Expanding access to biotherapeutics in low-income and middle-income countries through public health non-exclusive voluntary intellectual property licensing: considerations, requirements, and opportunities

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Biotherapeutics, such as recombinant proteins and monoclonal antibodies, have become mainstays of modern medicine as shown by their increasing number in the WHO Model List of Essential Medicines. However, despite frequently offering clinical advantages over standards of care, they remain largely out of reach for populations in low-income and middle-income countries (LMICs), partly because of high costs. Accordingly, the WHO Model List of Essential Medicines Expert Committee has requested that the Medicines Patent Pool explore intellectual property licensing to address this challenge. We therefore investigated how licensing could successfully improve affordability of and timely access to biotherapeutics in LMICs, by leveraging expert consultations, literature analysis, and internal technical knowledge. The key elements identified as relevant to support access to affordable biosimilars in LMICs through licensing include: prioritising potential biotherapeutic targets according to their potential for public health impact; supporting biosimilar product and clinical development (including through technology transfer to expedite regulatory approval); and facilitating biosimilars' entry and use in LMICs (by meeting procurement, supply chain, and health system requirements).

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Introduction

The biotherapeutics public health paradox: restricted access despite broad efficacy

Biotherapeutics such as recombinant proteins and monoclonal antibodies have become mainstays in the treatment of many diseases. Accordingly, the proportion of biotherapeutics among new US Food and Drug Administration drug approvals has increased in more recent years (26% between 2016 and 2020 compared with 14% between 1996 and 2000), as has the number of biotherapeutics included in the WHO Model List of Essential Medicines (24 in total by 2021).[1,2] However, a combination of health systems challenges, high prices of these biotherapeutics, and barriers to market entry of follow-on generic products (known as biosimilars) hinder broad access to biotherapeutics, especially in low-income and middle-income countries (LMICs). A 2020 report showed that only 20% of global sales of monoclonal antibodies occurred in territories outside the USA, Europe, or Canada.[3] Conversely, Africa, accounting for 17% of the global population, represented only 1% of monoclonal antibody sales.[3] This disparity particularly affects newer products, as these are sometimes not registered in LMICs, and non-communicable diseases (NCDs) for which the majority of essential biotherapeutics are indicated.[2,3] This inequity earlier resulted, according to some studies, in some patients from LMICs being left behind as treatments that markedly improve survival in some high-burden conditions (such as *HER2* [also known as *ERBB2*]-positive breast cancer) took a long time to be integrated into public health systems and be scaled up.[4–6] This unequal availability of essential medicines might be one of the contributing factors to the lower reduction of premature deaths from cancer observed between 2010 and 2015 in low-income countries (5%) compared with high-income countries (20%), reflecting the global inequality in access to care observed across non-communicable diseases and biotherapeutics.[7]

Intellectual property licensing for public health: a promising approach to support early entry of affordable biosimilars in LMICs

The introduction of biosimilar versions of important biotherapeutics could lead to improved affordability and better access to treatments, allowing patients to be treated (with optimal care), saving financial health resources, and possibly helping broaden the pool of eligible patients and indications (when relevant).[8–14] One way to achieve that is through voluntary licensing of intellectual property rights, whereby patent holders allow additional manufacturers to produce and sell generic or biosimilar versions of patented medicines in defined territories for specified uses, before patent expiry.[15–18] Licensing terms and conditions vary; the geographical scope and what a patent holder could provide to licensees (eg, technology transfer, data, and regulatory exclusivity waivers) are important elements, among others. The WHO Model List of Essential Medicines Expert Committee has recently requested that the Medicines Patent Pool explore licensing to address LMIC access challenges for biotherapeutics.[19–21] The Medicines Patent Pool is a non-profit organisation backed by the UN that negotiates non-exclusive public-health driven licences to accelerate access to patented medicines in LMICs before patent expiry through accelerated and strengthened generic competition, thereby maximising economic and

health impact, as has been shown for small molecule medicines.[22–30] Biotherapeutics, however, come with greater development and manufacturing complexity and higher costs compared with small molecule medicines. Thus, whether the Medicines Patent Pool's licensing model can be successfully applied to biotherapeutics to increase their availability and affordability, by triggering effective competition and reducing treatment prices in LMICs, remains to be shown. This study aimed to explore this hypothesis and the considerations, requirements, and opportunities of public health non-exclusive licensing (in particular through the Medicines Patent Pool) to improve access to biotherapeutics in LMICs. Although bilateral licensing, whereby a patent holder directly licenses to one or more generic companies, can have benefits in terms of access, this Review focuses on licensing through the Medicines Patent Pool, as a mechanism driven by public health considerations and therefore better suited to balance the commercial considerations of innovators and manufacturers with public health needs in LMICs. The discussion focuses on peptides, recombinant proteins, and monoclonal antibodies and excludes more complex and emerging biotherapeutics (eg, gene therapy, CRISPR-based therapy, chimeric antigen receptor T-cell therapy, and vaccines including mRNA vaccines).

For more on the **intellectual property landscape of essential medicines** see https://www.medspal.org

Identifying potential biotherapeutic targets for public health licensing

Clinical relevance and burden of disease

The first step in exploring the potential role that licensing could have on access to biotherapeutics is to identify biotherapeutics for which a licensing approach could be best suited. The Medicines Patent Pool's prioritisation framework to identify candidate drugs for licensing provides a good starting point. The framework includes an assessment of the medical need (eg, the number of patients having a condition in LMICs) and the additional clinical benefit a medicine could provide compared with available alternatives, to identify medicines with the highest potential for public health impact and suitable as candidates for licensing. However, given their likely higher complexity and cost, a biotherapeutic would need to confer a substantial advantage in terms of efficacy, safety, or convenience (eg, supporting better adherence) than might be the case with a promising new small molecule to justify a potentially higher cost. The analysis of the added clinical benefit of a biotherapeutic of focus should therefore be compared not only with the standard of care for the same therapeutic indication, but also to alternatives being developed, especially small molecules that are likely to be more affordable. As an example, various monoclonal antibodies for COVID-19 met this challenge: although some had shown efficacy for patients with mild to moderate COVID-19, they were likely to face competition in LMICs from more affordable small molecule antivirals that were at the time in late-stage development and were being licensed to the Medicines Patent Pool for generic supply in approximately 100 LMICs.[31,32]

For more on the **Medicines Patent Pool's prioritisation framework** see https://medicinespatentpool.org/what-we-do/prioritising-medicines-for-licensing

Patents and other exclusivities

A key variable for understanding how licensing through the Medicines Patent Pool could play a role in accelerating access to more affordable biotherapeutics in LMICs is the intellectual property landscape of these medicines in LMICs with regards to both manufacturing (ie, exporting) and recipient (ie, importing) countries. Five determinants were identified as particularly noteworthy with regard to the potential for licensing to create impact: the time to overall patent expiry (in particular the primary patents covering the active substance); the patent coverage across LMICs; foolw-on patents (such as secondary patents for key processes or formulations); the potential for multiple patent owners (requiring concerted or parallel licensing from third-party-owned intellectual property); and other exclusivities (such as regulatory exclusivity and trade secrets). Overall, in addition to trade secrets biosimilar entry is governed by a mix of patent protection, patent term extensions, data exclusivity, and market exclusivity periods, which might or might not exist across different countries, leading to a variety of dates when biosimilars could enter these markets. To create impact (ie, to allow substantially earlier access), licensing efforts should focus on biotherapeutics with intellectual property protection periods longer than expected biosimilar development timelines, which could be considerably longer than for small molecules.[33]

Patent holders' perspective and licensing incentives

Whether originators could be open to negotiating with the Medicines Patent Pool a licensing agreement for biotherapeutics and the amount of technology transfer, if any, they would be willing to provide, are crucial elements for the success of such an endeavour. To get some qualitative insights on these aspects, the Medicines Patent Pool commissioned an assessment to understand the main concerns and challenges of biopharmaceutical companies with regard to access to biotherapeutics in LMICs and their potential willingness to explore licensing (unpublished). In general, most interviewees recognised that they had had limited success in making their biotherapeutics available in the vast majority of LMICs and that they had so far rarely used licensing as an access mechanism. Among the challenges most frequently mentioned for licensing and technology transfer to manufacturers in LMICs, originators identified the substantial time, effort, and economic investment needed for any type of technology transfer and issues regarding the protection of intellectual property, including concerns relative to their larger portfolio of activities (especially if cell lines were included in the technology transfer). Compared with large multinational pharmaceutical companies, interviews

also highlighted that mid-sized organisations might be more inclined to engage in licensing, mainly because of their lower manufacturing capacity or less expansive network in LMICs. Among the large companies, those with a stronger commitment to global access might also be more open to explore licensing than those with less strong commitments.[34] Pharmaceutical companies might also be more open to negotiation for products that are not playing a key role in their commercial portfolio or that cover indications with particularly high unmet needs in LMICs. Robust mechanisms to ensure that intellectual property or transferred technology is well protected and high technical competence, quality standards, and wide geographical presence of potential licensees in LMICs were identified as important. The ability to pool demand across countries and to address health systems challenges that exist in many LMICs were also highlighted (and are discussed further on in this Review). The development of regulatory incentives—such as priority review vouchers (which offer pharmaceutical companies time and economic benefits) or other economic incentives—has been suggested as a mechanism to stimulate originators' interest in licensing to support access to their products in LMICs, and could be further explored.[35–37]

Supporting biosimilar development

Clinical development

The development of biosimilars is subject to high development costs and long lead times, which could hamper the success of licensing in expanding access.[38] We analysed the development process of filgrastim, oral semaglutide, pembrolizumab, sotrovimab, and trastuzumab including technical development and regulatory aspects, as well as manufacturing of clinical batches and performing of clinical studies required for product filing. We referred to the development standards required by stringent regulatory authorities (as defined by WHO) or the WHO Prequalification of Medicines Programme and used India as the reference country for development and manufacturing in our estimates because many of the largest generic pharmaceutical companies supplying medicines in LMICs are based in India, which points to the importance of considering costs structures (and timings) of development and manufacturing in this country.[39,40] Our findings suggest that for most biosimilars, development time and costs are driven by clinical work (ie clinical batch manufacturing and clinical trials), with design largely determined by indication (table 1). The cost of reference products needed to run both analytical comparability assays and preclinical and clinical trials also constitutes a substantial portion of the costs of development. For example, we estimated it at 73% of the investment needed for total pembrolizumab biosimilar development; representing a major barrier (table 1). Although extrapolation of indications might be possible in most cases, dedicated clinical trials might be required to confirm efficacy for each individual therapeutic use, increasing the number of clinical trials (and costs) to obtain marketing authorisation.[42,43] On the basis of these findings, the development of relatively complex

	Category	Indication	Estimated costs					Estimated timelines*			
			Patent licence only			With full technology transfer† (% reduction of total)		Patent licence only		With full technology transfer† (% reduction of total)	
			Total (million US$)	Clinical work‡ (% of total)	Reference product (% of total)	Current regulatory landscape	Accelerated regulatory landscape§	Total (years)	Clinical work‡ (% of total)	Current regulatory landscape	Accelerated regulatory landscape§
Filgrastim¶	Protein	Neutropenia	4·4	38%	14%	5%	31%	3·8	37%	17%	35%
Oral semaglutide	Peptide	Diabetes	9·9	71%	9%	57%	57%‖	5·2	41%	34%	34%‖
Pembrolizumab	mAb	Oncology	52·5	19%	73%	1%	44%	6·6	53%	8%	36%
Sotrovimab	mAb	COVID-19	10·8	55%	5%	4%	50%	2·6**	34%	11%	30%
Trastuzumab¶	mAb	Oncology	21·6	52%	29%	2%	69%	6·1	57%	8%	38%

Licensing of patents aims to provide freedom to operate to generic manufacturers. In addition to licensing patents, inclusion of a full technology transfer could have expanded the effect on development costs and timelines, depending on the product. The development costs and timelines presented here were estimated for the entire product development process, covering technical development, preclinical work, clinical batch manufacturing, and clinical trials (if needed), up to filing to a stringent regulatory authority. The structure of costs in India was used as a reference for cost estimations. mAb=monoclonal antibody. *Timeline estimations consider efficiencies arising from processes taking place in parallel, whenever possible (these estimated timelines are shorter than the sum of all processes if they would take place sequentially). †Full technology transfer refers to a situation in which an originator company provides complete documentation and process know-how, including the physical transfer of expertise and the sharing of the needed cell lines, plasmids, and other necessary material to a licensee. ‡These are cost and timeline contributions from clinical batch manufacturing and clinical trials, excluding the costs of reference products (indicated separately in the adjacent column). §Accelerated regulatory landscape refers to stringent regulatory authorities granting clinical trial waivers or allowing small bridging studies, without requirement for full comparative efficacy clinical trials. ¶The patent-licence-only scenario for off-patent products filgrastim and trastuzumab, for which biosimilars are already available on the market, refers to the costs and timelines for the development of an additional biosimilar. ‖For oral semaglutide, no further cost and time reductions are considered as a clinical trial waiver is already considered in the baseline scenario with full technology transfer (in line with the US Food and Drug Administration provision for establishing bioequivalence of small peptides such as oral semaglutide via a pharmacokinetic route).[41] **Estimated timelines for sotrovimab have been shortened, considering accelerated timelines (assuming 50% reduction) during the emergency response to the COVID-19 pandemic.

Table 1: **Estimates of possible effects of licensing on biosimilar development costs and timelines**

biotherapeutics (eg, monoclonal antibodies) for certain indications such as cancer would benefit substantially from access to reference products at low prices (which potentially could be included in a licensing agreement, as has happened in a recent Medicines Patent Pool licence on a COVID-19 antiviral), as well as from clinical trial waivers granted by regulatory authorities (which could substantially decrease both their costs and the time required for the development of biosimilars).[11,44] Phase 3 clinical trial waivers can already be obtained from regulatory authorities for well established recombinant proteins with strong pharmacodynamic markers, such as filgrastim. For example, US Food and Drug Administration guidelines now include a provision for establishing bioequivalence of small peptides such as oral semaglutide via a pharmacokinetic route.[41] The European Medicines Agency has also stated that "in specific circumstances, a confirmatory clinical trial may not be necessary", but that this "requires that similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and [pharmacokinetic] and/or [pharmacodynamic] profiles of the biosimilar and the reference product".[45,46] Accordingly, the European Medicines Agency regulatory framework has been described for its ability to adapt to continue striking an acceptable balance between patient safety and the feasibility of developing biosimilar products.[47] In addition, UK Medicines & Healthcare Products Regulatory Agency guidance has recently stated that comparative efficacy clinical trials are generally not considered necessary, although clinical comparability should be assessed through a pivotal comparative pharmacokinetics trial.[48,49] Broad acceptance of such regulatory pathways for other biotherapeutics (eg, monoclonal antibodies) and in LMICs might need to be assessed, and manufacturers will need to liaise with regulators early on when planning biosimilar development for access in LMICs; the Medicines Patent Pool involvement in regulatory strategising to support access across multiple LMICs could further contribute to alignment between regulators and across manufacturers.[46]

Licensing, technology transfer, and product development

As part of interventions aimed at easing biosimilar development and enabling affordable use of biotherapeutics in LMICs, we assessed the effect of different extents of technology transfer, provided by a patent holder (originator) to a licensed manufacturer, across different biosimilar categories. Costs of manufacturing for commercialisation were not assessed, given the inherent variability across manufacturers in terms of existing infrastructure, experience, location, size, portfolio, and human resources. We found that a full technology transfer (ie, wherein an originator company provides complete documentation and process know how, including the physical transfer of expertise and the sharing of the needed cell lines, plasmids, and other necessary material to a licensee) increases the likelihood of obtaining a clinical trial waiver, since bioequivalence is shown when biosimilar and reference products are identical in terms of biological origin, manufacturing method, and analytical characterisation, particularly in the case of simpler biologics. As an example, full technology transfer could potentially cut the time (by 34%) and cost (by 57%) of developing an oral semaglutide biosimilar as compared with a scenario in which a patent-only licence is provided with no technology transfer (table 1). However, more complex biotherapeutics, such as monoclonal antibodies are less likely to obtain a clinical trial waiver even with a full technology transfer from the originator: for a monoclonal antibody, a full technology transfer would potentially reduce the development time by 3–7 months (ie, an 8–11% reduction) and the development costs by US$0·4 million (ie, a 1–4% reduction) only, assuming that the licensee is an experienced manufacturer with a track record in obtaining stringent regulatory authority approval for biosimilar monoclonal antibodies.

Regulatory approval and quality assurance

Upon successful product development, registration with stringent and national regulatory authorities should follow (including to meet the standards established by international health and procurement agencies). For small molecules, the WHO Prequalification of Medicines Programme provides a quality assurance pathway that is widely used in global health.[40] For biotherapeutics, WHO has initiated a pilot programme for prequalification of trastuzumab, rituximab, and human insulin.[50] Several biosimilar products have accordingly been prequalified for both trastuzumab and rituximab adopting this procedure. In the future, as and if more molecules are included within the scope of this programme, the WHO Prequalification of Medicines Programme could become an important pathway for the registration of biosimilars for medicines listed on the WHO Model List of Essential Medicines. The WHO Collaborative Registration Procedure could then be used to accelerate registrations in participating countries.[51] For products not assessed by the WHO Prequalification of Medicines Programme, the European Medicines Agency's EU-Medicines for all (formerly known as Article 58 procedure) provides an alternative for obtaining stringent regulatory authority approval.[52] Through EU-Medicines for all, products can be assessed for use in LMICs, and this pathway is also available to biosimilar manufacturers.[53] Among the LMICs analysed for regulatory aspects in this study (ie, Belarus, Colombia, Democratic Republic of the Congo, El Salvador, India, Indonesia, Kenya, Nicaragua, Pakistan, Peru, South Africa, Uganda, Ukraine, and Uzbekistan) the vast majority had separate guidelines for biosimilar registrations, with high diversity in registration requirements, which could be a barrier to broad registration (unpublished data). In some countries

(eg, South Africa), comparability with an originator product that is already registered in that country is required. In others (eg, India) there are requirements for clinical trials in local populations.

Expanding the use of biosimilars in LMICs

Cost-effectiveness

Findings from the limited number of cost-effectiveness studies on biotherapeutics available for LMICs (mostly for trastuzumab) suggest that substantial price reductions are needed to achieve cost-effectiveness.[54,55] For example, Gershon and colleagues[56] evaluated the cost-effectiveness of 1-year treatment of trastuzumab in 11 countries in sub-Saharan Africa, finding that originator trastuzumab was not cost-effective in any of these countries (with incremental cost-effectiveness ratios above the country-specific gross domestic product per capita threshold suggested by WHO).[57] Similarly, a cost-effectiveness and price target analysis of emerging medicines for type 2 diabetes showed that GLP-1 receptor agonists (such as oral semaglutide) would need to have their costs reduced by 80% to reach cost-effectiveness, as suggested by WHO.[57,58] Also, although Gavi, the Vaccine Alliance considered inclusion of monoclonal antibodies for the prevention of rabies in its 2018 Vaccine Investment Strategy, it has subsequently decided not to fund those medicines on the basis of cost and cost-effectiveness considerations.[59] Registration and market entry of multiple biosimilars should contribute to reducing prices of biotherapeutics substantially. Data from multiple countries suggest that for monoclonal antibody price reductions to attain cost-effectiveness takes time, and is more likely with substantial biosimilar competition. In India, for example, trastuzumab had reached a 78% price rationalisation by 2020 (compared with its innovator launch price in 2002) through the availability of several competing biosimilars (ie, 11 by 2020; unpublished data). Licensing to multiple manufacturers and managing and supporting the pool of licensees should help build strong competition faster, as has been shown for Medicines Patent Pool licences for small molecule medicines.[15,22–25] In addition to this effect on competition, as discussed previously, licensing could reduce the costs of biosimilar development (eg, through technology transfer, access to low-cost reference products ideally facilitated by the patent holder, or waived clinical trial requirements) enabling steep and early price reductions in LMICs, accelerating the path towards affordability and cost-effectiveness.[27]

Procurement and supply chain considerations

Among 16 organisations involved in aggregating demand, tendering, negotiating prices, and pooling procurement of medicines for LMICs surveyed, at least half (including the Clinton Health Access Initiative; the Global Fund to Fight AIDS, Tuberculosis, and Malaria; the Kenya Medical Supplies Authority; the Pan American Health Organization Strategic Fund; the UN Population Fund; and UNICEF) had started including a small number of biotherapeutics, such as filgrastim and trastuzumab, in their product lists.[60–65] However, international procurement and supply chain efforts (including demand creation, market shaping, and catalytic procurement activities) to support uptake of biotherapeutics in LMICs have been both rare and small in terms of their size and scope. This reality is unsurprising as biotherapeutics on the WHO Model List of Essential Medicines are mostly for non-communicable diseases, for which market shaping activities have been scarce even for small molecule medicines.[2] As part of the COVID-19 pandemic framework shifts, the procurement of monoclonal antibodies for COVID-19 could help further stimulate large-scale roll out of biotherapeutics in LMICs both across other disease areas and over the long term. For example, in alignment with WHO guidance, tocilizumab can be procured through the Global Fund's COVID-19 Response Mechanism—making it the first biotherapeutic to be supplied by the Global Fund.[60,66] In addition to international pooled procurement mechanisms, other initiatives to support uptake of biotherapeutics in LMICs could involve originator and sometimes biosimilar manufacturers, and include pricing agreements, patient assistance programmes, and various amounts of health system strengthening (eg, the Clinton Health Access Initiative's Cancer Access Partnership negotiated pricing agreements include bevacizumab, filgrastim, rituximab, and trastuzumab, and cover some countries in sub-Saharan Africa and Asia).[61,67] Although tiered pricing, patient assistance programmes, and existing originator-led generic brands can play a role, biosimilar-induced competition generally helps reduce the costs of biotherapeutics further, especially in public markets in which price erosion might be more substantial (unpublished data).[68,69] Finally, defining the markets of biotherapeutics, across potentially various indications, and developing credible demand forecasts to guide investments from manufacturers, funders, procurement agents, and governments could also be crucial to reduce uncertainties and spur broad and timely uptake.[3]

Health system requirements

The successful uptake of a biotherapeutic in low-resource settings requires holistic and multistakeholder interventions aimed at strengthening the health system and its capacity for delivering care.[70] Beyond the high prices of biotherapeutics, procurement agencies, innovators, and biosimilars companies have cited limited health-care system infrastructure as a key barrier for the uptake of many biotherapeutics, particularly in the non-communicable disease space (unpublished data). Heavy monitoring and pharmacovigilance requirements associated with some biotherapeutics (eg, for cancer) have also been mentioned. Cold supply

chain capacity for biotherapeutics is often available at the tertiary care level (eg, cancer treatment centres) but often represents a substantial challenge at the primary care level. The availability of adequate diagnostic infrastructure (eg, pathology and radiology services, as well as established algorithms for diagnosis) is a precondition for administering many biotherapeutics (such as those analysed in our case studies) and is particularly challenging in relation to targeted therapies for cancer. Orally formulated biotherapeutics (eg, oral semaglutide) are rare but are substantially easier to manage, store, and administer compared with injectables. Handling requirements of biotherapeutics are generally more sophisticated than those of small molecules (eg, some might require reconstitution and intravenous infusion). In addition, the management of adverse reactions such as those of immune-checkpoint inhibitors for cancer treatment often requires specific training and expertise, and the delivery of care in many LMICs could be affected by a paucity of qualified human resources for health. All these factors could hinder access and patients' safety, and the required infrastructure and capacity could substantially change from one drug or indication to another. Accordingly, for complex biotherapeutics, biosimilar entry might need to be supported by the development of human and infrastructure capacity (eg, companion diagnostics), leveraging service delivery strengths as entry points to maximise further capacity building efforts. For example, the newly launched Access to Oncology Medicines coalition, convened by the Union for International Cancer Control, with several civil society, public, and private sector partners (including the Medicines Patent Pool), aims to provide coordinated efforts towards the provision of comprehensive cancer care in LMICs, including strengthening the supply chain, capacity building, advocacy, demand generation, and training.[71] In time, such an initiative could also facilitate the pooling of demand across multiple treatment centres or countries, which could contribute to addressing challenges around the fragmented demand.

Summary and next steps

Key elements and recommendations for early access to biosimilars in LMICs

Public health licensing of small molecule medicines has been highly effective in supporting the scale-up of WHO-recommended treatments in the areas of HIV and hepatitis C virus (and it holds promise for COVID-19 too).[15,22,31,32,72] Recommendations discussed previously to support the successful use of public health licences to expand and accelerate access to affordable

	Considerations	Recommendations
Identifying potential biotherapeutic targets for public health licensing		
Clinical relevance and burden of disease Patents and other exclusivities Patent holders' perspective and licensing incentives	Burden of disease in LMICs, public health unmet needs, and additional benefits of biotherapeutics compared with available standards of care (and potential alternatives in the development pipeline) Intellectual property aspects (patents and other exclusivities) limiting competition, with potential consequences on affordability (and availability) in LMICs Molecule characteristics (eg, complexity, therapeutic category, and indications) and other aspects influencing the cost of development (and manufacturing) and market entry Substantial time, effort, and economic investments needed for technology transfer, in addition to issues regarding the protection of patent holders' intellectual property, especially around their broader portfolio of activities	Consider the burden of disease but also the associated epidemiological transitions Assess the clinical value of target biotherapeutics compared with current standards of care and drug development pipelines (especially for small molecules) Focus on biotherapeutics with the broadest and longest intellectual property protections to maximise the effect of a licence Identify biotherapeutics with potential for phase 3 clinical trial waivers Work with governments and stringent regulatory agencies to develop incentives to increase originators' willingness to agree to (early) licensing and technology transfers
Supporting biosimilar development		
Licensing, technology transfer, and product development Clinical development Regulatory approval and quality assurance	Development time and costs, and regulatory complexity of target biotherapeutics Role of technology transfer and costs of access to reference products—and the extent to which a patent holder might be willing to collaborate with potential licensees Regulatory requirements for biosimilar approvals and potential patent holder support for dossier submission Role of overarching regulatory mechanisms (eg, EU-Medicines for all, the WHO Prequalification of Medicines Programme, and the WHO Collaborative Registration Procedure) in facilitating quality assurance and in-country registration	Explore with patent holders the possibility of providing a licence including full technology transfer and an at-cost reference product (bundling in a licence of access terms for companion diagnostics might also help alleviate any health system limitations with regards to specific biomarker screening or monitoring requirements) Consider the WHO Prequalification of Medicines Programme and the Collaborative Registration Procedure scope expansion to additional biotherapeutic products Work closely and early with regulators to explore the possibility of obtaining some amount of regulatory waivers
Expanding the use of biosimilars in LMICs		
Cost-effectiveness Procurement and supply chain considerations Health system requirements	Cost-effectiveness thresholds in relation to potential target pricing Existing market shaping, demand creation, and health system strengthening initiatives Health systems capacity in relation to a biotherapeutic (and specific indication) diagnosis, administration, and monitoring requirements	Link licensing to (existing and new) health system strengthening and market shaping initiatives Align with countries disease priorities and focus on their infrastructure strengths and strengthening efforts (eg, regarding the availability of needed monitoring diagnostics and staff training) as starting points

LMICs=low-income and middle-income countries.

Table 2: **Considerations and recommendations to address requirements and seize opportunities for early access to biosimilars in LMICs**

biotherapeutics in LMICs are presented in table 2. Key takeaways include recommendations for the Medicines Patent Pool to (1) identify biotherapeutic priority targets for licensing, focusing on drugs that have the longest remaining patent protection and that show the largest incremental benefit over the standard of care and any expected alternative pipeline candidate. The possibility of benefitting from phase 3 clinical trial waivers to reduce costs and timelines could also be a desirable selection criterion. (2) Explore licensing with patent holders and the possibility for them to provide technology transfer (especially when it can substantially reduce costs or timelines) and reference products at affordable pricing as part of licensing agreements; (3) support biosimilar development, including assistance around regulatory strategies, to reduce costs

Search strategy and selection criteria

For this Review, we aimed at assessing how and when public health licensing of intellectual property rights might be applicable to biotherapeutics. We accordingly performed a comprehensive assessment, between Sept 2, 2019 and Oct 7, 2022, of potential challenges and enabling conditions that could make licensing a suitable model to increase access to biotherapeutics in low-income and middle-income countries (LMICs). Background information was retrieved from a multipronged literature review supported by expert assessments. We started by consulting the Geneva Graduate Institute Global Health Centre's Knowledge Portal on innovation and access to medicines, in particular the research syntheses on: "patent pools", "pooled procurement", "priority review vouchers", "tiered pricing", and "voluntary licensing". We then extended our exploration of the literature by manually inspecting the results (mostly in English, and published between 2010 and mid 2022, but with a focus on the most recent references, given the rapid pace of technical, regulatory, and medical progress in this area) of multiple PubMed searches (with a focus on reviews, systematic reviews, and meta-analyses) using the following keywords: "biologic", "biotherapeutic", and "biosimilar" (including in association with "access to", "affordability", "cost effectiveness", "generic", and "low- and middle-income countries"); and "voluntary licences" (including variations: "voluntary licenses", "voluntary licensing", "intellectual property licensing", and "Medicines Patent Pool"). Our searches also included association of those keywords with the names of the following biotherapeutic medicines (which we used as illustrative case studies): "filgrastim", "oral semaglutide", "pembrolizumab", "sotrovimab", and "trastuzumab". In addition, we gathered patent information from the World Intellectual Property Organization PATENTSCOPE database, as well as from the online databases of national patent offices in LMICs on the patented essential biotherapeutics listed on the WHO Model List of Essential Medicines; this information was added to the Medicines Patent Pool's fully public medicines patents and licences database MedsPaL. Information on the regulatory requirements for biotherapeutics was collected from the websites of regulatory authorities of 14 LMICs (in Asia: India, Indonesia, Pakistan; in Latin America: Colombia, El Salvador, Nicaragua, Peru; in Africa: the Democratic Republic of the Congo, Kenya, South Africa, Uganda; and in Eastern Europe: Belarus, Ukraine, Uzbekistan), as well as from the European Medicines Agency, the US Food and Drug Administration, and the UK Medicines and Healthcare Products Regulatory Agency. Procurement considerations and practices around biotherapeutics for LMICs were collected through interviews with procurement agencies and reviews of their websites and product catalogues. To complement the literature review, patent landscaping, and analysis of regulatory requirements and procurement considerations, several input papers were also commissioned to a diverse group of pharmaceutical, biotherapeutics, clinical, and access to medicines experts (unpublished). These papers aimed to assess clinical benefits, health system requirements, and market considerations enabling access to biosimilar products in various disease areas such as cancers, COVID-19, HIV, and type 2 diabetes across a diverse set of LMICs (including the Democratic Republic of the Congo, Kenya, Indonesia, Nicaragua, Pakistan, Peru, South Africa, Uganda, and Uzbekistan). Another commissioned report included analysis of 14 blinded interviews of representatives from 11 originator and biosimilar pharmaceutical companies involved in biotherapeutics (unpublished). This paper particularly looked at current strategies, gap analysis, and future opportunities for pharmaceutical companies to expand access to their portfolios of biotherapeutics in LMICs. These inputs built on the Medicines Patent Pool's experience in licensing medicines for HIV, hepatitis C virus, and COVID-19. As a complement, Medicines Patent Pool's business development experts had direct bilateral discussions on specific products with representatives of three innovator companies. New data was also produced as part of this work, with five products (ie, filgrastim, oral semaglutide, pembrolizumab, sotrovimab, and trastuzumab) serving as case studies representing the diversity of biotherapeutics across molecules of varying complexity and in multiple disease areas (ie, COVID-19, diabetes, neutropenia, and oncology; table 1) in terms of development, production, administration, past (ie, filgrastim and trastuzumab) or future (ie, oral semaglutide, pembrolizumab, and sotrovimab) patent expiry, disease burden, and product maturity. These case studies were used to outline different scenarios exploring the potential effects licensing and technology transfer could have on development costs, development timelines, and regulatory aspects, as well as market entry and uptake. The inclusion of two products for which key patents had already expired (ie, filgrastim and trastuzumab) provided historical comparators, as biosimilars for these products were already on the market.

For more on the **Geneva Graduate Institute Global Health Centre's Knowledge Portal** see https://www.knowledgeportalia.org

For more on the **World Intellectual Property Organization PATENTSCOPE database** see https://patentscope.wipo.int/search/en/search.jsf

For more on **MedsPaL** see https://www.medspal.org

and timelines from development to market entry; and (4) align efforts to expand the use of biosimilars in LMICs with country-specific and region-specific treatment priorities and relevant infrastructure strengthening efforts.

Other elements for which collaboration with and contributions from third parties will be essential for successful application of Medicines Patent Pool licensing in the biotherapeutics space include; (1) collaboration with governments and regulatory agencies (in particular stringent regulatory authorities) to explore incentive schemes to encourage early licensing and technology transfer; (2) coordination with regulators (including the WHO Prequalification of Medicines Programme and the WHO Collaborative Registration Procedure) with regards to regulatory requirements in the case of biosimilars developed in the context of licensing and technology transfer agreements and explore the possibility of waivers and simplification of clinical trial requirements, when appropriate; and (3) alignment of licensing efforts, processes, and goals with those of implementing stakeholders (ie, patent holders, biosimilar manufacturers, procurement agencies, funders, governments, civil society, and the communities of people affected by diseases treatable with biotherapeutics), in particular around market shaping, demand creation, and health system strengthening initiatives.

Moving forward: enabling access to optimal therapies for populations in LMICs

The elements discussed in this Review (table 2) provide a starting point on how to apply public health non-exclusive licensing agreements as part of multistakeholder efforts to expand access to affordable biotherapeutics in LMICs.[15,73] These key considerations, requirements, and opportunities offer levers to work on. As such, the Medicines Patent Pool Governance Board recently approved the inclusion of biotherapeutics in the Medicines Patent Pool's scope of work on facilitating affordable access to medicines in LMICs, with a focus on biotherapeutics that are "either on the WHO EML [Model List of Essential Medicines] or have strong potential for future inclusion".[74] This decision aligns well with the WHO Model List of Essential Medicines Expert Committee request for the Medicines Patent Pool to "explore the application of its licensing model" to several medicines, including biotherapeutics, such as immune checkpoint inhibitors (eg, atezolizumab, durvalumab, nivolumab, and pembrolizumab).[20] The expansion of the Medicines Patent Pool mandate is an important step towards more equity in access to biotherapeutics and fulfilling the human right to health of people living in LMICs. As such, the Medicines Patent Pool has started adapting its prioritisation framework to identify target biotherapeutics for in-licensing.[75] This framework assesses the public health needs and gaps, the clinical relevance of a medicine, and any associated access challenges (and whether these could be addressed through a Medicines Patent Pool intervention). Accordingly, biotherapeutic medicines are being listed as part of Medicines Patent Pool's priorities for in-licensing, which will trigger outreach to relevant patent holders, with the aim of starting licensing discussions.

Contributors

EB and SN provided strategic guidance on the project. AD, AL, EV, GS, KM, MD, MP, NL, and SM contributed background data collection and analysis informing the paper. EB, GS, MP, and SM planned, designed, and wrote the paper. SM, GS, and MP contributed equally.

Declaration of interests

AD, AL, EB, GS, MD, MP, NL, SM, and SN are employees of the Medicines Patent Pool. KM is a former employee of the Medicines Patent Pool. EV has acted as a global health and access policy consultant for the Medicines Patent Pool for this work.

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