilar PDPs. Biosimilar Dev. 2017.

https://www.biosimilardevelopment.com/doc/a-deep-dive-into-brazil-s-biosimilar-pdps-0001 (accessed Feb 21, 2018).

95 Cooperberg MR, Broering JM, Carroll PR. Time Trends and Local Variation in Primary Treatment of Localized Prostate Cancer. *J Clin Oncol* 2010; 28: 1117–23.

Slamon DJ, Leyland-Jones B, Shak S, *et al.* Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2. *N Engl J Med* 2001; 344: 783–92.

7 New antibiotics to combat antimicrobial resistance

7.1 Background

Antibiotics comprise a significant part of the WHO Essential Medicines List (EML). The EML includes 61 antibiotic medicines, antibiotic groups, or combinations. Of these, 20 are TB treatments. None of the antibiotics currently listed, outside of TB, are patented. The absence of patented antibiotics on the EML is indicative of systematic underinvestment in the discovery of new antimicrobials over the last several decades.^{1–6} This underinvestment, in turn, has contributed to growing antimicrobial resistance (AMR), in which the medicines that are currently available are less and less effective in treating infections.

The rising threat of AMR has received greater attention in recent years, with discussions at the United Nations,⁷ World Health Assembly,⁸ the G7,⁹ the G20,¹⁰ and elsewhere¹¹ highlighting the gravity of the situation. The international community has stressed the imperative of increased research and development (R&D) of new antimicrobials, as well as fostering better stewardship in order to preserve their effectiveness. Novel initiatives, such as the Global Antibiotic Research and Development Partnership (GARDP) and CARB-X, have been established to facilitate the development of new antimicrobials against priority pathogens, and other incentive mechanisms have been proposed to stimulate greater R&D in antimicrobials, for example, large end-stage prizes.^{1,3,12}

The increased focus on the need to respond to rising antimicrobial resistance will likely translate to a growing pipeline of new drug candidates to target priority pathogens in the coming years. And, given the clear public health need for these drugs, antimicrobials that effectively target drug-resistant microbes will likely be added to the WHO EML soon after regulatory approval. This chapter will focus on the potential role that the MPP could play in relation to these drugs, with a particular focus on how the MPP could contribute to both affordable access and good stewardship of new antimicrobials.

7.2 The challenges of development, access and stewardship in AMR

Although precise data are unavailable, it is conservatively estimated that 700,000 people die every year from drug-resistant infections, and this number is estimated to reach 10 million by 2050 (Figure 1).¹ These figures include the estimated number of deaths from drug-resistant strains of HIV and TB, but also includes projected deaths from other drug-resistant forms of bacteria.



Figure 1. Deaths attributable to antimicrobial, compared to other causes.

Figure reproduced from the O'Neill AMR Review.¹

In an effort to guide and promote R&D to combat AMR, the WHO published a priority pathogen list (PPL) in 2017, highlighting those bacteria (apart from drug-resistant TB, which remains the largest global killer in AMR) for which there is an urgent need for new treatments (Table 1).¹³ All three critical priority pathogens in the PPL, and seven of the nine listed as critical or high priority are Gram-negative bacteria. The WHO Expert Panel consequently noted that "future R&D strategies should particularly focus on the discovery and development of new antibiotics specifically active against multidrug- and extensively drug-resistant Gram-negative bacteria."¹³ At the same time, the panel noted that antibiotic stewardship programmes are urgently required.¹³

Antibiotic	Key antibiotic to which there is resistance	
Critical priority		
Acinetobacter baumanii	Carbapenem	
Pseudomonas aeruginosa	Carbapenem	
Enterobacteriaceae	Carbapenem, 3 rd -generation cephalosporins	
High priority		
Enterococcus faecium	Vancomycin,	
Staphylococcus aureus	Vancomycin, methicillin	
Helicobacter pylori	Clarithromycin	
Campylobacter species	Fluoroquinolones	
Salmonella species	Fluoroquinolones	
Neisseria gonorrhoeae	3 rd -generation cephalosporins, fluoroquinolones	

Table 1. WHO priority pathogen list.¹³

Medium priority			
Streptococcus pneumoniae	Penicillins*		
Haemophilus influenza	Ampicillin		
Shigella species Fluoroquinolone			
*non-susceptible.			
Adopted from the WHO Antibacterial agents in clinical development report.14			

Following the publication of the PPL, the WHO published a pipeline report that analysed antibiotics in clinical development in terms of their expected activity against priority pathogens and their level of innovativeness^V.¹⁴ Although the report identified a number of potentially valuable agents, the analysis concluded that the current pipeline was insufficient to meet the rising challenge of AMR. For example, given an estimated phase 1 success rate of 14%,¹⁴ only one or two of the ten anti-Gram-negative compounds in phase 1 are likely to eventually be approved.

In an effort to facilitate antibiotic stewardship efforts, the 2017 EML adopted a new categorization system for antibiotics.¹⁵ The new classification categorises antibiotics into three groups – *Access, Watch* and *Reserve* – to balance the need for broad access to some antibiotics against the need to preserve other classes of antibiotics as a last resort for highly resistant cases. The *Access* category includes antibiotics that are the first- or second-choice treatment for common infectious syndromes, for which the aim should be to have affordable and quality-assured versions widely available. The *Watch* category includes antibiotic classes that are considered to be especially susceptible to the development of resistance, but which are still important in some indications (the *Access* and *Watch* categories have some overlap). The third, *Reserve* category includes last-resort antibiotics and antibiotic classes that are to be used when alternatives have failed or would be inadequate. Newly developed antibiotics may automatically fall under the *Watch* or *Reserve* categories due to their class – for example, pipeline fluoroquinolones (a class included in the *Watch* category), or pipeline oxazolidinones (a class included in the *Reserve* category).

While sound stewardship of antimicrobials is critically important, access to existing antimicrobials remains limited in low- and middle-income countries (LMICs). An estimated 5.7 million deaths occur annually from infections that would in most cases have been treatable with existing antimicrobials if they were accessible (Table 2).¹⁶

^v In the WHO report on the antibiotic pipeline, innovativeness is described in terms of the medicine not having cross-resistance to existing antibiotics, being of a new chemical class, having a new target, or having a new mechanism of action.¹⁴

able 2. Global deaths due to infections amenable to treatment with existing					
antimicrobials (thousands).					
Lower respiratory tract infections*	2,466				
Tash an and a size	1 200				

Lower respiratory tract infections*	2,466
Tuberculosis	1,290
Malaria	855
Neonatal infections and sepsis	366
Meningitis	304
Gastrointestinal infections*	221
Sexually transmitted infections*	142
Maternal infections and sepsis	24
Total:	5,668
*Excludes cases due to viral causes.	
Table from Daulaire et al. ¹⁶	

Thus, while there is a need to develop new antimicrobials to treat drug-resistant infections and ensure that they are used appropriately, there is also a need to expand access to existing and recently-approved antimicrobials, particularly in LMICs. As Daulaire et al note: "Ensuring universal and appropriate access to essential medicines is a necessary precondition to any policy on restricting the use of antimicrobials in low-income settings; absent this, any restriction is likely to be ethically and politically challenged, or simply ignored."¹⁶ This is the 'policy tripod' of aims in tackling antimicrobial resistance (Figure 1): improving access to existing antimicrobials, boosting the development of new antimicrobials, and developing effective stewardship practices to protect existing antimicrobials from becoming ineffective.¹⁷

Figure 2. The 'policy tripod' for tackling antimicrobial resistance.



107

7.3 The potential role of the MPP in contributing to access and stewardship for new antimicrobials

The MPP has previously worked on antimicrobial resistance in the context of HIV and TB. In HIV, the MPP holds numerous licences on second-line antiretrovirals – i.e. antiretrovirals used in patients whose HIV infection has developed resistance to first-line treatment – as well as products such as dolutegravir, which is recommended by the WHO for first-line use in countries with high levels of pre-treatment resistance to one class of medicines.¹⁹ In TB, the licence signed by MPP and the Johns Hopkins University on sutezolid includes provisions to ensure that commercialization of the product follows proper stewardship.

We consulted with a number of key stakeholders in the area of AMR (Table 2). This list supplements the large number of stakeholders that the MPP consulted during the preparation of its TB Stewardship Report,²⁰ which examined how MPP licences could contribute to both affordable access and responsible stewardship for new TB drugs.

Table 2. Stakeholders consulted specifically in the area of AMR, as part of this feasibility study.

Manica Balesagaram, Global Antibiotic Research & Development Partnership (GARDP) Peter Beyer and Nicola Magrini, WHO Kevin Outterson, CARB-X Tim Jinks and Jeremy Knox, The Wellcome Trust Anna Zorzet and Helle Aagaard, ReAct Sanne Fournier-Wendes, Unitaid Ursula Theuretzbacher, Center for Anti-Infective Agents Gabrielle Breugelmans and Adrian Alonso Ruiz, Access to Medicines Index/AMR Benchmark Numerous other civil society organisations and originator and generic pharmaceutical companies with whom semi-structured interviews were conducted in the course of the overall study (see *Acknowledgements*).

The stakeholder feedback echoed much of what was gathered during the preparation of the TB Stewardship Report: that there was a potential role for MPP, through its licences, to play in promoting good stewardship practices while enabling affordable access to new antimicrobials. For example, a number of stakeholders pointed out that many of the developers of pipeline antimicrobials identified in the WHO Pipeline Report were smaller biotechnology companies, with little to no presence in LMICs and no current plans for stewardship or access in these countries. Indeed, the AMR Benchmark published recently by the Access to Medicine Foundation found that only two of 28 antibiotics in late stages of clinical development had any access or stewardship plans in place.²¹

Stakeholder feedback also indicated that the MPP's model would need to be adapted to address the specific challenges in antimicrobial resistance. In antibiotics, for instance, the MPP should not aim to make new antibiotics broadly available from multiple manufacturers. Rather, the MPP should target just products of public health priority, particularly those for which there are limited or no existing alternatives or that significantly improve on existing options. And, rather than broadly licensing to multiple manufacturers to promote wide availability and generic competition, the MPP would
need to limit the number of licensees to ensure that the products are made affordably available to those who need them while preventing overuse.

7.3.1 Role of the MPP in relation to initiatives to stimulate antibiotic R&D

Recent high-level reports have recommended that the MPP could play an important role in new mechanisms for financing antimicrobial R&D.^{1,3,12} The Review on Antimicrobial Resistance Chaired by Jim O'Neill recommended that incentive mechanisms such as market entry rewards should be linked to requirements to ensure access and stewardship – for example, by requiring recipients of payouts to license their discovery to the MPP under appropriate provisions.¹ Analyses from Chatham House, a prominent international affairs think tank based in the United Kingdom and DRIVE-AB, a consortium supported by the European Innovative Medicines Initiative, made similar recommendations.^{3,12}

CARB-X is an initiative to stimulate the early-stage pipeline for antimicrobials targeting priority pathogens, established by two divisions of the US Department of Health and Human Services,^W and funded by one of these divisions along with the Wellcome Trust. CARB-X indicated that it would contractually require its grantees to develop an access and stewardship plan for its drug candidates that advance through the pipeline and viewed licensing to the MPP as one key option for grantees to fulfil this requirement. Likewise, GARDP envisioned a role for MPP in AMR, both as a potential in-licensor of promising candidate compounds for further development, as well as a licensee of products successfully developed by GARDP.

7.3.2 Role of the MPP in relation to good antimicrobial stewardship

An access and stewardship licensing framework for the AMR context would build upon the substantial work that the MPP has already completed in exploring how stewardship-related practices could be integrated into its licensing model.²⁰ The development of such a framework would begin with the recognition that many of the most important measures for ensuring proper stewardship of new antimicrobials lie outside of the licensing context; for example, strengthening regulatory systems in LMICs, expanding the availability of proper diagnostics, and developing and implementing sound treatment guidelines will be key to achieving good stewardship but cannot be addressed in a licence agreement with a manufacturer. However, interviews with stakeholders indicated that the MPP could nevertheless make an important contribution by addressing certain aspects of stewardship that can be influenced through licensing agreements. Potential areas in which antimicrobial stewardship could be promoted through MPP licensing are explored further below.

^w These two divisions are the Biomedical Advanced Research and Development Authority (BARDA) and the National Institute of Allergy and Infectious Diseases (NIAID).

7.3.2.1 Quality standards

Ensuring that a drug meets quality standards, that it is safe and effective, contains the correct amount of active ingredient, has a stable shelf-life, and is manufactured in accordance with current Good Manufacturing Practices (cGMP) – is a central pillar of ensuring responsible antimicrobial stewardship.²⁴ In its licences for HIV and HCV products, the MPP requires that all licensees manufacture the product in a manner consistent with WHO pre-qualification (PQ) or stringent regulatory authority (SRA) standards, or approval through an Expert Review Panel (ERP).^X This is consistent with the standards used by the the Global Fund, Unitaid and the Global Drug Facility (GDF). The MPP would continue to implement strict quality standards in any licences for other antimicrobials.

7.3.2.2 Release of active pharmaceutical ingredients into the environment

The O'Neill Review on AMR observed that improper treatment of wastewater by manufacturers of antibacterial active pharmaceutical ingredients (APIs) and the resultant release of the APIs into the local environment can act as a "driver for the development of drug resistance, creating environmental 'reservoirs' of antibiotic-resistant bacteria."¹ The AMR Industry Alliance recognised the importance of reducing the environmental impact from the production of antibiotics and committed to establish targets for limiting discharge by 2020.²⁵ The AMR Benchmark, in turn, is tracking the pharmaceutical industry's performance with regard to such commitments.²¹ MPP licences in antimicrobials could seek similar commitments from its licensees regarding environmental discharge and incorporate rigorous standards for acceptable levels of discharge once these are developed in the coming years.

7.3.2.3 Marketing and promotional practices

Concerns have been raised that aggressive sales promotion could result in overuse of an antibiotic.¹² In particular, it would be appropriate to have strict controls on the sublicensee's promotion and marketing for antibiotics that have been (or are likely to be) classified as "Watch" or "Reserve" in the WHO EML. In order to ensure that MPP sublicensees do not engage in inappropriate promotional activities, the MPP could, as part of its Expression of Interest (EOI) process, ask potential sublicensees to submit marketing plans that are in line, for example, with the recommendations in the WHO's Ethical Criteria for Medicinal Drug Promotion, or other relevant standards, and in line with national laws and regulations. Such plans could then become binding obligations as part of the licensing agreement. Prohibitions on over-promotion may need to be coupled with an incentive mechanism that would delink the licensee's revenue from the volume of sales, such as, for example, advance purchase commitments.¹² This sort of

^x For example, the quality provision in the MPP-ViiV Form Sublicense for dolutegravir, in section 4.2, provides as follows: *"Licensee agrees that it will manufacture Raw Materials and Product in a manner consistent with (i) World Health Organization ("WHO") pre-qualification standards; or (ii) the standards of any Stringent Regulatory Authority ("SRA"), defined as regulatory authorities which are members, observers or associates of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, as may be updated from time to time. Where such approvals are not yet available, the Licensee will obtain temporary approval through a WHO Expert Review Panel, as appropriate and if applicable." A similar provision could be included in MPP licences covering other antimicrobials.*

delinkage mechanism, of course, would have to be implemented by or in partnership with donors, governments, or procurement agencies capable of financing such a mechanism.

7.3.2.4 Selection of licensees

For its HIV and HCV licences, the MPP selects licensees through its Expression of Interest (EoI) system, which allows the organisation to assess a potential licensee's ability to promptly bring a quality-assured product to market at an affordable price in the countries included in the licence.^Y This existing framework can be leveraged to require interested licensees to submit additional information that is relevant to good stewardship, such as marketing plans (as discussed above) and manufacturing environmental controls.

Unlike with MPP-licensed products with high sales volumes, such as medicines used in first-line HIV treatment where the MPP seeks a large number of licensees in order to generate market competition, in antimicrobials the MPP may need to limit the number of licensees in order to better control the medicines' use in line with good stewardship. Under this practice, because the number of licensees – and thus competition – would be limited, there may be a need for additional measures to ensure that the end product is made available at an affordable price. This could be done, for example, by specifying a 'cost-plus' formula that establishes the maximum allowable price based on the manufacturer's production costs, while ensuring a sustainable profit margin for the licensee.

7.3.2.5 Definition of permissible buyers

If guidelines such as the WHO EML recommend that an antimicrobial licensed to the MPP is used only in restricted settings (e.g. only in hospitals), it may be appropriate for the MPP to define in sublicence agreements the types of entities to whom sub-licensees may sell the product. This would be in line with the AMR Industry Alliance Roadmap, in which the signatories have committed to "collaborate with governments, their agencies and other stakeholders to reduce uncontrolled antibiotic purchase, such as via over-the-counter and non-prescription internet sales".²⁵ Permissible buyers could be limited to, for example, public-sector hospitals, tertiary care centres, or certain NGOs. Specific restrictions included in sublicences would need to be sensitive to factors such as a product's recommended scope of use or the level of public provision of healthcare in a given country.

7.3.2.6 Limitations on irrational combinations and use

The inappropriate use of antimicrobials, including in irrational combinations, can contribute to the development of resistance. Recently, for example, an alarming proliferation of irrational fixed-dose combinations of antibiotics has been reported in India.²⁶ New antimicrobials may also have potential applications in veterinary use, but such use may not be conducive to good stewardship. In close consultation with the

^Y See <u>http://www.medicinespatentpool.org/expressions-of-interest/</u>

WHO and other experts, MPP licences could define permissible uses and permissible combinations.

7.4 Conclusion

As recognised in the MPP's earlier TB Stewardship Report,²⁰ the use of patent licences is an imperfect tool for enforcing stewardship obligations. Such obligations could only be enforced on drugs that are under patent and as long as patents are in force. Moreover, such obligations would not be binding on non-licensees based in jurisdictions in which the product is not patented. However, stewardship-related activities at the manufacturing, commercialisation, and distribution levels could make an important contribution towards good stewardship, and, to the extent that a patent licence can place binding requirements for stewardship, it would seem counterproductive not to use this tool.

Within the aforementioned constraints, the MPP is uniquely positioned to implement and enforce stewardship obligations. The MPP is already implementing, monitoring, and enforcing stewardship-related obligations in its current licences with drug manufacturers in the fields of HIV, hepatitis C and TB. These practices include the careful evaluation and selection of licensees through its EoI system, strict quality requirements, and provisions for pharmacovigilance. Through these binding requirements and close monitoring of licensees' compliance, the MPP has demonstrated success in encouraging its licensees to adhere to such obligations and has sought remedies up to and including termination of licences for those who fail to perform. The existing licence management infrastructure within the MPP could readily be adapted to encompass a broader set of stewardship-related obligations along the lines set forth in this chapter.

The MPP's work in the field of AMR could be further strengthened if the MPP were to partner with existing initiatives, such as the Access to Medicine Foundation's AMR Benchmark. In HIV, the Access to Medicine Index (ATMI) has recognised that MPPnegotiated licences set the standard for public health-oriented licensing. Licensing to the MPP could similarly be included as requirements in milestone prizes offered by CARB-X and other innovative R&D financing mechanisms. Indeed, should a large endstage prize for the development of antimicrobials eventually be established, several stakeholders felt that the MPP could play an important role as the mechanism to ensure equitable access and responsible stewardship, particularly in LMICs, by manufacturers for any new antimicrobial that is rewarded an end-stage prize.

7.5 References

1 The Review on Antimicrobial Resistance Chaired by Jim O'Neill. Tackling drug-resistant infections globally: final report and recommendations. 2016. https://amr-review.org/sites/default/files/160525_Final paper_with cover.pdf (accessed Feb 18, 2018).

2 Renwick MJ, Simpkin V, Mossialos E. International and European Initiatives Targeting Innovation in Antibiotic Drug Discovery and Development: The Need for a One Health – One Europe – One World Framework. 2016. http://static.diariomedico.com/docs/2016/02/12/2016-report-on-antibiotic-rd-initiaitives-1.pdf (accessed March 26, 2018).

3 DRIVE-AB. Revitalizing the antibiotic pipeline: Stimulating innovation while driving sustainable use and global access. 2018. http://drive-ab.eu/wp-content/uploads/2018/01/DRIVE-AB-Final-Report-Jan2018.pdf (accessed Feb 19, 2018).

4 Silver LL. Challenges of Antibacterial Discovery. Clin Microbiol Rev 2011; 24: 71-109.

Coates AR, Halls G, Hu Y. Novel classes of antibiotics or more of the same? Br J Pharmacol 2011; 163: 184-5 94.

Outterson K, Gopinathan U, Clift C, So AD, Morel CM, Røttingen J-A. Delinking Investment in Antibiotic 6 Research and Development from Sales Revenues: The Challenges of Transforming a Promising Idea into Reality. PLOS *Med* 2016; **13**: e1002043.

7 United Nations General Assembly. Political Declaration of the high-level meeting of the General Assembly on antimicrobial resistance. 2016.

http://www.un.org/ga/search/view_doc.asp?symbol=A/71/L.2&referer=/english/&Lang=E (accessed March 12, 2018).

8 Sixty-Eighth World Health Assembly. WHA68.7 Global action plan on antimicrobial resistance. 2015. http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R7-en.pdf?ua=1 (accessed May 26, 2015).

G7 Health Ministers. G7 Milan Health Ministers' Communiqué: 'United towards Global Health: common 9 strategies for common challenges'. 2017.

http://www.g7italy.it/sites/default/files/documents/FINAL_G7_Health_Communique_Milan_2017_0.pdf (accessed March 26, 2018).

Berlin Declaration of the G20 Health Ministers. 2017. 10

https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/G/G20-

Gesundheitsministertreffen/G20_Health_Ministers_Declaration_engl.pdf (accessed March 12, 2018). 11

AMR Industry Alliance Secretariat. AMR Industry Declaration. 2016.

https://www.amrindustryalliance.org/wp-content/uploads/2017/12/AMR-Industry-Declaration.pdf (accessed March 26, 2018).

Chatham House. Towards a New Global Business Model for Antibiotics Delinking Revenues from Sales: 12 Report from the Chatham House Working Group on New Antibiotic Business Models. 2015.

https://www.chathamhouse.org/sites/files/chathamhouse/field_field_document/20151009NewBusinessModelAnti bioticsCliftGopinathanMorelOuttersonRottingenSo.pdf (accessed Feb 15, 2018).

World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, 13 and development of new antibiotics. http://www.who.int/medicines/publications/WHO-PPL-

Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1 (accessed March 26, 2018). 14

World Health Organization. Antibacterial agents in clinical development. 2017. http://apps.who.int/iris/bitstream/handle/10665/258965/WHO-EMP-IAU-2017.11-eng.pdf?sequence=1 (accessed March 27, 2018).

15 WHO EML Expert Committee. Report of the WHO Expert Committeeon Selection and Use of Essential Medicines. WHO Tech. Rep. Ser. 2017.

http://www.who.int/medicines/publications/essentialmedicines/EML_2017_EC21_Unedited_Full_Report.pdf?ua=1 (accessed Sept 14, 2017).

Daulaire N, Bang A, Tomson G, Kalyango JN, Cars O. Universal Access to Effective Antibiotics is Essential for 16 Tackling Antibiotic Resistance. J Law, Med Ethics 2015; 43: 17-21.

17 Hoffman SJ, Outterson K. What will it take to address the global threat of antibiotic resistance? J Law, Med Ethics 2015: 43: 363-8.

Bever P. Options for a global development and stewardship framework to combat AMR. In: WHO 18 consultation of Member States and relevant partners. Geneva, 2016.

http://www.who.int/phi/news/amr_ppt_consultation2016%0A-%0A02%0A-%0A29.pdf?ua=1.

World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and 19 preventing HIV infection, 2nd edn. WHO Press, 2016

http://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf;jsessionid=939637CE96EB31 0F2D06E5FCBEC2FF95?sequence=1.

20 The Medicines Patent Pool Foundation. TB Stewardship Report. 2016.

https://medicinespatentpool.org/uploads/2017/07/STEWARDSHIP-REPORT_FINAL-1.pdf (accessed March 8, 2018).

21 Access To Medicine Foundation. Antimicrobial Resistance Benchmark. 2018.

https://amrbenchmark.org/wp-content/uploads/2018/03/Antimicrobial-Resistance-Benchmark-2018.pdf (accessed April 2, 2018).

Shields RK, Potoski BA, Haidar G, et al. Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-2.2 Avibactam Resistance Among Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections: Table 1. Clin Infect Dis 2016; 63: 1615-8.

23 Temkin E, Torre-Cisneros J, Beovic B, et al. Ceftazidime-avibactam as salvage therapy for infections caused by carbapenem-resistant organisms: a case series from the compassionate-use program. Antimicrob Agents Chemother 2016; : AAC.01964-16.

24 Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis 2013; 13: 1057-98.

25 Industry Roadmap for Progress on Combating Antimicrobial Resistance –September 2016. 2016.

26 McGettigan P, Roderick P, Kadam A, Pollock AM. Access, Watch, and Reserve antibiotics in India: challenges for WHO stewardship. Lancet Glob Heal 2017; 5: e1075-6.

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 firstline 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 HER2negative, 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

 $^{^{\}rm Z}$ 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.

8.9 References

1 World Health Organization. The Selection and Use of Essential Medicines: Report of the WHO Expert Committee. 2015. http://apps.who.int/iris/bitstream/10665/189763/1/9789241209946_eng.pdf?ua=1 (accessed Oct 17, 2017).

2 Lopez-Olivo MA, Amezaga Urruela M, McGahan L, Pollono EN, Suarez-Almazor ME. Rituximab for rheumatoid arthritis. *Cochrane Database Syst Rev* 2015; published online Jan 20.

DOI:10.1002/14651858.CD007356.pub2.

3 Bauer K, Rancea M, Roloff V, *et al.* Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia. *Cochrane Database Syst Rev* 2012; published online Nov 14. DOI:10.1002/14651858.CD008079.pub2.

4 Vidal L, Gafter-Gvili A, Leibovici L, Shpilberg O. Rituximab as maintenance therapy for patients with follicular lymphoma. *Cochrane Database Syst Rev* 2009; published online April 15.

DOI:10.1002/14651858.CD006552.pub2.

5 Pfreundschuh M, Trümper L, Österborg A, *et al.* CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MINT) Group. *Lancet Oncol* 2006; 7: 379–91.

National Cancer Institute. New Rituximab Formulation Approved for Some Lymphomas, Leukemia. 2017.
 https://www.cancer.gov/news-events/cancer-currents-blog/2017/fda-rituxan-hycela (accessed Feb 24, 2018).
 De Cock E, Kritikou P, Sandoval M, *et al.* Time Savings with Rituximab Subcutaneous Injection versus

Rituximab Intravenous Infusion: A Time and Motion Study in Eight Countries. *PLoS One* 2016; 11: e0157957. Medicines Patent Pool. MedsPaL, http://www.medspal.org/ (accessed Feb 28, 2018).

Medicines Patent Pool. MedsPaL. http://www.medspal.org/ (accessed Feb 28, 2018).
 Generics and Biosimilars Initiative. Biosimilars of rituximab. 2017.

http://www.gabionline.net/Biosimilars/General/Biosimilars-of-rituximab.

10 World Health Organization. Report of the WHO Expert Committee on the Selection and Use of Essential Medicines. 2013. http://apps.who.int/iris/bitstream/10665/112729/1/WHO_TRS_985_eng.pdf (accessed Jan 30, 2018).

11 Generics and Biosimilars Initiative. Biosimilars of bevacizumab. 2017.

http://gabionline.net/Biosimilars/General/Biosimilars-of-bevacizumab (accessed Feb 26, 2018).

12 Glenmark Pharmaceuticals Ltd. Glenmark Pharmaceuticals receives ANDA approval for Bendamustine Hydrochloride for Injection, 25 mg/vial and 100 mg/vial. 2016.

http://www.glenmarkpharma.com/sites/default/files/Glenmark Pharmaceuticals receives ANDA approval for Bendamustine Hydrochloride for Injection.pdf (accessed Feb 28, 2018).

13 World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis B infection. 2015. http://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf?sequence=1 (accessed April 25, 2018).

European Association for the Study of the Liver (EASL). EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; 67: 370–98.

15 World Health Organization. Fact sheet on hepatitis B. 2017.

http://www.who.int/mediacentre/factsheets/fs204/en/ (accessed April 4, 2018).

16 WHO EML Expert Committee. Report of the WHO Expert Committee on Selection and Use of Essential Medicines. WHO Tech. Rep. Ser. 2017.

http://www.who.int/medicines/publications/essentialmedicines/EML_2017_EC21_Unedited_Full_Report.pdf?ua=1 (accessed Sept 14, 2017).

17 Carlson Caspers Intellectual Property Law. Laboratoire HRA Pharma v. Teva Pharmaceuticals USA, Inc. http://www.carlsoncaspers.com/laboratoire-hra-pharma-v-teva-pharmaceuticals-usa-inc-ulipristal/ (accessed Feb 28, 2018).

18 Pfizer Ltd. Depot-medroxyprogesterone acetate (DMPA -SC) (Sayana ® Press): Application for Inclusion in the WHO Essential Medicines List. 2016.

http://www.who.int/selection_medicines/committees/expert/21/applications/s18_medroxyprogesterone_acetate_f orm.pdf (accessed Feb 26, 2018).

19 U.S. Food and Drug Administration. Patent and Exclusivity for: N021583. 2018.

https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=021583&Appl_type= N (accessed Feb 26, 2018).

20 Beall RF, Attaran A. Patent-based Analysis of the World Health Organization's 2013 Model List of Essential Medicines. 2016.

21 IFPMA Health Partnerships Directory. IMPLANON Access Initiative.

http://partnerships.ifpma.org/partnership/implanon-access-initiative (accessed Feb 28, 2018).

22 Mathieu C, Gillard P, Benhalima K. Insulin analogues in type 1 diabetes mellitus: getting better all the time. *Nat Rev Endocrinol* 2017; 13: 385–99.

23 Beran D, Ewen M, Laing R. Constraints and challenges in access to insulin: a global perspective. *Lancet Diabetes Endocrinol* 2016; 4: 275–85.

ACCISS/HAI. Insulin patent profile. 2016.

http://apps.who.int/medicinedocs/documents/s22481en/s22481en.pdf (accessed Oct 7, 2017).

Luo J, Kesselheim AS. Evolution of insulin patents and market exclusivities in the USA. *Lancet Diabetes Endocrinol* 2015; 3: 835–7.

26 Price WN, Rai AK. Are trade secrets delaying biosimilars? *Science (80-)* 2015; 348: 188–9.

27 Llano A, Fisher M, McKay G. Biosimilar insulin: the current landscape. *Pract Diabetes* 2017; 34: 51–4.

28 Beran D, Ewen M, Laing R. Access to insulin - Current Challenges & Constraints. 2015.

http://apps.who.int/medicinedocs/documents/s22269en/s22269en.pdf.

29 Beran D, Yudkin JS. Looking beyond the issue of access to insulin: What is needed for proper diabetes care in resource poor settings. *Diabetes Res Clin Pract* 2010; 88: 217–21.

30 Atun R, Davies JI, Gale EAM, *et al.* Diabetes in sub-Saharan Africa: from clinical care to health policy. *Lancet Diabetes Endocrinol* 2017; 5: 622–67.

31 Union for International Cancer Control. Bisphosphonate therapy. 2016.

http://www.who.int/selection_medicines/committees/expert/21/applications/s8_zoledronic_acid_add.pdf?ua=1 (accessed Feb 24, 2018).

Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res* 2006; 12: 6243s–9s.

33 Kyle R, Gertz M, Witzig TE, Lust JA. Review of 1027 Patients With Newly Diagnosed Multiple Myeloma. *Mayo Clin Proc* 2003; 78: 21–33.

Hortobagyi GN, Theriault RL, Porter L, *et al.* Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. *N Engl J Med* 1996; 335: 1785–91.

F S, DM G, R M. A randomized, placebo-controlled trial of zoledronic acid in patients with hormonerefractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002; 94: 1458–68.

Rosen LS, Gordon D, Tchekmedyian S et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial--the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003; : 3150.

Theriault RL, Lipton A, Hortobagyi GN, *et al.* Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: A randomized, placebo-controlled trial. *J Clin Oncol* 1999; 17: 846–54.
Brown JE, Coleman RE. Denosumab in patients with cancer — a surgical strike against the osteoclast. *Nat Rev Clin Oncol* 2012; 9: 110–8.

Health Canada. Xgeva. http://pr-rdb.hc-sc.gc.ca/pr-rdb/din.do?din=02368153&lang=fr (accessed Feb 28, 2018).

40 Vos T, Allen C, Arora M, *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1545–602.

41 Verslype C, Rosmorduc O, Rougier P. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; 23: vii41-vii48.

42 Burki TK. Indian government awards compulsory licence for sorafenib. *Lancet Oncol* 2012; 13: e146.

43 Sharma P, Allison JP. The future of immune checkpoint therapy. *Science (80-)* 2015; 348: 56–61.

44 Robert C, Long G V., Brady B, *et al.* Nivolumab in Previously Untreated Melanoma without BRAF Mutation. *N Engl J Med* 2015; 372: 320–30.

45 Reck M, Rodríguez-Abreu D, Robinson AG, *et al.* Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. *N Engl J Med* 2016; 375: 1823–33.

46 Turner NC, Ro J, André F, *et al.* Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer. *N Engl J Med* 2015; 373: 209–19.

47 World Health Organization. mhGAP Intervention Guide version 2.0. 2016.

http://apps.who.int/iris/bitstream/handle/10665/250239/9789241549790-eng.pdf?sequence=1 (accessed March 26, 2018).

48Vos T, Abajobir AA, Abate KH, *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1211–59.

49 Polman CH, O'Connor PW, Havrdova E, *et al.* A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. *N Engl J Med* 2006; 354: 899–910.

50 Lehrer-Graiwer J, Howard J, Hemmaway CJ, *et al.* GBT440, a Potent Anti-Sickling Hemoglobin Modifier Reduces Hemolysis, Improves Anemia and Nearly Eliminates Sickle Cells in Peripheral Blood of Patients with Sickle Cell Disease. *Blood* 2015; 126: 542 LP-542.

51 Montalembert M d. Management of sickle cell disease. *BMJ* 2008; 337: a1397–a1397.

52 Giudice LC. Endometriosis. *N Engl J Med* 2010; 362: 2389–98.

53 Soliman AM, Yang H, Du EX, Kelley C, Winkel C. The direct and indirect costs associated with endometriosis: a systematic literature review. *Hum Reprod* 2016; 31: 712–22.

Taylor HS, Giudice LC, Lessey BA, *et al.* Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. *N Engl J Med* 2017; 377: 28–40.

55 World Health Organization. WHO to develop Essential Diagnostics List. 2017.

http://www.who.int/medicines/news/2017/WHO_develop_essential_diagnostics_list/en/ (accessed Feb 20, 2018).

9 Discussion and conclusions

This chapter presents an overall discussion on the findings of the feasibility study. We begin by discussing public health considerations, followed by market considerations and, finally, outline some strategic considerations. The discussion draws from the preceding chapters as well as from consultations with multiple stakeholders. We then provide general conclusions for the study.

9.1 Public health considerations

Some of the therapeutic areas analysed in the feasibility study represent a large and growing disease burden in low- and middle-income countries (LMICs). For example, the prevalence of diabetes in the population is estimated to be over 7% in all income categories and is rapidly rising. In such areas, even small improvements in treatment access could help millions, improving the quality of care and reducing the number of diabetes-related complications such as heart attacks and stroke. In other cases, where the disease in question is not as prevalent, the medicines discussed represent important treatments for patients that may otherwise have few alternatives, such as in the case of chronic myeloid leukaemia.

Improving standards of care in LMICs can have a significant impact on public health. MPP licences could enable access to standard-of-care treatment for people in countries where it is currently unavailable or accessible only to a few. In the field of HIV, MPP licences have contributed to improving the standard of care by substantially shortening the time from the approval of new improved medicines to their availability at affordable prices 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 reducing mortality.

"Making medicines affordable changes everything."^{AA} Enabling access to affordable essential medicines can have positive effects on other parts of health systems that are necessary for universal health coverage. Several stakeholders mentioned ethical dilemmas concerning screening for certain cancers and investing in diagnostic infrastructure if there is little or no affordable treatment available to patients in the event of a positive test. Some specific examples are mentioned throughout the study. The case of hepatitis C was also often mentioned in this regard, in which significant reductions in prices for new treatments allowed some countries to develop national strategies and begin to scale up screening, diagnosis, and treatment.

Increased access to NCD treatments would contribute to reducing health system costs and catastrophic health expenditures for patients. Globally, about 150 million people suffer catastrophic health expenditures every year.¹ The majority of health expenditure, particularly in relation to NCDs, is out-of-pocket in many LMICs, of which a substantial proportion is expenditure on medicines.² ³ Expanded access to affordable essential medicines could reduce costs to health systems, as well as decrease

AA A comment made by several key stakeholders in discussions and interviews.

catastrophic health expenditures by lowering direct and indirect treatment costs to patients. Lower treatment costs could in some cases facilitate the inclusion of treatments in public health programmes or reimbursement schemes.

The MPP could play a role in tackling what is considered by many to be one of the most pressing challenges in global health today, that of increasing resistance to antimicrobials.^{4,5} Recent high-level reports have concluded that overcoming the growing threat of widespread antimicrobial resistance will require the development of new antimicrobials, along with strategies for enabling access while ensuring proper stewardship and rational use to prevent the development of resistance.⁵⁻⁷ Patent pooling through the MPP for new antibiotics that treat priority pathogens has been identified as one way to contribute to addressing the access-innovation-stewardship 'tripod'.⁸

Other barriers to treatment access may limit MPP impact. The 2011 UN High-Level Meeting on NCDs noted some of the main challenges faced by LMICs in the area of NCDs: a lack of awareness and data, the unprecedented healthcare needs associated with a rising epidemic of NCDs, the link between economic inequality and NCDs, and the need for strengthening of health systems, infrastructure, and human resources.^{9,10} Further, even at affordable prices, and with generics on the market, many essential medicines for NCDs are not consistently available or accessible in some LMICs, highlighting the multitude of factors that need to be addressed to ensure sustainable access.¹¹ In certain therapeutic areas (e.g. certain cancers), medicines are only one component of a comprehensive package of care, which can include, for example, surgery, radiotherapy, and palliative care, requiring specialized healthcare workers and infrastructure. The increasing political focus on NCDs and universal health coverage may contribute to mitigating some of these challenges. In many regions, governments as well as global health actors are either launching new programmes or strengthening existing programmes to work on access to care in NCDs. Significant efforts from governments, service delivery organisations, and technical organisations would be important for MPP licences to translate in increased access on the ground, for example, by supporting the uptake of generic products enabled through the licences. Partnering with such organizations may be an important part of an MPP strategy in relation to NCDs.

Availability of diagnostic equipment, laboratories, and specialists is a major challenge in some areas. The availability of certain diagnostics is a prerequisite for the use of some of the medicines with potential for MPP licensing. Examples of such medicines include many of the cancer treatments discussed in the case studies, which require identification of tumour receptor positivity before the medicines can be used. As argued above, the MPP's work in these disease areas could complement increased screening efforts and investment in diagnostic infrastructure. However, for certain other therapeutic areas, such as atrial fibrillation or diabetes, diagnosis may not be as technologically challenging. For these areas, local experts and WHO surveys have confirmed that screening and diagnostic capacity is generally available in many LMICs.¹¹

9.2 Market-based considerations

For many of the medicines analysed in this study, the current volume of sales for originator products is limited in many LMICs. National background papers

commissioned to inform the feasibility study, as well as published data, suggest that many of the medicines analysed were unavailable in the public sector in focus countries and were either completely unavailable or affordable only to a few in the private market. Commercial profits in many of the countries in past MPP licences are thus likely to be negligible. MPP licensing could be a strategy that would contribute to making patented essential medicines more widely available from quality-assured suppliers in such countries, while compensating originator companies through reasonable royalty rates. MPP licensing may represent a more sustainable strategy for enabling access to affordable essential medicines than the donation schemes or discounted prices that are currently in place for some of the treatments analysed in this feasibility study.

There is interest from manufacturers in developing generic versions of many of the medicines analysed in the case studies for supply in LMICs. Interviews with generics manufacturers, review of companies' websites, and filings with the US FDA suggest that numerous companies are already developing, or are interested in developing, generic versions of many of the medicines analysed for supply in LMICs. In addition, based on cost-of-goods analysis and generic price projections, we expect that most medicines could be manufactured at relatively low cost (biologics may be an important exception).

With the exception of HIV, tuberculosis, and malaria, there are no international mechanisms to fund the procurement of medicines for use in resource-limited settings. For the most part, NCD treatments are funded with domestic resources and, in some cases, out-of-pocket payments.^{12,13} Multiple stakeholders raised this as a concern and a likely limitation on uptake of new treatments. However, there is growing political will for scaling up NCD treatment, including through the universal health coverage (UHC) agenda, and domestic efforts are increasing, although slowly and unevenly across countries.¹⁴ Pooled procurement mechanisms may also become increasingly important in relation to NCDs for accessing more affordable treatments and for integration in public health programs.^{15,16}

The market size may be limited in some disease areas. Certain new medicines may offer significant clinical benefit for a relatively small patient population. Medicines for the second-line treatment of CML provide one example of a small market given the relatively low incidence of the disease. The same may be true for other targeted cancer treatments. Nevertheless, we found that a number of generics manufacturers are developing these medicines, suggesting that even limited market potential may still attract generic manufacturers. In cases like this, MPP licences could be tailored to enable more affordable access even with a limited number of sub-licensees. In the case of new antibacterials, where certain new, effective agents would likely fall into the WHO EML Watch or Reserve categories rather than being recommended for widespread use, the market would also be small.⁸ Various approaches to incentivise and reward the development and manufacturing of such products while supporting good stewardship principles have been proposed to address these challenges.¹⁷

Internationally recognized quality assurance standards will be important for sublicensing medicines to manufacturers. In HIV, hepatitis C and tuberculosis, MPP licences have relied on approval by stringent regulatory authorities (in particular the US FDA 'tentative approval') or the WHO Prequalification Programme for quality assurance. At present, the WHO Prequalification Programme does not cover all products in the WHO EML nor those with potential for future inclusion but has been gradually expanding the range of medicines it reviews.¹⁸ The definition of "stringent regulatory authorities" is also likely to evolve in the near future, following ongoing discussions at the WHO.¹⁹ These discussions could inform appropriate standards for the MPP's future licensing agreements.

Additional market and regulatory challenges exist for biologic medicines.

Regulatory pathways are more complex for biologics than for small molecules, partly due to the relatively recent emergence of biosimilars and the lack of regulatory capacity to review biosimilar applications in certain countries.²⁰ The WHO prequalification programme has played a central role in overcoming regulatory challenges in the HIV, TB, and malaria generics markets,²¹ and its recently launched pilot project for prequalifying biosimilars may provide important support in the future.¹⁸ Another challenge for biosimilars is the higher cost and lengthy development and regulatory processes compared to small molecule generics, which may limit the number of potential sub-licensees and the potential for significant price reductions. Technology transfer, in addition to IP licensing, may be key to accelerating development of biosimilars and could be part of a potential MPP licensing model for biologics. Despite the various challenges, a number of governments and other stakeholders highlighted the need to find affordable solutions for several biologics.

Concerns relating to the risk of market leakage would need to be addressed.

Discussions with pharmaceutical companies highlighted the need for strategies to prevent leakage of any licensed medicines into unlicensed territories. Previous experience in addressing these concerns in relation to HIV and hepatitis C would put the MPP in a good position to develop approaches that would be acceptable to all stakeholders. Packaging and labelling requirements, close monitoring of licensee activities, as well as auditing and termination clauses where appropriate are some of the strategies that could be implemented in coordination with patent holders and licensees.

9.3 Strategic considerations

The MPP model is adaptable. The MPP model centres on negotiating and implementing licensing agreements. A wide range of tailored terms and conditions can be developed to suit the needs of various types of medicines, populations and stakeholders. Tailored approaches could include, for example: the use of differentiated royalties to enable a greater number of countries to be covered by a licence; the inclusion of terms to support good antimicrobial stewardship practices; targeted licences to address specific challenges in specific countries or therapeutic areas; and affordability provisions in cases where competition alone may not achieve affordable prices. This list is by no means exhaustive.

The number of patented treatments outside of HIV included in the EML has been increasing. In recent years, the range of patented medicines included in the WHO EML has expanded with the addition of a number of new medicines for hepatitis B, hepatitis C, drug-resistant tuberculosis, various cancers, and reproductive health, in addition to patented medicines for HIV. The convening of an EML cancer medicines working group

this year, may also continue that trend. The recent review of diabetes medicines also identified a class of medicines that may be promising candidates for inclusion in the EML (see Chapter 3) and increasing efforts in supporting the development of new antimicrobials may result in new additions to the EML. Expansion of the MPP's mandate to include patented essential medicines would ensure that the MPP can act swiftly when new medicines emerge that have a strong potential for improving public health in LMICs. Recent experience with hepatitis C medicines, where the MPP was initially unable to respond to patent holder interest in discussing licensing opportunities due to mandate limitations, highlighted the importance of being able to respond quickly to opportunities that can offer significant public health impact.

In recent WHO EML review cycles, there have been examples of medicines that have not been included in the EML in part due to affordability concerns. There are medicines that may offer relevant clinical benefits but may be unaffordable in LMICs, and therefore do not meet the comparative cost-effectiveness criterion for inclusion in the WHO EML. Licensing by the MPP could contribute to making these medicines affordable, thus facilitating access to such medicines in LMICs.

Early licensing of medicines with significant potential for future public health impact in LMICs can be key to accelerating access. For example, the WHO's work in identifying opportunities for future treatment optimization helped to identify the HIV medicine dolutegravir as a promising candidate early on, leading to a licence agreement with ViiV Healthcare on the treatment only two months after its approval at the European Medicines Agency. Early licensing of dolutegravir by the MPP facilitated the timely development of generic versions, which in turn contributed to the inclusion of dolutegravir in treatment guidelines and in the WHO EML. As illustrated by this experience, candidates for in-licensing could be identified through various WHO processes, including, for example, the WHO EML Expert Committee, the WHO Prequalification Programme and WHO treatment guidelines. Discussions with various stakeholders, including industry and civil society organizations, also highlighted the importance of maintaining a degree of flexibility to be able to respond to opportunities where significant public health impact is possible and patent holders may be willing to engage early on, as was the case with dolutegravir.

There are limited precedents for access-oriented licensing outside of HIV, TB, and hepatitis C treatments. Access-oriented licensing for LMICs is a relatively new approach to increasing treatment coverage, which until recently was mainly used in the field of HIV. Before the establishment of the MPP, its use was rare even in HIV and the licences were more restrictive in their application and scope. Today, to a large extent through MPP's work, public-health oriented and transparent licensing has become almost standard practice in HIV and an integral part of industry access strategies for most new HIV and hepatitis C treatments. Expansion into new areas will not be without its challenges. Nevertheless, this study suggests that opportunities may exist. Further discussions with patent holders would be key 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.

9.4 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. The cases analysed in this feasibility study have described a need for affordable generic versions of newer treatments beyond HIV, hepatitis C and tuberculosis. A number of specific medicines were identified for which there are significant public health needs in LMICs. Further prioritization of candidates for in-licensing, in consultation with relevant stakeholders, would be required if the MPP were to expand its mandate.

Patented essential medicines on the WHO EML would be natural candidates for MPP licensing. Some of the medicines reviewed in this study are already included in the EML and could be candidates for licensing by the MPP under an expanded mandate, and new patented medicines are likely to be added at every biennial review. In some cases, generics may already be available in certain countries and licensing could contribute to making them available in additional countries. Licences could also complement existing access policies by pharmaceutical companies.

This study also identified a number of medicines that have been highlighted by the WHO Expert Committee as having relevant clinical benefits but have not yet been added to the WHO EML due to concerns about affordability or pending additional clinical data. MPP licensing could contribute to overcoming affordability concerns by facilitating affordable access to quality-assured generics and enabling valuable new treatments to become available sooner in LMICs. As some of the case studies note, there appear to be incidences where patent holders' commercial interests in countries analysed may be limited, and where MPP licensing could lead to win-win solutions in which all stakeholders benefit. Suitable royalty provisions, including tiered royalties, could play a role in providing adequate compensation to patent holders, where necessary. Other incentives may also be explored as well as terms and conditions that are adapted to specific contexts, products and therapeutic areas.

Many stakeholders active in the field of antimicrobial resistance noted that the MPP could play a significant role in relation to access and stewardship of new antibiotics that treat priority pathogens, for which there may be limited alternatives. The MPP could partner closely with various recently launched or future initiatives in this area and contribute to addressing access and stewardship needs through terms and conditions in the licences and active monitoring of compliance.

Robust mechanisms to monitor recently approved and pipeline medicines, in close consultation with WHO and other key stakeholders, could be important to identify candidates for early licensing. Promising methods include linking to WHO processes such as the WHO EML Expert Committee reviews, the WHO's Prequalification programme's invitations for expression of interest. Additional *ad hoc* mechanisms could also be considered. Some flexibility should remain to allow the exploration of opportunities where patent holders are willing to engage early-on, and where the medicines in question have a strong potential for improving public health outcomes in developing countries.

Given the limited precedents for access-oriented licensing outside 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.

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

At first, the MPP could 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, including of a regulatory nature, may be easier to overcome. However, the MPP should continue to monitor developments and opportunities relating to biologics and consider whether MPP licences on selected medicines could play a role in facilitating access. A separate paper is exploring the potential role of the MPP in relation to vaccines, which is not covered in this study.

The MPP should seek partnerships with public health organisations in relevant clinical areas. Partnerships with governments, established public health organisations and civil society and patient groups would be valuable in encouraging uptake of generic versions when sub-licensees bring these to market, as well as in identifying candidate medicines for in-licensing. Given the multifaceted challenges for access to many NCD medicines, the MPP's licensing work is more likely to lead to significant improvements in access if it is coordinated with the activities of other key players working to provide a comprehensive package of care for NCDs in LMICs.

In relation to new antimicrobials, the MPP could work closely with leading organisations involved in undertaking or funding the development of new antimicrobials, and monitor closely developments in relation to stewardship frameworks to ensure the MPP can follow best practices in this area.

The potential for work in diagnostics and medical devices may also need to be examined. The central importance of access to effective diagnostics was evident throughout the feasibility study, particularly in conversations with stakeholders. While the scope of this analysis did not include consideration of the feasibility of expansion to diagnostics, this issue may bear careful consideration in the future, particularly as an Essential Diagnostics List is currently in development at the WHO.²² Similarly, for some areas that were explored in this study, such as for insulins, it appeared that patent protection on some of the medicine substances was limited, but patent protection for the delivery devices may be a key factor limiting the development of a competitive market. These areas would merit separate consideration and are beyond the scope of this study.

9.5 References

1 Xu K, Evans DB, Carrin G, Aguilar-Rivera AM, Musgrove P, Evans T. Protecting Households From Catastrophic Health Spending. *Health Aff* 2007; **26**: 972–83.

2 Wirtz VJ, Hogerzeil H V, Gray AL, *et al.* Essential medicines for universal health coverage. *Lancet* 2017; **389**: 403–76.

3 Saksena P, Xu K, Evans DB. Impact of out-of-pocket payments for treatment of noncommunicable diseases in developing countries: a review of literature. World Heal. Organ. Discuss. Pap. 2011. http://www.who.int/health_financing/documents/dp_e_11_02-ncd_finburden.pdf (accessed Feb 14, 2018).

4 United Nations General Assembly. Resolution adopted by the General Assembly on 5 October 2016. 2016. http://www.who.int/antimicrobial-resistance/interagency-coordination-group/UNGA-AMR-RES-71-3-N1631065.pdf (accessed Feb 15, 2018).

5 The Review on Antimicrobial Resistance Chaired by Jim O'Neill. Tackling drug-resistant infections globally: final report and recommendations. 2016. https://amr-

review.org/sites/default/files/160525_Final paper_with cover.pdf (accessed Feb 18, 2018).
Chatham House. Towards a New Global Business Model for Antibiotics Delinking Revenues from
Sales: Report from the Chatham House Working Group on New Antibiotic Business Models. 2015.
https://www.chathamhouse.org/sites/files/chathamhouse/field/field_document/20151009NewBusines
sModelAntibioticsCliftGopinathanMorelOuttersonRottingenSo.pdf (accessed Feb 15, 2018).

7 DRIVE-AB. Revitalizing the antibiotic pipeline: Stimulating innovation while driving sustainable use and global access. 2018. http://drive-ab.eu/wp-content/uploads/2018/01/DRIVE-AB-Final-Report-Jan2018.pdf (accessed Feb 19, 2018).

8 WHO EML Expert Committee. Report of the WHO Expert Committeeon Selection and Use of Essential Medicines. WHO Tech. Rep. Ser. 2017.

http://www.who.int/medicines/publications/essentialmedicines/EML_2017_EC21_Unedited_Full_Repor t.pdf?ua=1 (accessed Sept 14, 2017).

9 United Nations General Assembly. Political Declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases. 2012.

http://www.who.int/nmh/events/un_ncd_summit2011/political_declaration_en.pdf (accessed March 4, 2018).

10 UN High-level Meeting on NCDs: Summary report of the discussions at the round tables. 2011. http://www.who.int/nmh/events/moscow_ncds_2011/round_tables_summary.pdf (accessed March 4, 2018).

11 World Health Organization. Assessing national capacity for the prevention and control of noncommunicable diseases. 2016.

http://apps.who.int/iris/bitstream/10665/246223/1/9789241565363-eng.pdf (accessed Oct 5, 2017). 12 Cavalli F, Atun R. Towards a global cancer fund. *Lancet Oncol* 2015; **16**: 133–4.

13 Farmer P, Frenk J, Knaul FM, *et al.* Expansion of cancer care and control in countries of low and middle income: a call to action. *Lancet* 2010; **376**: 1186–93.

14 World Health Organization. Global status report on noncommunicable diseases. 2014. http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf (accessed March 5, 2018).

15 Pan American Health Organization. PAHO Strategic Fund.

http://www.paho.org/hq/index.php?option=com_content&view=article&id=12163%3Apaho-strategic-fund&catid=8775%3Aabout&Itemid=42005&lang=en (accessed Feb 19, 2018).

16 Ruttenberg L. Update by IDA Foundation. http://www.docslides.com/update-by-ida-foundation (accessed Feb 19, 2018).

17 Outterson K. New Business Models for Sustainable Antibiotics. 2014.

18 World Health Organization. WHO to begin pilot prequalification of biosimilars for cancer treatment. 2017.

19 World Health Organization. Proposal for updating the definition of 'stringent regulatory authority'. 2017. http://www.who.int/medicines/areas/quality_safety/quality_assurance/SRA_QAS17-728Rev1_31082017.pdf?ua=1 (accessed April 27, 2018).

20 Hurley P, Boren J, Congiatu C. Challenges in Global Biosimilar Development: A Regulatory Perspective. *Contract Pharma* 2015; published online June.

²¹ 't Hoen EFM, Hogerzeil H V, Quick JD, Sillo HB. A quiet revolution in global public health: The World Health Organization's Prequalification of Medicines Programme. *J Public Health Policy* 2014; **35**: 137–61.

22 World Health Organization. WHO to develop Essential Diagnostics List. 2017.

http://www.who.int/medicines/news/2017/WHO_develop_essential_diagnostics_list/en/ (accessed Feb 20, 2018).



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METHODOLOGICAL APPENDIX

for the feasibility study of the public health needs and potential impact of an EXPANSION OF THE MEDICINES PATENT POOL'S MANDATE TO PATENTED ESSENTIAL MEDICINES

Table of contents

1 diseas	Incidence, all-age disability-adjusted life years and prevalence of relevant ses	t 3
2	Estimation of number of clinically eligible cases	.5
3	General methodology for impact calculations	11
4	References	16

1 Incidence, all-age disability-adjusted life years and prevalence of relevant diseases

The table below provide the incidence, prevalence and all-age disability adjusted life years (DALYs) by income group for the different therapeutic areas that were analysed in the various case studies included in the MPP's feasibility study.

Disease group	Incidence (thousands of cases per year) DALYs					DALYs	(thousands, all-age)				Prevalence (thousands)							
	Global	UMI	LMI	LI	CPL	UMI not in	Global	UMI	LMI	LI	CPL	UMI not in	Global	UMI	LMI	LI	CPL	UMI not in
						CPL						CPL						CPL
Tracheal, bronchus, and lung cancer	2,019	875	252	26	289	865	36,419	18,063	6,052	732	7,032	17,816	3,300	1,298	344	33	391	1,285
Pancreatic cancer	426	132	66	11	80	129	8,237	3,054	1,665	304	1,969	3,054	394	107	52	7	59	107
Prostate cancer	1,618	310	129	23	169	294	6,281	1,996	1,194	342	1,635	1,898	14,434	2,309	866	137	1,119	2,192
Chronic myeloid leukaemia	64	18	20	3	23	18	945	297	390	54	451	289	298	85	93	11	106	83
Acute lymphoid leukaemia	161	68	62	12	76	67	5,058	2,337	1,919	402	2,370	2,287	875	346	352	78	439	337
Breast cancer	2,422	697	608	109	743	670	15,411	5,116	4,703	795	5,700	4,914	21,362	5,968	5,024	880	6,110	5,762
Diabetes	22,728	8,161	8,953	1,065	10,371	7,807	64,135	21,476	28,275	3,462	33,202	20,011	435,328	169,895	160,207	16,876	182,564	164,414
Chronic lymphocytic leukaemia	191	73	32	4	38	72	1,269	534	254	43	306	525	904	371	153	18	175	366
Non-Hodgkin's leukaemia	666	194	139	28	171	190	6,284	2,024	1,952	509	2,513	1,972	4,292	1,242	860	178	1,061	1,219
Multiple myeloma	154	36	24	4	29	35	2,182	653	562	114	704	625	488	105	56	6	64	102
Rheumatoid arthritis	1,288	499	342	69	430	480	6,333	2,593	1,508	280	1,877	2,504	24,491	9,766	5,911	1,079	7,325	9,431
Atrial fibrillation/flutter	2,461	786	550	58	619	776	4,434	1,411	934	95	1,044	1,396	33,294	10,465	6,816	689	7,628	10,342
Venous thromboembolism*	9,900	No data	6,000	No data	3,555	No data	7,700	No data	5,400	No data	3,200	No data	No data	No data	No data	No data	No data	No data

Table 1. Incidence, all-age disability-adjusted life years, and prevalence of relevant diseases.

Data for 2015, from the Global Burden of Disease study,¹ except for venous thromboembolism (see below).

GBD – the Global Burden of Disease study, UMI – upper middle income by World Bank classification, LMI – lower middle income by World Bank classification, LI – low income by World Bank classification, DALYs – all-age disability-adjusted life years, CPL – countries included in past MPP licences (see Appendix point 2.1.).

*In-hospital venous thromboembolism (VTE) events only, based on Jha et al.² DALYs and incidence for VTEs in CPL estimated as proportion of LMI country populations that lives in CPL (59.25% based on 2015 World Bank population data (2011 data for Eritrea)) multiplied by estimates by Jha et al for LMI countries.

2 Estimation of number of clinically eligible cases

For the cancer medicines in Chapter 6 and rituximab in Chapter 8 we did not quantitatively estimate public health or economic impact but estimated the number of cases that would be clinically eligible for treatment in CPL, as well as the DALYs attributable to these cases.

Country-specific 2015 data for incidence, DALYs, and prevalence for relevant disease groups were collected from the Global Burden of Disease (GBD) study (Table 1).¹ The number of patients and burden of disease theoretically eligible for treatment with each medicine was then calculated by multiplying the GBD disease group incidence/DALYs/prevalence with percentage values representing the proportion of patients that would fit certain criteria in the indication. These percentage values, and final estimates for number of eligible patients, are given in Tables 19–23. Additional assumptions for estimate calculation are noted below the respective Table. Similar methodology has been used in previous studies.³

Indications were retrieved from US FDA and the electronic Medicines Compendium (which lists approved indications from both the UK Medicines and Healthcare products Regulatory Agency and the European Medicines Agency). The table includes all approved indications for each drug except where otherwise indicated.

Drug	Indication(s)	Subgroup 1	Subgroup 2	Subgroup 3	CPL epidemio	logy	
					Incidence	DALYs	Prevalence
Erlotinib	first-line for locally advanced or metastatic EGFR+ NSCLC	NSCLC 85% ⁴	EGFR+ & possible to evaluate EGFR status 14.6% ^{3,5,6}	Locally advanced or metastatic 83.5% ^{3,4,7}	29,942	728,644	40,477
	in combination with gemcitabine for the treatment of metastatic pancreatic cancer	Advanced /metastatic 75% ⁸			60,128	1,534,529	45,884
				Total:	90,070	2,263,173	86,361
Afatinib	EGFR TKI-naïve adult patients with locally advanced or metastatic EGFR+ NSCLC	NSCLC 85% ⁴	EGFR+ & possible to evaluate EGFR status 14.6% ^{3,5,6}	Locally advanced or metastatic 83.5% ^{3,4,7}	29,942	728,644	40,477
	locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy	NSCLC 85% ⁴	Squamous histology 35% ⁹	Locally advanced or metastatic 83.5% ^{3,4,7}	71,780	1,746,750	97,034
				Total*:	91,242	2,220,369	123,344
Crizotinib	first-line or second-line treatment of adults with ALK+ advanced NSCLC	NSCLC 85% ⁴	ALK+ 4.5% ¹⁰	Locally advanced or metastatic 83.5% ^{3,4,7}	9,229	224,582	12,476
	treatment of adults with ROS1+ advanced NSCLC	NSCLC 85% ⁴	ROS1+ 1% ¹¹	Locally advanced or metastatic 83.5% ^{3,4,7}	2,051	49,907	2,772
		11,280	274,489	15,248			
Gefitinib	treatment of adult patients with EGFR+ locally advanced or metastatic NSCLC	NSCLC 85% ⁴	EGFR+ & possible to evaluate EGFR status 14.6% ^{3,5,6}	Locally advanced or metastatic 83.5% ^{3,4,7}	29,942	728,644	40,477

Table 2. Erlotinib, afatinib, crizotinib, gefitinib.

For calculation of total, in order to avoid double-counting between the indications, subgroup 2 for a fatinib adjusted to be "squamous histology and not EGFR+ or not possible to evaluate EGFR status" by the calculation 0.35(1-0.146) = 29.89%.

EGFR(+) – epidermal growth factor receptor (a cancer that demonstrates a mutation causing overexpression of this receptor), NSCLC – non-small cell lung cancer, TKI – tyrosine kinase inhibitor, ALK(+) – anaplastic lymphoma kinase (a cancer that demonstrates a mutation affecting this enzyme), ROS1(+) – a receptor tyrosine kinase encoded by the ROS1 gene (a cancer that demonstrated a mutation affecting this enzyme)

For afatinib, the present calculations assumed 100% of patients progress on, or after platinum-based chemotherapy. No adjustment made to restrict estimate to adults. For crizotinib, assumed no cases of both ALK+ and ROS+. No adjustment made to restrict estimate to adults.

Drug	Indication(s)	Subgroup 1	Subgroup 2	CPL epidemiology		
				Incidence	DALYs	
Enzalutamide	treatment of metastatic castration- resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated, or whose disease has progressed on or after docetaxel therapy	Castrate- resistant prostate cancer 15% ¹²		25,319	245,176	
Abiraterone	treatment of metastatic castration- resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated, or whose disease has progressed on or after docetaxel therapy	Castrate- resistant prostate cancer 15% ¹²		25,319	245,176	
	treatment of adult men with castrate- sensitive prostate cancer deemed 'high- risk'	Castrate- sensitive prostate cancer 85% ¹²	High-risk prostate cancer 15% ¹²	21,521	208,399	
			Total:	46,840	453,575	

Table 3. Abiraterone and enzalutamide.

For enzalutamide, assumed that all patients will eventually progress on or after docetaxel therapy.¹³ We assumed that 'high-risk' status and castrateresistance are independent of one another, 100% of castrate-resistant and high-risk prostate cancers become rapidly metastatic, and 100% eventually progress on or after docetaxel therapy.

Prevalen

167,840

167,840

142,664

310,505

ce

Table 4. Lenalidomide.				
Drug	Indication(s)	CPL epidemiology		
		Incidence	DALYs	Prevalence
Lenalidomide	Maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation; treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant; treatment of multiple myeloma in adult patients who have received at least one prior therapy, in combination with dexamethasone.	29,494	703,652	64,163

As the indications for lenalidomide cover both first- and second-line use as well as both patients who have undergone autologous stem cell transplantation (ASCT) as well as patients who will not undergo ASCT, no assumptions were necessary to narrow the number of clinically eligible cases for lenalidomide. Two additional indications for myelodysplastic syndrome and mantle cell lymphoma were excluded.

Drug	Indication(s)	Subgroup 1	Subgroup 2	CPL epidemiology		
				Incidence	DALYs	Prevalence
Trastuzumab	treatment of adult patients with HER2 positive early or metastatic breast cancer, as first- or second-line therapy	HER2+ 17.5% ¹⁴		130,059	997,571	1,069,191
	in combination with capecitabine or 5-fluorouracil and cisplatin for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.	HER2+ 15% ¹⁵	Metastatic 40% ¹⁶	17,066	287,902	42,499
			Total:	147,125	1,285,473	1,111,691
Ado-trastuzumab emtansine (T-DM1)*	treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination	HER2+ 17.5% ¹⁴	Locally advanced or metastatic 50% ^{17,18}	65,030	498,785	534,596
Pertuzumab*	treatment in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.	HER2+ 17.5% ¹⁴	Locally advanced or metastatic 50% ^{17,18}	65,030	498,785	534,596
Lapatinib*	treatment in advanced or metastatic HER2-positive disease with progression following prior therapy (restriction to ombination	HER2+ 17.5% ¹⁴	Locally advanced or metastatic 50% ^{17,18}	65,030	498,785	534,596

Table 5. Trastuzumab, trastuzumab emtansine, pertuzumab, lapatinib.

HER2(+) - receptor tyrosine kinase erbB-2 (a cancer that demonstrates a mutation affecting this enzyme)

All patients with advanced HER2+ breast cancer are eligible for taxane and/or trastuzumab treatment, assuming no contraindications.¹⁹ For T-DM1 calculations, assumed that they all eligible patients received trastuzumab and/or a taxane, and that all eventually progress. No adjustment made to restrict estimate to adults. For trastuzumab, many overlapping indications exist for use in various combinations with other chemotherapeutic agents, which are all included in the summarized indication of use as first- or second-line in HER2 positive early or metastatic breast cancer. The EML Expert Committee included trastuzumab for the indications of early and metastatic breast cancer, but indications for gastric cancer were not mentioned.

*Trastuzumab is indicated first-line for all HER2+ breast cancers (i.e. both early and advanced cancers). Pertuzumab is indicated in metastatic HER2+ breast cancer. Lapatinib and T-DM1 are indicated in metastatic HER2+ breast cancer after failure of trastuzumab. For the purposes of these estimates, we assumed that all patients with metastatic breast cancer treated with trastuzumab would eventually become resistant and would therefore become eligible for T-DM1 and/or lapatinib (in the landmark trial for trastuzumab monotherapy in the metastatic setting, around 80% of patients eventually became resistant²⁰). For this reason, the estimated 'eligible burden' is the same for pertuzumab, T-DM1, and lapatinib, although pertuzumab is indicated earlier in the disease (some additional indications are excluded for simplicity). These eligibility estimates may therefore be slightly overestimated for T-DM1 and lapatinib, as a significant proportion of patients will pass away while on trastuzumab (with or without pertuzumab) therapy.

Drug	Indication(s)	Subgroup 1	Subgroup 2	Subgroup 3	CPL epidemi		
					Incidence	DALYs	Prevalence
Rituximab	treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy*	Follicular subtype 18.6% ²¹	Stage 3–4 at diagnosis 80% ²²		25,456	373,900	157,813
	is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with "CHOP" chemotherapy.	Diffuse large B cell subtype 47.8% ²¹	CD20 positive 98.5% ²³		80,546	1,183,088	499,349
	in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia.				37,916	306,080	175,369
	in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease- modifying anti-rheumatic drugs (DMARDs) including one or more tumour necrosis factor (TNF) inhibitor therapies.	Not controlled with methotrexat e alone 70% ²⁴	Inadequate response to anti-TNF 33.33% ²⁵		100,425	438'030	1,709,098
				Total:	244,342	2,301,098	2,541,629

Table 6. Rituximab.

*We assumed that the following additional indications are accounted for in the estimate for this indication and were not separately calculated: "maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy", "monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy".

An indication for the use of rituximab for severe, active granulomatosis with polyangitis (GPA) and microscopic polyangitis (MPA) has not been included due to the rarity of these conditions, and technical difficulty in diagnosis. For bendamustine in the treatment of multiple myeloma, we assumed 0% autologous stem cell transplantation. No adjustment made to restrict estimate to adults.

3 General methodology

3.1 Countries

For the purpose of estimating public health and economic impacts, we used a set list of countries that have generally been included in past MPP licences. We use the term 'countries in past licences' (CPL) for this group of countries. This number is used as a proxy and is purely based on precedent.

The list was defined as all countries defined as low-income or lower-middle-income by the World Bank,²⁶ plus all other countries in sub-Saharan Africa. These 90 countries represent a total population of 3.7 billion, equivalent to 49.8% of the global population or 59.3% of the total population of low- and middle-income countries in 2015.²⁷

3.2 Review of selected National Essential Medicines Lists

We gathered NEMLs and/or national reimbursable medicines lists, as applicable, from LMICs where a version updated in the last 3 years was available. We were kindly assisted in gathering of NEMLs, and advised on the availability of NEMLs, by Dr Jane Robertson and Kotoji Iwamoto from the Health Technologies and Pharmaceuticals programme of the WHO Regional Office for Europe.

The presence of the medicine(s) in question on NEMLs/reimbursement lists was recorded for each country for which these documents could be accessed.

3.3 Estimating burden of disease

Data on disease burden were gathered from the Global Burden of Disease (GBD) study's online database for 2015,¹ the GLOBOCAN online tool,²⁸ for venous thromboembolism burden from a study using literature review and hospital surveys commissioned by WHO,² and from the International Diabetes Federation's Diabetes Atlas project.²⁹ Some therapeutic indications with very small patient populations were excluded.

Where the indication for a medicine was for a subtype of a disease, GBD estimates for the epidemiology of the larger disease group were multiplied by estimates made in other studies of the proportion of cases that fit into the relevant subtype. For example, dasatinib and nilotinib are indicated for the treatment of the Philadelphia chromosome-positive subtype of chronic myeloid leukaemia. As GBD reports only the epidemiology of chronic myeloid leukaemia as a whole, we multiplied this by 87.5% to estimate the prevalence and incidence of Philadelphia chromosome-positive cases.³⁰

Various sources were used to generate projections for future disease burden. For type 2 diabetes, projections made by the IDF Atlas project were used.²⁹ For cancers, these were generated by applying the proportional change over time in mortality projected by the GLOBOCAN project to GBD (current) estimates of prevalence and incidence in CPL.^{1,28} For atrial fibrillation, linear regression was used to extrapolate a trend for prevalence in CPL using GBD data.¹ For VTE, the incidence was assumed to remain constant as no projections were found.
3.4 Estimating the potential public health and economic impact of MPP intervention

The 'MPP intervention' considered in these impact estimates is the hypothetical enabling of generic market entry before patent expiry, for the medicine(s) in question in CPL, where generic entry would otherwise not have been possible until patent expiry. For many of the assumptions included in the model, we have relied on the model developed by the MPP for HIV,³¹ while in places adapting this for the specific context of each therapeutic area.

We estimated the potential public health and economic impact for MPP interventions in SGTL2 inhibitors as second-line treatment for type 2 diabetes, novel oral anticoagulants (NOACs) for clot prevention, and second-generation tyrosine kinase inhibitors (TKIs) for the treatment of chronic myeloid leukaemia.

While the general methodology is similar for all three cases, methodologies were tailored with respect to epidemiological considerations and measures of clinical effect. For all three groups, we started by estimating the number of people that could be treated with MPP-enabled generic versions per year, based on epidemiology and assumptions regarding diagnosis and treatment access, duration of impact, and market dynamics. For public health impact, the number of people treated (or number of patient-years of treatment, as applicable) was multiplied by measures of effect to give an estimated sum effect in the population, for example, number of strokes averted. For economic impact, patient-years of treatment were multiplied by projected differences in price between potential MPP-enabled generic versions and originator products in relevant countries, to estimate overall monetary savings to health systems.

A scheme of the overall model, illustrating individual contributing components, is shown in Figure 1.

Figure 1. Scheme of overall model for estimating public health and economic impact of medicines in case studies.



3.5 Assumptions regarding the duration of MPP's potential impact

For all medicine(s) in question, we assumed licence signing in 2019. The duration of impact for MPP interventions was assumed to last from generic market entry to one year beyond the year of expiry of patent protection.

As generic market entry would not occur instantaneously as soon as an MPP licence were signed, we made assumptions regarding the lag in generic market entry. The lag in generic market entry – that is, the time taken for generic manufacturers to develop a generic version and bring it to CPL markets following an MPP licence becoming available – was assumed to be

- 1 year from licence signing when generic versions were found to already be available in India and/or South Africa
- 2 years from licence signing when generic versions were not found to be available in India and/or South Africa, but manufacturers' websites indicated that generic versions were in development, and
- 3 years from licence signing in all other cases.

We assumed that MPP impact ends one year after the expiry of all LMIC patents that are in the same family as those listed in the US FDA Orange Book patents.³² In most cases, we also assumed that expiry for one drug in the class under consideration (e.g. SGLT2 inhibitors) would

impact on other medicines in the class. That is, once one drug within the group becomes available at an affordable price, it will likely be used as a preferred alternative to the others.

As in the MPP's HIV model,³¹ the impact of MPP interventions was generally assumed to persist one year beyond the expiry of Orange Book patents, as in the counterfactual scenario of no MPP intervention, there would likely be a lag in generic market entry after the expiry of all blocking patents. The expiry dates of blocking patents in LMICs (as opposed to the US) were also included in the impact estimation model, as described in the following section, *Market dynamics*.

3.6 Market dynamics

We defined MPP-enabled products as medicines that could be manufactured and sold by generic manufacturers if a voluntary licence were negotiated between the MPP and the originator, and for which a generic version would otherwise be unlikely to enter the market until after expiry of the originator patents.

Not all generic products entering the market while an MPP licence is available would necessarily be considered MPP-enabled products: for example, products brought to market by manufacturers who are able to design around (secondary) patent protection would not be considered MPP-enabled products, as these products would have been brought to market even if an MPP licence had not been available. To account for the reduction in impact attributable to MPP intervention once generics become available due to loss of patent protection in some LMICs, we halved the estimated MPP impact after expiry of the main compound patent in LMICs. Given the large number of unpredictable factors, we have estimated the reduction in attributable impact at half, though in various scenarios it could be more or less than this.

We assumed that maximum market penetrance was reached after 5 years, with a linear increase from 0% market share to a maximum percentage determined by assumptions regarding the proportion of cases diagnosed, the proportion of the affected population with access to healthcare, and clinical factors (these assumptions were specific to each therapeutic area).

3.7 Collection of current prices

Data on the current originator price available in India were collected from online price comparison websites (*CIMS* and *1mg*) and converted from Indian rupees to US dollars assuming an exchange rate of 1 Indian rupee to 0.016 US dollars.

Indian prices were used as a proxy for price in LMICs, due to data availability, as well as because India is a historically important pharmaceutical market, and represents a large proportion of the total population.

3.8 Estimating generic prices

Potential generic prices were estimated by applying a standard industry generic price erosion curve (Figure 2) to the current originator price for each medicine in India.





We additionally calculated estimated generic prices based on cost-of-goods analysis, following previously published methodology,³³ and using data on the price of active pharmaceutical ingredient exported from India available from an online database.³⁴

3.9 Estimated economic impact

To calculate potential savings for each year within the assumed period of MPP impact, the price difference between Indian originator price (which we assumed remains constant) and the projected generic price for each year was multiplied by the estimated patient-years^A of treatment with MPP-enabled generics for that year. Savings for each year were discounted at the UK Treasury recommended rate of 3.5% per year.³⁵ Estimated potential savings for each year were summated to yield total savings, see point 2.1..

^A Except for treatment of acute VTE with NOACs, for which 6 months of treatment per incident case was assumed.

4 References

- 1 Institute for Health Metrics and Evaluation. GBD Results Tool. http://ghdx.healthdata.org/gbd-results-tool (accessed April 13, 2017).
- Jha a K, Larizgoitia I, Audera-Lopez C, Prasopa-Plaizier N, Waters H, Bates DW. The global burden of unsafe medical care: analytic modelling of observational studies. *BMJ Qual Saf* 2013; 22: 809–15.
- 3 Hill A, Gotham D, Fortunak J, *et al.* Target prices for mass production of tyrosine kinase inhibitors for global cancer treatment. *BMJ Open* 2016; **6**: e009586.
- 4 Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin Proc* 2008; **83**: 584– 94.
- 5 Ellison G, Zhu G, Moulis A, Dearden S, Speake G, McCormack R. EGFR mutation testing in lung cancer: a review of available methods and their use for analysis of tumour tissue and cytology samples. *J Clin Pathol* 2013; **66**: 79–89.
- 6 NICE. Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK. 2012. https://www.nice.org.uk/guidance/ta258.
- 7 da Cunha Santos G, Shepherd FA, Tsao MS. EGFR mutations and lung cancer. *Annu Rev Pathol* 2011; **6**: 49–69.
- 8 Kelley RK, Ko AH. Erlotinib in the treatment of advanced pancreatic cancer. *Biologics* 2008; **2**: 83–95.
- 9 Youlden DR, Cramb SM, Baade PD. The International Epidemiology of Lung Cancer: geographical distribution and secular trends. *J Thorac Oncol* 2008; **3**: 819–31.
- 10 Kwak EL, Bang Y-J, Camidge DR, *et al.* Anaplastic lymphoma kinase inhibition in nonsmall-cell lung cancer. *N Engl J Med* 2010; **363**: 1693–703.
- 11 Gainor JF, Shaw AT. Novel targets in non-small cell lung cancer: ROS1 and RET fusions. *Oncologist* 2013; **18**: 865–75.
- 12 Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: A systematic review. *Int J Clin Pract* 2011; **65**: 1180–92.
- 13 Hwang C. Overcoming docetaxel resistance in prostate cancer: a perspective review. *Ther Adv Med Oncol* 2012; **4**: 329–40.
- 14 Jackisch C, Lammers P, Jacobs I. Evolving landscape of human epidermal growth factor receptor 2-positive breast cancer treatment and the future of biosimilars. *The Breast* 2017; **32**: 199–216.
- 15 Boku N. HER2-positive gastric cancer. *Gastric Cancer* 2014; **17**: 1–12.
- 16 Riihimäki M, Hemminki A, Sundquist K, Sundquist J, Hemminki K. Metastatic spread in patients with gastric cancer. *Oncotarget* 2014; published online Nov 9. DOI:10.18632/oncotarget.10740.
- 17 Bhoo-Pathy N, Verkooijen HM, Tan E-Y, *et al.* Trends in presentation, management and survival of patients with de novo metastatic breast cancer in a Southeast Asian setting. *Sci Rep* 2015; **5**: 16252.
- 18 Agarwal G, Pradeep P V., Aggarwal V, Yip CH, Cheung PSY. Spectrum of breast cancer in Asian women. *World J Surg* 2007; **31**: 1031–40.
- 19 Cardoso F, Costa A, Senkus E, *et al.* 3rd ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). *Ann Oncol* 2016; : mdw544.
- 20 Slamon DJ, Leyland-Jones B, Shak S, *et al.* Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2. *N Engl J Med* 2001; **344**: 783–92.
- 21 Smith A, Crouch S, Lax S, *et al.* Lymphoma incidence, survival and prevalence 2004-2014: sub-type analyses from the UK's Haematological Malignancy Research Network. *Br J Cancer* 2015; **112**: 1575–84.
- Hiddemann W, Cheson BD. How we manage follicular lymphoma. *Leukemia* 2014; **28**:

Methodological appendix

1388-95.

- 23 Castillo JJ, Chavez JC, Hernandez-Ilizaliturri FJ, Montes-Moreno S. CD20-negative diffuse large B-cell lymphomas: biology and emerging therapeutic options. *Expert Rev Hematol* 2015; **8**: 1–12.
- 24 O'Dell JR, Mikuls TR, Taylor TH, *et al.* Therapies for active rheumatoid arthritis after methotrexate failure. *N Engl J Med* 2013; **369**: 307–18.
- 25 Gottenberg J-E, Brocq O, Perdriger A, *et al.* Non-TNF-Targeted Biologic vs a Second Anti-TNF Drug to Treat Rheumatoid Arthritis in Patients With Insufficient Response to a First Anti-TNF Drug: A Randomized Clinical Trial. *Jama* 2016; **316**: 1172–80.
- The World Bank. World Bank Country and Lending Groups.
 https://datahelpdesk.worldbank.org/knowledgebase/articles/906519 (accessed Jan 5, 2018).
- 27 The World Bank. Population, total. http://data.worldbank.org/indicator/SP.POP.TOTL (accessed May 1, 2017).
- 28 Ferlay J, Soerjomataram I, Ervik M, *et al.* GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. 2013. http://globocan.iarc.fr (accessed Feb 1, 2015).
- 29 International Diabetes Federation. IDF diabetes atlas 8th edition. http://www.diabetesatlas.org/ (accessed Sept 10, 2017).
- 30 Demiroglu A, Joanna Steer E, Heath C, *et al.* The t(8;22) in chronic myeloid leukemia fuses BCR to FGFR1: Transforming activity and specific inhibition of FGFR1 fusion proteins. *Blood* 2001; **98**: 3778–83.
- 31 Juneja S, Gupta A, Moon S, Resch S. Projected savings through public health voluntary licences of HIV drugs negotiated by the Medicines Patent Pool (MPP). *PLoS One* 2017; **12**: e0177770.
- Hill LL. The Orange Book. *Nat Rev Drug Discov* 2005; **4**. DOI:10.1038/nrd1804.
- 33 Hill A, Barber MJ, Gotham D. Estimated costs of production and potential prices for the WHO Essential Medicines List. *BMJ Glob Heal* 2018; **0**: e000571.
- 34 Infodrive India. http://www.infodriveindia.com/.
- 35 HM Treasury. The Green Book: Appraisal and Evaluation in Central Government. 2003. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/2205 41/green_book_complete.pdf (accessed Jan 9, 2018).



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