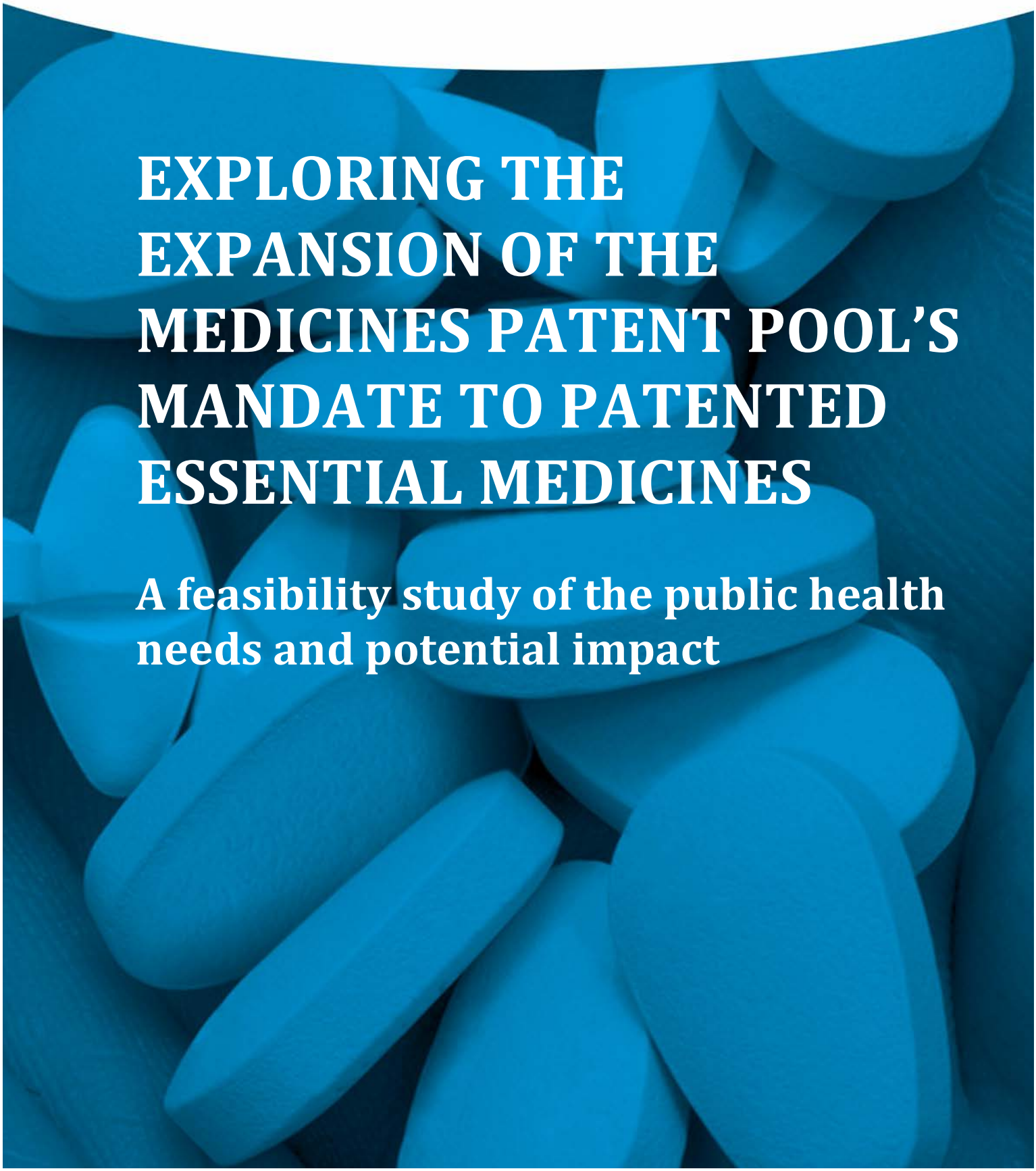
medicines patent pool



EXPLORING THE EXPANSION OF THE MEDICINES PATENT POOL'S MANDATE TO PATENTED ESSENTIAL MEDICINES

A feasibility study of the public health needs and potential impact

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*

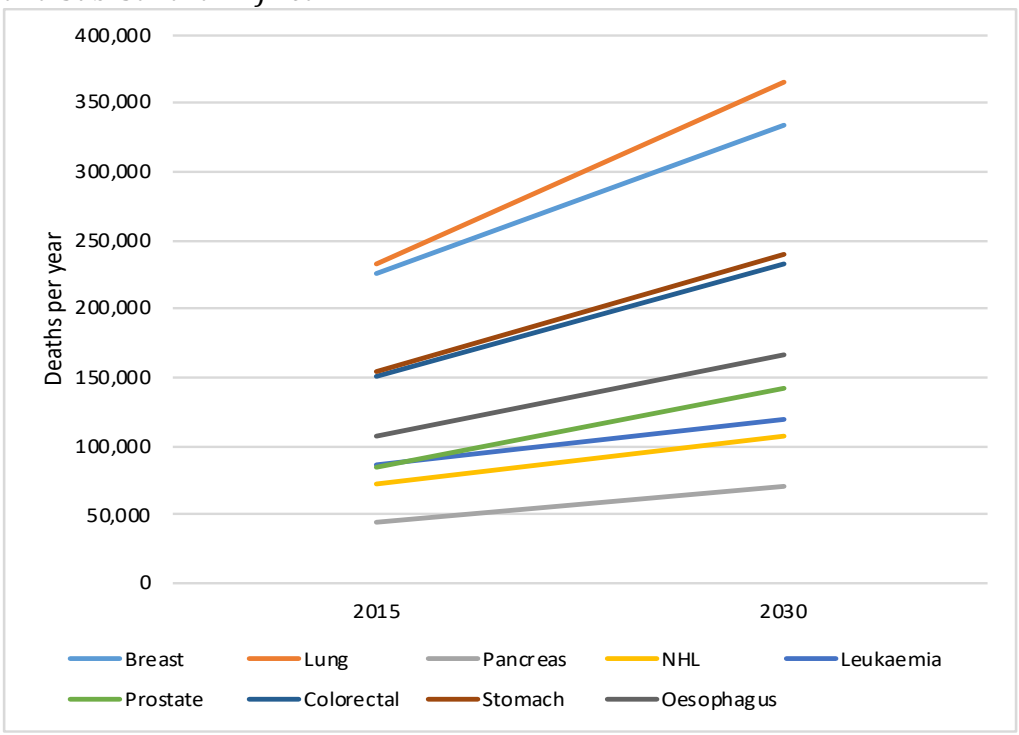
6.1 Background

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.

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 sources[31–33]).

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

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

*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

[N] 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.

Table 3. Patent landscape for lung TKIs.

Lung Cancer	Expected date of expiry	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZAF	VNM
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	.

*. – 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 low-resource 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).

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

Medicine	Incidence	DALYs	Prevalence
Abiraterone	47,000	454,000	311,000
Enzalutamide	25,000	245,000	168,000

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 radiotherapy with curative intent are in general not recommended in metastatic prostate 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 sources[31–33]).[P]

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

Country	Lowest available price per patient per month (USD)	
	Enzalutamide	Abiraterone
Uzbekistan	N	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

*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.

Table 6. Patent landscape for enzalutamide and abiraterone.

	Expected date of expiry	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZAF	VNM
Enzalutamide															
Product	2026/2027	.	F	G	G*	.	G	R/A	.	.	.	.	.	G	.
Abiraterone															
Method of treatment with abiraterone and prednisone	2027	.	.	F	.	?	.	.	?	?	.	.	?	.	.

*. – 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

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

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

*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	PHL	THA	UKR	ZA	VNM
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).

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]

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

[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]).

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

Country	Price per month (USD)			
	Trastuzumab	T-DM1	Pertuzumab	Lapatinib
Uzbekistan	$873*	N	$4,667	N
Kenya	$789*	N	N	N
Haiti	N	N	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*	N	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.

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.

Table 12. Patent landscape for HER2-targeted medicines.

Breast cancer	Expected date of expiry	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	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	.

*. – 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. non-biologics).[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.

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