Regulatory opportunities for treating age-related macular degeneration with bevacizumab biosimilars in low-middle income countries.

Writing Assignment

Ivar van der Zee

5693225

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Supervisors:

Prof. dr. Arnold G. Vulto, KU Leuven

Dr. Liese Barbier, KU Leuven

Examiner:

Prof. dr. Aukje Mantel-Teeuwisse, Utrecht University

Second-reviewer:

Prof. dr. Toine Egberts, University Medical Center Utrecht

Abstract

Neovascular age-related macular degeneration (nAMD) is a progressive eye-disease that can be treated through off-label intravitreal administration of bevacizumab, an anti-VEGF antibody registered for oncologic indications. Despite its inclusion in the WHO essential medicines list, bevacizumab remains mostly inaccessible to nAMD patients in low- and middle-income countries (LMICs), partly due to regulatory hurdles preventing bevacizumab from being registered in LMICs. This paper assesses whether LMIC-oriented regulatory pathways like EU-M4all are effective tools for overcoming these hurdles and improving patient access to bevacizumab or bevacizumab biosimilars in LMICs.

We found that while multiple LMIC-oriented regulatory pathways are available, they are generally aimed at addressing acute public health issues in the short-term. As a result, bevacizumab would likely not meet the eligibility criteria for most of them due to either its limited perceived urgency, pathways being solely aimed at specific therapeutic areas (e.g., HIV), or pathways not allowing biological products. This is unfortunate since nAMD poses an ever-increasing disease- and economic burden to LMICs. Therefore, we suggest stringent national regulatory authorities to either extend the scope of their existing pathways, or design novel ones aimed gradually worsening, non-acute, disease burdens like the one nAMD causes.

Layman's summary

Neovascular age-related macular degeneration (nAMD) is an eye-disease that gradually worsens and results in blindless if left untreated. In most wealthy and developed countries such Germany or North America, nAMD is treated with a drug called bevacizumab which was originally intended to treat certain cancers. Using a drug for something other than what it was officially approved for by a drug regulatory authority (NRA) like the European Medicines Agency is called '*off-label*' usage. The reason bevacizumab is used to treat nAMD 'off-label' is not because no officially approved alternatives exist, but because the alternatives are far more expensive while bevacizumab is just as effective. This cost difference exists because one vial of bevacizumab meant for cancer treatment contains enough medicine to fill roughly one hundred syringes meant for nAMD patients, which greatly reduces the per-patient treatment costs. This led the World Health Organization to include bevacizumab in its list of most important medicines rather than an officially approved alternative.

However, in low- and middle-income countries (LMICs) like Egypt and South-Africa, bevacizumab is not accessible to the majority of nAMD patients. One of the reasons for this is that before patients can get access, NRAs in LMICs give authorization for nAMD to be treated with bevacizumab or a so-called '*biosimilar*' of bevacizumab. Bevacizumab biosimilars are almost identical copies of bevacizumab that are often less expensive since they are manufactured by different companies trying to compete with the original product. Authorizing bevacizumab biosimilars in multiple LMICs is difficult since their NRAs are often under-resourced and inexperienced when it comes to complex drugs like bevacizumab and biosimilars in general.

Well-resourced organizations such as the World Health Organization, the European Medicines Agency, and the United States Food and Drug organization aim to address the challenges through *"LMIC-oriented regulatory pathways"*. These are programmes designed to give resource restricted LMIC NRAs access to trustworthy external assessments which they can subsequently use to authorize products locally. This way, LMIC NRAs do not have to carry out the complete assessment by themselves, enabling them to save resources and obtain access to external regulatory know-how they might not have in-house. Hundreds of products have been successfully authorized through LMIC-oriented regulatory pathways before, and they could be very effective at improving bevacizumab biosimilar availability in LMICs.

Unfortunately, bevacizumab biosimilars are unlikely to be eligible for most of these pathways because their eligibility requirements only allow products meant for treating the most urgent of diseases like HIV, malaria, and tuberculosis. This is a shame, since nAMD accounts for 8.7% of blindness worldwide and not only severely effects patients' personal lives, but also has a significant economic effect since

vision-loss prevents people from being productive. On top of that, the number of people suffering from nAMD is projected to increase in LMICs as life-expectancy rises. Of course, nAMD is not the only severe disease that falls just outside the eligibility requirements set by LMIC-oriented regulatory pathways. Therefore, we recommend organization that run these pathways to make them more accessible to product meant to treat diseases like nAMD, diseases that never make the news but nonetheless create enormous burdens on both individual patients and whole economies.

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Introduction

Age-related macular degeneration (AMD) is a progressive disease characterized by the deterioration of the macula; the area of the retina responsible for central, high-resolution vision (2). This deterioration causes symptoms such as blurry vision, black or grey spots in the visual field (scotomata), and distorted vision (metamorphopsia) (2,3). Symptomatic AMD manifests itself as geographic atrophy ('dry' AMD) and/or neovascular 'wet' AMD (nAMD). This paper is concentrates on 'wet' nAMD, as it responsible for 80% of AMD cases which result in severe vision loss despite making up just 10% of all AMD cases (3). Neovascular AMD arises when breaks in the retinal pigment epithelium and Bruch's membrane in the retina allow vessels from the underlying choroid to grow into the subretinal space (2) (Figure 1). These neovascular vessels tend to leak and bleed (hence the term 'wet'), causing fibrous scar tissue to replace the outer layers of the retina, with vision impairment as a result (2). There are several risk factors related to developing AMD, the strongest of which is age. AMD occurrence was shown to exponentially increase with age and clinically apparent AMD generally begins after 55 (2). Other risk factors include smoking, insufficient physical activity, hypertension, high BMI, and diabetes mellites (2,4).

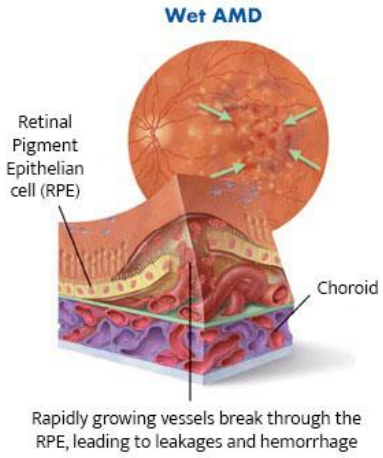

Figure 1: Pathology of neovascular AMD. The unwanted formation of blood vessels is stimulated by VEGF. Source: Macular Disease Foundation Australia.

The global prevalence of nAMD is estimated to be 0.46% (95%CI 0.18-1.08) in 2014 and this is expected to increase, especially in countries where life-expectancy is rising (3,5). The high prevalence and severity of AMD make it a leading cause of legal blindless, as it accounts for 8.7% of blindless globally (5),

Currently, the most effective way to treat nAMD is through inhibiting the vascular endothelial growth factor (VEGF) protein with anti-VEGF monoclonal antibodies. VEGF stimulates the unwanted formation of new blood vessels in the subretinal space, causing nAMD symptoms (figure 1) (2). Therefore, inhibiting VEGF

Table 1. Overview of Anti-VEGF products used for nAMD

Trade name (Active compound)	***Drug Sponsor***	***Year first approved***	***Class***
Avastin* (bevacizumab)	Genentech	2004 (FDA)	recombinant humanized monoclonal antibody
Lucentis (ranibizumab)	Genentech	2006 (FDA)	monoclonal antibody fragment
Eylea (aflibercept)	Regeneron	2011 (FDA)	recombinant fusion protein
Beovu (brolucizumab)	Novartis	2019 (FDA)	humanized single-chain antibody fragment

Source: Drugbank.ca (1)

*Used off-label

reduces the likelihood of further vision loss and legal-blindness, and can even restore visual acuity previously lost to nAMD (2,3). Today, there are four different anti-VEGF drugs available to treat nAMD, all of which are administered via intravitreal injection, table 1 provides an overview. Bevacizumab (Avastin) is not approved for nAMD but is commonly utilized off-label for nAMD treatment.

As soon as the first results of ranibizumab for nAMD treatment became available in 2006, clinical studies were started to understand whether off-label bevacizumab was suitable for nAMD treatment as well (6). After all, both products were anti-VEGF antibodies. Since then, multiple large trials directly comparing bevacizumab to ranibizumab have taken place. A 2019 Cochrane review of ten of these trials, with 3657 patients in total, found no clinically relevant differences in prevention of blindness, visual acuity, visual function, and adverse events between ranibizumab and off-label bevacizumab (3). It was not, however, formally registered for nAMD treatment since registered alternatives were available and little commercial incentives existed.

Since bevacizumab's efficacy and safety were demonstrated to be equal to ranibizumab, treating nAMD with bevacizumab vials intended for oncologic use became the preferred method in several countries including most of the EU. The reason this is preferred over approved alternatives lies in the cost difference. One vial of bevacizumab can be used for roughly 50 intravitreal injections, hence the cost per treatment dramatically decreases (7). In the Netherlands, this equates to reducing the cost of a one-year nAMD treatment from €14.412 with ranibizumab to €297 with off-label bevacizumab, roughly 50 times less. Similar costs-saving compared to ranibizumab are seen in India (8) and the United Kingdom (7).

Off-label use of bevacizumab for nAMD works by splitting a single vial meant for systemic administration into around 50 smaller syringes suitable for intravitreal use (7). This must be done carefully and under aseptic conditions as contaminations can increase risks of infection. Cases of endophthalmitis after multiple intravitreal injections from a single use vial of bevacizumab have been reported (9). However, the incidence of post-injection endophthalmitis is low and it is not always a result of improper dose splitting. For example, in India, counterfeit bevacizumab vials are the most common cause of endophthalmitis (10).

In 2013 the World Health Organization (WHO) decided to include bevacizumab in the Essential Medicines List (EML) for nAMD treatment on grounds of public health need, demonstrated safety and effectiveness, and favourable cost-effectiveness despite its lack of stringent regulatory authority approval (11). Novartis, the authorization holder of ranibizumab, subsequently requested ranibizumab to be included in the EML for nAMD treatment in 2015, but WHO rejected, arguing bevacizumab is preferred since ranibizumab offers no clinical benefits while coming at a greater cost (12). Given WHO's

preference for off-label use of bevacizumab and the absence of evidence that registered alternatives provide any clinical benefits in comparison, this paper will concentrate on bevacizumab and its biosimilars when exploring anti-VEGF availability in low- and middle-income countries (LMICs). Subsequently, this paper will aim to answer the question whether regulatory pathways specifically aimed at LMICs like the EU-M4all programme are effective tools for improving availability bevacizumab (biosimilars) in LMICs.

Bevacizumab in low- and middle-income countries

In contrast to developed regions, treatment options for eye health conditions, including nAMD, remain limited in LMICs. Furthermore, a major gap exists in solutions-focused eye-health research which is contextually relevant to LMICs (13). Hence, decision-makers in LMICs are limited in effectively improving accessibility to eye-health related treatments. Meanwhile, LMICs are faced with the greatest age-standardized burden of disease (DALY) from AMD, since they typically have a lower human-development index (HDI) which was shown to correlate to roughly 1.5 times more DALYs per capita caused by AMD (figure 2) (14,15). Moreover, per capita productivity loss because of visual impairment is up to 3 times higher in developing countries compared to developed ones (figure 3). Thus, not only the disease burden, but also the relative economic burden of nAMD is highest in LMICs. On top of all that, the prevalence of nAMD in LMICs is expected to rise due to increasing life-expectancy and obesity rates (5). This will further amplify the economic and societal burden of nAMD and with it the necessity for accessible treatment options like anti-VEGF.

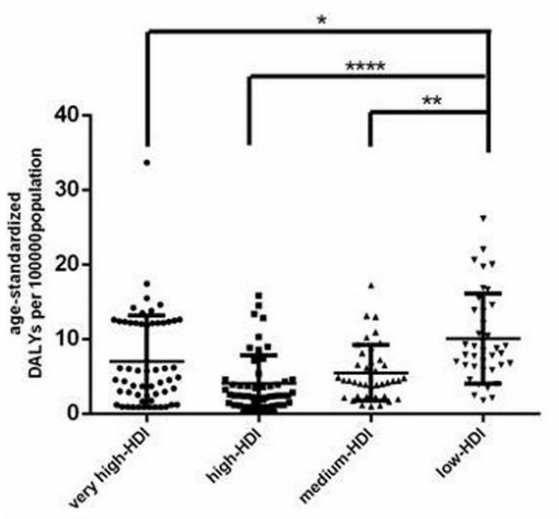

Figure 2: Burden of AMD in age-standardized disability-adjusted life years by national socioeconomic development in 2017. (14)

**P < 0.05, ***P < 0.001, ****P < 0.0001*

Anti-VEGF treatments such as bevacizumab are, despite the clear necessity for accessible and effective nAMD treatment, rarely available in LMICs. Anti-VEGF treatments cost hundreds to thousands of dollars per patient per year, while most LMICs' yearly public health expenditure is less than $100 per capita (fig 4a) (16). Hence, current pricing for bevacizumab, even when dose splitting for intravitreal use, does not allow for widespread use there. It is simply too expensive. Apart from pricing, off-label bevacizumab requires aseptic facilities and trained personal for splitting vials into multiple syringes (7). Such facilities and staff are not available everywhere, meaning either large capital investments would be necessary to establish them, or the import of pre-filled syringes needs to be arranged. A possible solution to these pricing limitations surrounding bevacizumab would be the use of biosimilar products, as these are generally cheaper since their availability introduces competition to the market (17,18).

Since bevacizumab's patent expired in 2019, several biosimilars have become available and over 20 are in the pipeline worldwide (20). Eight bevacizumab biosimilars have been authorized in the EU (19) (Table 2). Of these, four have identical formulations to bevacizumab. This is important for off-label

usage because formulation disparities can have unknown consequences when administering intravitreally and would thus require additional, expensive, safety studies. Therefore, off-label nAMD treatment is only feasible with biosimilars formulated identically to bevacizumab. These biosimilars are MVasi, Oyavas, Alymsis, and Abevmy. So far, however, these have failed to reach LMICs. A brief web-search showed no indication that any are currently registered or used in any LMIC except for Abevmy, which was 'launched' in India for oncologic use according to its sponsor (21).

Although some biosimilars are available in LMICs (22), they have trouble gaining a significant foothold, as LMICs typically have maturing National Regulatory Agencies (NRAs) that lack regulatory capacities and standardized pathways to efficiently register biosimilars (23–25). A method to deal with such shortcoming which has gained popularity over the last decade is *regulatory reliance*, the practice of one NRA relying on the expertise and work-done by another NRA to inform one's own decision. However, a prerequisite for such reliance pathways is an existing registration by a trusted NRA, which does not exist in case of bevacizumab for intravitreal use since it is used off-label. This inability to use existing reliance pathways combined with regulatory capacity restrictions will potentially cause review times that can already take years in LMICs (26,27) to be prolonged even further. Additionally, varying requirements and legislative frameworks found in LMICs are known to severely delay and complicate registering drugs in multiple countries, as every country requires a separate dossier to be created, which requires substantial amounts of resources and time from the drug sponsor (27). These discrepancies between countries are likely even larger for off-label and biosimilar registration requests, as these procedures are relatively novel and therefore less standardized. Altogether, it seems improbable the current regulatory institutions in LMICs by themselves would allow for widespread bevacizumab availability, especially considering the limited monetary incentives these regions provide to commercial parties.

One possible way to partly circumvent these regulatory obstacles, however, could be by having a bevacizumab biosimilar assessed through a specialized LMIC-oriented regulatory pathways. These are offered by several stringent NRAs including the European Medicines Agency (EMA), who run the EU-M4all programme (article 58).

Table 2. Overview of bevacizumab biosimilars registered in Europe

Brand name (Bevacizumab)	***Drug Sponsor***	***Year first approved***
Mvasi*	Amgen	2018 (EMA)
Zirabev	Pfizer	2019 (EMA)
Aybintio	Samsung Bioepis	2020 (EMA)
Equidacent	Centus	2020 (EMA)
Onbevzi	Samsung Bioepis	2021 (EMA)
Alymsys*	mAbxience	2021 (EMA)
Oyavas*	Stada	2021 (EMA)
Abevmy*	Viatris	2021 (EMA)

Source: EMA medicines database (19)

*Products with formulation identical to Avastin

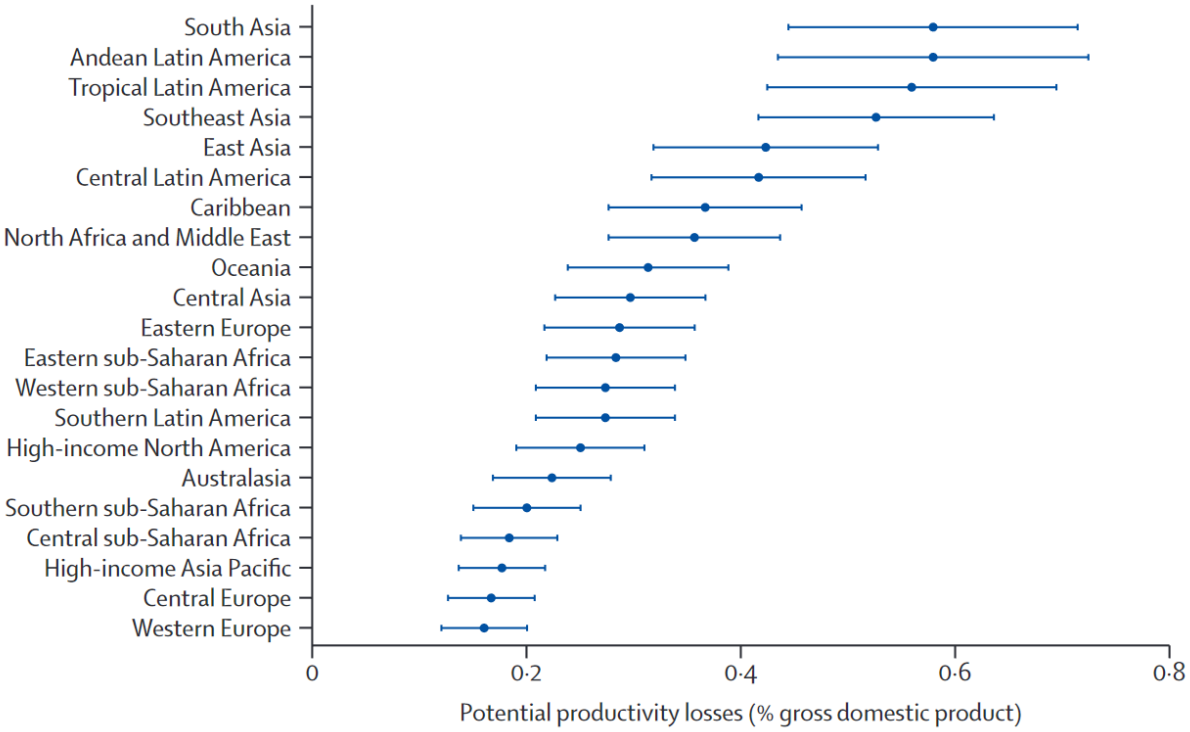

Figure 3: Estimated productivity losses of people who were blind or had moderate and severe vision impairment per region, as a percentage of GDP. (13)

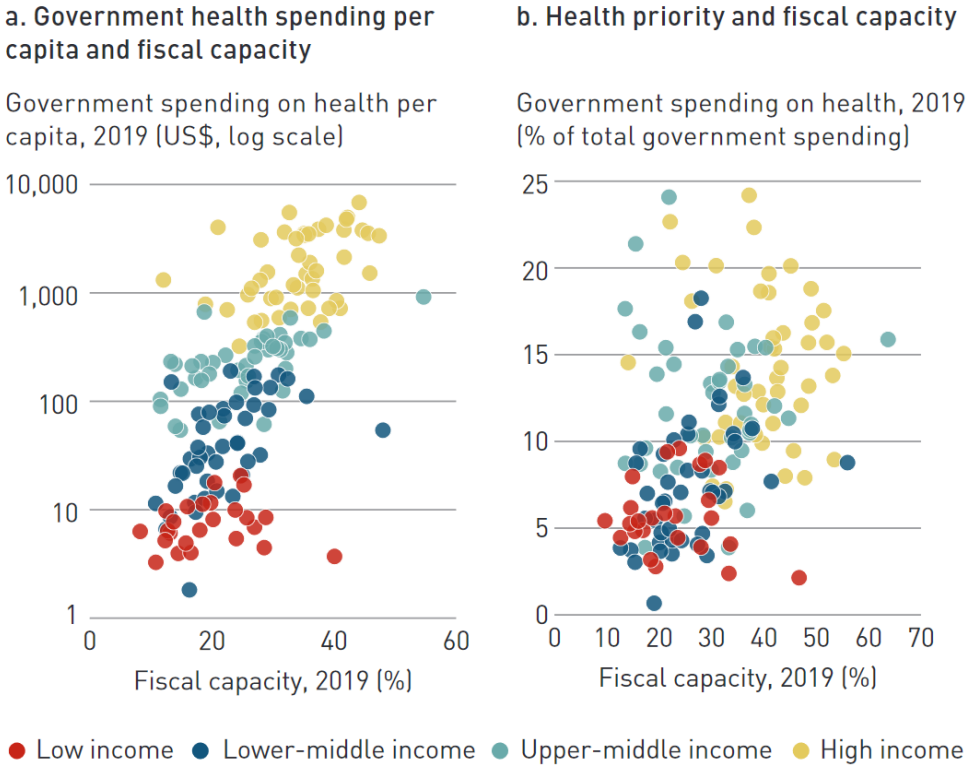

Figure 4: Dot-plots of per capita health spending (a) and relative government spending on health (b) against fiscal capacity per country. Countries categorized by World Bank income groups. Fiscal capacity is measured by a proxy of general government expenditure as a share of GDP. Source: WHO (16)

EU-M4all and WHO Prequalification procedure for bevacizumab biosimilars

As a part of its international collaboration efforts and its goal to contribute global health, EMA issues scientific opinions on medicines meant for use outside the EU through the EU-Medicines4all (EU-M4all) procedure, previously known as Article 58 (28). The procedure allows EMA to assess and provide scientific opinions for medicines meant for use in countries with limited regulatory capacities. Eligible medicines include new chemical and biological medicines, vaccines, generics, and biosimilars for the prevention or treatment of diseases of major public health interest (29). So far, EU-M4all has successfully led to 142 registrations in 92 countries for mostly endemic diseases such as HIV/AIDS, malaria, and African trypanosomiasis. While EU-M4all is meant for products that will be used exclusively outside of the EU (29), four of 11 medicines that went through the EU-m4all were already centrally authorized in the EU before being considered for EU-M4all (30). A 2020 assessment of EU-M4all concluded that the procedure has true public health impact and facilitates patient access to medicines, although further analysis of patient level impact is required (28).

The procedure follows the same principles as the centralized procedure for use in the EU. First, a drug sponsor requests eligibility for EU-M4all, which is then considered by the Committee for Medicinal Products for Human Use (CHMP) and the WHO. If they are eligible, they submit a dossier that is reviewed by the CHMP in collaboration with WHO and experts from relevant countries. Their input helps the CHMP consider local factors that may not be applicable in the EU, so that the opinion is relevant to the population for which the product is intended. For EU-M4all assessments, the CHMP applies the same regulatory rigor as in the centralized procedure, meaning the same safety, efficacy and quality standards apply. The fees for EU-M4all are equal to the centralized procedure and EU-M4all applicants get the same access to EMA support mechanisms such as scientific advice, business pipeline meetings, and the SME office (31). As of May 2020, a parallel procedure for centralized registration in the EU and EU-M4all is also available (32).

Despite the similarities to the centralized procedure, a positive EU-M4all opinion does not equal a registration. Therefore, drug sponsors need to seek registration locally after receiving a positive opinion from the CHMP. A common way to accomplish this is through first applying for WHO prequalification. WHO's prequalification programme assesses medicines meant for use in LMICs to ensure products in those markets meet acceptable standards of quality, safety and efficacy (33). Translating a EU-M4all opinion into a WHO prequalification is relatively straight forward since EU-M4all medicines can be prequalified through the 'alternative listing procedure' without further review by WHO (29). WHO prequalification is more widely recognised than EU-M4all and serves as the most common axis for interactions between NRAs from high- income countries, LMICs NRAs, and

manufacturers (27). As a result, most EU-M4all products are prequalified before registration in LMICs (34).

While such a regulatory pathway is very fitting on paper, its applicability to bevacizumab remains uncertain. EU-M4all guidelines indicate eligible products should be intended to prevent or treat diseases of major health impact (29). Of course, one could argue bevacizumab falls in this category. However, the examples listed in EMA guidelines are for WHO public health priority diseases and WHO target diseases such as HIV, malaria, and tuberculosis. Given that all these diseases represent greater disease burdens than AMD, it remains to be seen whether the CHMP will consider a bevacizumab biosimilar eligible. Similar eligibility issues apply to a subsequent WHO prequalification, since biologicals are not allowed to get prequalified yet (35). However, this might change soon since a pilot resulted in successful prequalification of trastuzumab in 2019 (36). Still, even if biologicals become eligible, WHO's current list of therapeutic areas eligible for prequalification does not include AMD (37). This could hamper a potential prequalification, yet bevacizumab's inclusion in the EML shows WHO does acknowledge its necessity. As a result, predicting whether prequalification is feasible remains hard, but chances will likely improve as WHO extends its prequalification programme to biologicals.

Alternatives pathways outside the European Union

A similar pattern arises when looking at other regulatory pathways specifically aimed at LMICs offered by stringent NRAs (Table 3). For example, the FDA offers both the PEPFAR and the TD PRV pathway for products used in LMICs (38,39). However, these are limited to HIV and tropical diseases, respectively. Similarly, Health Canada runs an LMIC focused pathways called CAMR, yet this is solely aimed at providing compulsory licenses for patented drugs (40). All in all, most of these existing regulatory pathways do effectively target drug availability in LMICs but are quite restrictive in what products are eligible, which could hinder products like bevacizumab.

One novel registration pathway that breaks this trend is Swissmedic's Marketing Authorization for Global Health Products (MAGHP) programme, which aims to facilitate access to high-quality, essential medicines for populations living in LMICs and is not limited to specific therapeutic areas (41). It was successfully piloted in collaboration with the NRAs of Uganda, Kenya, Tanzania, South Sudan, Nigeria, Democratic Republic of Congo and Ethiopia in 2020, resulting in the authorization of Carbetocin Ferring for prevention of postpartum haemorrhage (42). Like EU-M4all, the MAGHP follows the same criteria as a regular authorization and is also performed in collaboration with WHO. The regional NRAs involved in the procedure can provide their own input to the evaluation process and get access to Swissmedic's assessment and inspection reports. As a result, they are expected to formally register the product within 90 days of Swissmedic's decision (41). This largely takes away the necessity of an intermediary

step like WHO prequalification and expedites the often-lengthy local registration procedures. Furthermore, MAGHP allows products with a known active pharmaceutical ingredient to be registered for new indications, which could allow a bevacizumab biosimilars to be registered for intravitreal administration, bypassing the regulatory difficulties related to off-label usage.

Regular registration pathways

Besides the LMIC-focussed pathways, a regular nAMD registration in the EU or US could also advance bevacizumab biosimilar availability in LMICs since this eliminates the complexities that come with off-label usage. Additionally, this would bypass any LMIC-specific eligibility criteria as it concerns a regular registration. Given the enormous amount of real-world evidence of bevacizumab's efficacy for AMD, extending its label to nAMD would not require large additional clinical studies. Yet, neither the originator nor any biosimilar have so far been formally registered for nAMD. This might seem counterintuitive given the prevalence of nAMD combined with bevacizumab's effectiveness. However, formally extending the label of off-label products like bevacizumab poses a high administrative burden and substantial costs to drug sponsors, while the return-on-investment is limited given the already widespread off-label use (43). **T**herefore, the commercial incentive is almost non-existent. Despite that, efforts to nevertheless register bevacizumab biosimilars for nAMD are currently being made by Outlook Therapeutics (Lytenava) and Rotterdam Biologics (Ipique). Ipique was refused market authorization in the EU because its dossier was considered incomplete (44), but Lytenava is expected to receive FDA approval by the end of 2022, based on 3 clinical trials comparing their bevacizumab biosimilar to ranibizumab (Lucentis) (45)**.** Such a registration for nAMD in the US could create the possibility to utilize existing reliance pathways in LMICs. Regulatory reliance is endorsed by WHO (46) and numerous LMICs have reliance pathways in place. For instance, 65% of Latin-American NRAs were found to use reliance pathways (47) and promoting reliance is one of the aims of the recently established African Medicines Agency (48,49). Hence, registering bevacizumab for nAMD by a stringent NRA, and subsequently making it available in LMICs through reliance pathways could also prove to be a feasible option. Although this approach nicely circumvents any eligibility requirements of LMIC specific pathways, it does rely more on regional expertise. This could be problematic in case of bevacizumab since regulatory capacity in LMICs regarding biologicals is often limited (24,25,50) and while reliance pathways can alleviate such shortcomings, they are no silver bullet. Furthermore, this approach is heavily dependent on Outlook Therapeutics since their registration would not automatically extend the labels of existing bevacizumab biosimilars to nAMD, so they would be the only sponsor able to attempt reliance registration in LMICs.

Table 3. LMIC-oriented regulatory pathway overview

Pathway	**EU-M4all** (29)	**MAGHP** (41)	**PEPFAR** (38)	**TD PRV** (39)	**CAMR** (40)	**WHO PQ** (37)	**Regular registration**
NRA*	EMA	Swissmedic	FDA	FDA	Health Canada	WHO	n.a.
Active since	2004	2017	2003	2007	2005	2001	n.a.
Product type	Innovative & Generic	Innovative & Generic	Innovative & Generic	Innovative	Generics	Innovative & Generic	Innovative & Generic
Eligibility requirements	Diseases of major public health interest in LMICs.	Unrestricted, but focused on diseases affecting LMICs	HIV/AIDS	Tropical diseases	Patented products	Therapeutic areas considered vital by WHO**	n.a.
Time in days* (excl. clock stops)	332 (innovative) 82 (previously approved)	290-430	<180	<180	180-290	206 (full dossier) 23 (previously approved)	EMA: 210 FDA: 300
Completed procedures	12 (April 2022) (19)	1 (April 2022) (42)	239 (April 2022) (51)	8 (2018) (52)	1 (May 2020) (53)	157 Active ingredients (54) 620 pharmaceutical products (34) (March 2022)	
Pro's	Pathway has proven effective. Same regulatory rigor as centralized procedure	Lenient eligibility requirements. Direct involvement of regional NRAs.				Very widely recognized and used procedure. Efficiently able to reach multiple countries.	No special eligibility requirements. Allows utilization of existing reliance pathways.
Con's	Eligibility requirements might hinder bevacizumab. Subsequent prequalification currently not yet possible for bevacizumab.	Less established, has only been used once.	Bevacizumab not eligible.	Bevacizumab not eligible.	Bevacizumab not eligible.	Currently does not accept biologicals like bevacizumab, although this will likely change in future.	Relies more heavily on regional regulatory capacity in LMICs,

*Timeline data taken from EMA Presentation (55)

**Subject to change, current list of eligible therapeutic areas available online (37)

Discussion

Bevacizumab (biosimilar) availability in LMICs for treatment of nAMD requires a sponsor, adequate commercial incentives, and regulatory registration. Naturally, these three necessities cannot be met independently. After all, no sponsor is interested without commercial incentives, commercial incentives cannot exist without registration, and no registration takes place without a sponsor. Simply put, resolving one part directly influences the others. In case of this paper, availability of effective LMIC-oriented regulatory pathways could prompt drug sponsors to register bevacizumab biosimilars for nAMD, thereby improving accessibility.

Several LMIC-oriented regulatory pathways like EU-M4all exist to facilitate regional registrations, but it's uncertain whether intravitreal bevacizumab is eligible for most of these. In essence, this uncertainty stems from the limited sense of urgency surrounding AMD, as eligibility for these pathways is based on the perceived urgency of the therapeutic area that the product addresses. This is where the characteristics of AMD give it a disadvantage. Although nAMD is a serious condition, it is not acutely life-threatening, and patients develop vision impairments gradually. While this (justly) lowers its perceived sense of urgency, it also distracts from the enormous disease burden it poses, especially in LMICs, where the economic consequences of vision lost are largest (figure 3) and the prevalence of AMD is set to grow as life-expectance rises (5). Perhaps, meeting with regulators to convince them of this perspective is an option to make bevacizumab eligible for EU-M4all, but this is a long shot. Alternatively, patient advocacy groups could raise the perceived urgency of nAMD. However, similar to LMIC-oriented pathways, advocacy groups in LMICs are mainly exist for the most urgent diseases (56).

Besides potential eligibility issues, bevacizumab's registration in LMICs is further complicated by the fact that regulatory capacity gaps in LMICs exist for biologicals (24,50) and the WHO prequalification process —meant to facilitate patient access to medicines in LMICs — does not currently allow biological products (35). On top of that, regulatory reliance pathways are not an option since bevacizumab is used off-label, although this might change soon. All in all, registering bevacizumab or a bevacizumab biosimilar in many LMICs will likely not be straightforward. However, some of the regulatory barriers are in the process of being resolved already. WHO recently prequalified the first biological through a pilot (36) and Swissmedic introduced a novel LMIC-oriented pathway without strict eligibility requirements (41). Furthermore, Outlook pharmaceuticals expects to obtain a formal registration of their bevacizumab biosimilar this year, opening possibilities for reliance registrations.

Still, improving availability of anti-VEGF therapy in LMICs is not merely a matter of registration. For a product to become widely available, it needs to be affordable, but despite the already relatively low price of bevacizumab, a significant price reduction is still necessary it to be affordable in LMICs. Besides pricing, products need to be distributed to and properly stored in places where patients can get access. Multiple mechanism designed to overcome these post-registration hurdles exist. Examples of these are value-based tiered pricing (57), voluntary licensing agreements (58), compulsory licensing (59), and public-private partnerships (60). While an increasing number of corporate actors have established access programmes around these mechanisms, a 2021 benchmark by the Access to Medicines Foundation found their use to be limited and too often focused on just a handful of countries (61). Furthermore, not all access initiatives prove effective. For instance, in 2018 Gilead announced it would expedite registration of liposomal amphotericin B in 116 LMICs while asking a (tiered) no-profit price to improve accessibility. However, a year after its announcement the drug was still neither broadly registered nor affordable, leading Médecins Sans Frontières (MSF) to declare the initiative nothing but a PR stunt (62). For bevacizumab, an ambitious but effective solution could be establishing a local manufacturing site through technology transfer (63). Such a site could directly produce intravitreal syringes, circumventing the need for dose-splitting and thus reducing complexity. Initiatives geared towards developing local manufacturing capacity in LMICs like the Emerging Biopharmaceutical manufacturing network (EBPMN) could prove to be valuable partners in attempting to accomplish this.

Apart from whether one of these processes works out best for treating nAMD in LMICs, this will certainly not be the last case of a major disease burden caused by inadequate biological accessibility. The growing presence of biologicals and biosimilars on the WHO essential medicines list shows they are becoming an ever more vital part of everyday care (64). Accordingly, stringent NRAs should increase their efforts to facilitate their availability in LMICs. Currently, however, LMIC-oriented registration pathways, are generally designed to address acute public health issues in the short-term. Long-term issues like gradually increasing prevalence and economic burden remain mostly overlooked in the short-term strategies that LMIC-oriented regulatory pathways are meant to facilitate. Herein lies an opportunity for stringent NRAs, who could design novel LMIC-oriented regulatory pathways specifically aimed at addressing gradually worsening, non-acute, disease burdens like the one AMD causes. Such pathways would require a fundamentally different way of determining eligibility, shifting from present-day urgency to a more anticipatory view. Inspiration for these could be drawn from diabetes treatment access programmes for LMICs, since diabetes is similar to nAMD in that it also poses a slow but severe disease burden that requires long-term treatment. Alternatively, NRAs could extend the scope of their existing LMIC-oriented regulatory pathways to a broader range of products, especially biologicals and biosimilars since LMIC NRAs often lack the capacity to effectively register

those. While both options will not remove the necessity for a drug sponsor and a commercial incentive, they would nevertheless stimulate biological and biosimilar registrations in LMICs, thereby building regional regulatory capacity and enhancing treatment options in LMICs for nAMD and other diseases not considered top public health priorities.

1. Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Res [Internet]. 2018 Jan 1 [cited 2022 Apr 21];46(D1):D1074–82. Available from: https://pubmed.ncbi.nlm.nih.gov/29126136/

2. Fleckenstein M, Keenan TDL, Guymer RH, Chakravarthy U, Schmitz-Valckenberg S, Klaver CC, et al. Age-related macular degeneration. Nat Rev Dis Prim 2021 71 [Internet]. 2021 May 6 [cited 2022 Mar 2];7(1):1–25. Available from: https://www.nature.com/articles/s41572-021-00265-2

3. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular agerelated macular degeneration. Cochrane Database Syst Rev [Internet]. 2019 Mar 4 [cited 2022 Mar 2];2019(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005139.pub4/full

4. Chakravarthy U, Wong TY, Fletcher A, Piault E, Evans C, Zlateva G, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC Ophthalmol [Internet]. 2010 [cited 2022 Mar 8];10(1). Available from: https://pubmed.ncbi.nlm.nih.gov/21144031/

5. Wong WL, Su X, Li X, Cheung CMG, Klein R, Cheng CY, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Heal [Internet]. 2014 Feb [cited 2022 Mar 2];2(2). Available from: https://pubmed.ncbi.nlm.nih.gov/25104651/

6. Rosenfeld PJ. Intravitreal Avastin: The Low Cost Alternative to Lucentis? Am J Ophthalmol. 2006 Jul 1;142(1):141–3.

7. International Council of Ophthalmology. Bevacizumab - WHO EML Application for addition submitted by International Council of Ophthalmology [Internet]. WHO; Available from: https://www.who.int/selection_medicines/committees/expert/19/applications/Bevacizumab_21_A_Ad.pdf?ua=1,

8. Jose V, Radhakrishna S, Pipalava P, Singh I. Bevacizumab for eye diseases – Legal, regulatory, and ethical overview. Indian J Pharmacol [Internet]. 2019 Nov 1 [cited 2022 Mar 9];51(6):377. Available from: /pmc/articles/PMC6984021/

9. Khan P, Khan L, Mondal P. Cluster endophthalmitis following multiple intravitreal bevacizumab injections from a single use vial. Indian J Ophthalmol [Internet]. 2016 Sep 1 [cited 2022 Mar 9];64(9):694. Available from: /pmc/articles/PMC5151169/

10. Vitreo Retina Society of India (VRSI). Guidelines for intravitreal injections of Avastin (bevacizumab) [Internet]. 2017. Available from: https://vrsi.in/wp-content/uploads/2018/02/Avastin_Guidlines_Book.pdf

11. World Health Organization. The Selection and Use of Essential Medicines (2013) - TRS 985 [Internet]. 2013. Available from: https://www.who.int/publications/i/item/9789241209854

12. Cohen D. Lucentis excluded from WHO list of essential medicines. BMJ [Internet]. 2015 May 13 [cited 2022 Mar 10];350:h2573. Available from: https://www.bmj.com/content/350/bmj.h2573

13. Burton MJ, Ramke J, Marques AP, Bourne RRA, Congdon N, Jones I, et al. The Lancet Global Health Commission on Global Eye Health: vision beyond 2020. Lancet Glob Heal [Internet]. 2021 Apr 1 [cited 2022 Mar 9];9(4):e489–551. Available from: http://www.thelancet.com/article/S2214109X20304885/fulltext

14. Xu X, Wu J, Yu X, Tang Y, Tang X, Shentu X. Regional differences in the global burden of age-

related macular degeneration. BMC Public Health [Internet]. 2020 Mar 30 [cited 2022 Mar 7];20(1):1–9. Available from: https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-020-8445-y

15. Lin X, Lou L, Miao Q, Wang Y, Jin K, Shan P, et al. The pattern and gender disparity in global burden of age-related macular degeneration. Eur J Ophthalmol [Internet]. 2021 May 1 [cited 2022 Mar 9];31(3):1161–70. Available from: https://journals.sagepub.com/doi/10.1177/1120672120927256?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed

16. World Health Organization. Global expenditure on health: Public spending on the rise? [Internet]. 2019 [cited 2022 Mar 11]. Available from: https://www.who.int/publications/i/item/9789240041219

17. Frank RG, Shahzad M, Kesselheim AS, Feldman W. Biosimilar competition: Early learning. Heal Econ (United Kingdom). 2022 Apr 1;31(4):647–63.

18. Dickson SR, Kent T. Association of Generic Competition With Price Decreases in Physician-Administered Drugs and Estimated Price Decreases for Biosimilar Competition. JAMA Netw Open [Internet]. 2021 Nov 1 [cited 2022 Apr 21];4(11):e2133451–e2133451. Available from: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2786133

19. European Medicines Agency. EMA online medicines database [Internet]. [cited 2022 Mar 15]. Available from: https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/search_api_aggregation_ema_active_substance_and_inn_common_name/bevacizumab/ema_group_types/ema_medicine/field_ema_med_status/authorised-36

20. Generics and biosimilar Initiative. Biosimilars of bevacizumab [Internet]. 2021 [cited 2022 Mar 15]. Available from: https://www.gabionline.net/biosimilars/general/Biosimilars-of-bevacizumab

21. Mylan. Mylan Launches Biosimilar Bevacizumab, ABEVMY®, in India [Internet]. 2017 [cited 2022 Mar 15]. Available from: https://www.mylan.in/en/news/press-releases/2016/mylan-launches-abevmy-in-india

22. Kang HN, Thorpe R, Knezevic I, Casas Levano M, Chilufya MB, Chirachanakul P, et al. Regulatory challenges with biosimilars: an update from 20 countries. Ann N Y Acad Sci [Internet]. 2021 [cited 2022 Mar 16];1491(1):42–59. Available from: https://pubmed.ncbi.nlm.nih.gov/33222245/

23. Sithole T, Mahlangu G, Salek S, Walker S. Evaluation of the Regulatory Review Process in Zimbabwe: Challenges and Opportunities. Ther Innov Regul Sci [Internet]. 2021 [cited 2021 Jan 12]; Available from: https://pubmed.ncbi.nlm.nih.gov/33387356/

24. Roth L, Bempong D, Babigumira JB, Banoo S, Cooke E, Jeffreys D, et al. Expanding global access to essential medicines: Investment priorities for sustainably strengthening medical product regulatory systems. Global Health [Internet]. 2018 Nov 1 [cited 2022 Apr 26];14(1):1–12. Available from: https://globalizationandhealth.biomedcentral.com/articles/10.1186/s12992-018-0421-2

25. Dube-Mwedzi S, Kniazkov S, Nikiema JB, Kasilo OMJ, Fortin A, Tumusiime P, et al. A rapid assessment of the National Regulatory Systems for medical products in the Southern African Development Community. J Pharm Policy Pract. 2020 Oct 5;13(1).

26. Centre for Innovation in Regulatory Science. CIRS Annual Regulatory and Access Factbook

2020. London, UK; 2020.

27. Ahonkhai V, Martins SF, Portet A, Lumpkin M, Hartman D. Speeding access to vaccines and medicines in low- and middle-income countries: A case for change and a framework for optimized product market authorization. PLoS One. 2016;11(11):1–12.

28. Cavaller Bellaubi M, Harvey Allchurch M, Lagalice C, Saint-Raymond A. The European Medicines Agency facilitates access to medicines in low- and middle-income countries. https://doi.org/101080/1751243320201724782 [Internet]. 2020 Mar 3 [cited 2022 Mar 11];13(3):321–5. Available from: https://www.tandfonline.com/doi/abs/10.1080/17512433.2020.1724782

29. European Medicines Agency. EMA procedural advice for medicinal products intended exclusively for markets outside the European Union in the context of co-operation with the World Health Organisation (WHO) 2/28. 2021.

30. Mezher M. EMA offers parallel Article 58, centralized authorization reviews | RAPS. Regulatory Focus [Internet]. 2021 [cited 2022 Mar 18]; Available from: https://www.raps.org/news-and-articles/news-articles/2021/1/ema-offers-parallel-article-58-centralized-authori

31. European Medicines Agency. Support for applications on Article 58 [Internet]. 2014 [cited 2022 Mar 29]. Available from: https://www.ema.europa.eu/en/documents/regulatory-

32. Sharma V. EMA Offers Simultaneous Review Of Products For EU And Non-EU Markets :: Scrip [Internet]. 2020 [cited 2022 Mar 18]. Available from: https://scrip.pharmaintelligence.informa.com/PS142268/EMA-Offers-Simultaneous-Review-Of-Products-For-EU-And-Non-EU-Markets

33. World Health Organization. What We Do | WHO - Prequalification of Medical Products [Internet]. [cited 2022 Apr 21]. Available from: https://extranet.who.int/pqweb/medicines/what-we-do

34. World Health Organization. WHO Prequalification Database [Internet]. 2022. [cited 2022 Apr 21]. Available from: https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products

35. World Health Organization. Pilot Prequalification of Biotherapeutic Products [Internet]. [cited 2022 Apr 21]. Available from: https://extranet.who.int/pqweb/medicines/pilot-prequalification-biotherapeutic-products

36. World Health Organization. WHO prequalifies first biosimilar medicine to increase worldwide access to life-saving breast cancer treatment [Internet]. Geneva; 2019 Dec [cited 2022 Apr 14]. Available from: https://www.who.int/news/item/18-12-2019-who-prequalifies-first-biosimilar-medicine-to-increase-worldwide-access-to-life-saving-breast-cancer-treatment

37. World Health Organization. FPPs & APIs Eligible for Prequalification ("EOIs") [Internet]. [cited 2022 Apr 14]. Available from: https://extranet.who.int/pqweb/medicines/products-eligible-prequalification

38. Singh Chahal H, Koukounas K, Capella P, Presto R, Murray JS, Shimer M, et al. An Evaluation of US Food and Drug Administration's Program to Register HIV Drugs for Use in Resource-Constrained Settings. JAMA Netw Open [Internet]. 2019 [cited 2022 Apr 14];2(11):1915787. Available from: https://jamanetwork.com/

39. U.S. Food & Drug Administration. Tropical Disease Priority Review Voucher Program | FDA [Internet]. [cited 2022 Apr 14]. Available from: https://www.fda.gov/about-fda/center-drug-

evaluation-and-research-cder/tropical-disease-priority-review-voucher-program

40. Health Canada. Canada's Access to Medicines Regime: Application Process for Drugs for Export to Developing and Least Developed Countries - Canada.ca [Internet]. 2006 [cited 2022 Apr 14]. Available from: https://www.canada.ca/en/health-canada/services/canada-access-medicines-regime/documentation/health-canada-guidance-documents/application-process-drugs-export-developing-least-developed-countries.html

41. Swissmedic. Guidance document MAGHP Procedure [Internet]. 2021 Mar [cited 2022 Apr 15]. Available from: https://www.swissmedic.ch/dam/swissmedic/en/dokumente/stab/networking/maghp_procedure.pdf.download.pdf/maghp_procedure.pdf

42. Swissmedic. Swissmedic authorises a medicinal product under the Marketing Authorisation for Global Health Products (MAGHP) procedure for the first time [Internet]. 2020 Mar [cited 2022 Apr 15]. Available from: https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/information/first-maghp-approval-inswitzerland.html

43. Verbaanderd C, Rooman I, Meheus L, Huys I. On-label or off-label? overcoming regulatory and financial barriers to bring repurposed medicines to cancer patients. Front Pharmacol. 2020;10:1664.

44. European Medicines Agency. Ipique | EMA [Internet]. 2022 [cited 2022 May 6]. Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/ipique

45. Outlook Therapeutics. Outlook Therapeutics Submits Biologics License Application to the U.S. Food and Drug Administration for ONS-5010 as a Treatment for Wet AMD [Internet]. 2022 Apr [cited 2022 Apr 20]. Available from: https://ir.outlooktherapeutics.com/news-releases/news-release-details/outlook-therapeutics-submits-biologics-license-application-us

46. World Health Organization. WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report [Internet]. Geneva: World Health Organization; 2021. Annex 10. (WHO technical report series;1033). Available from: https://apps.who.int/iris/handle/10665/340323

47. Durán CE, Cañás M, Urtasun MA, Elseviers M, Andia T, Vander Stichele R, et al. Regulatory reliance to approve new medicinal products in Latin American and Caribbean countries. Rev Panam Salud Pública [Internet]. 2021 [cited 2021 Apr 28];45:1–10. Available from: /pmc/articles/PMC8040933/

48. Makoni M. African Medicines Agency to be established. Lancet [Internet]. 2021 Oct 23 [cited 2022 Apr 20];398(10310):1475. Available from: http://www.thelancet.com/article/S0140673621023102/fulltext

49. Pincombe M, Guzman J. A Defining Moment for Medicines Regulation in Africa: The Establishment of the African Medicines Agency [Internet]. 2022 Feb [cited 2022 Apr 20]. Available from: https://www.cgdev.org/blog/defining-moment-medicines-regulation-africa-establishment-african-medicines-agency

50. World Health Organization. Towards access 2030: WHO essential medicines and health products strategic framework 2016-2030. World Health Organization; 2017.

51. U.S. Food & Drug Adminstration (FDA). President's Emergency Plan for AIDS Relief (PEPFAR) Database [Internet]. [cited 2022 Apr 21]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=pepfar.page

52. Ridley DB, Ganapathy P, Kettler HE. US Tropical Disease Priority Review Vouchers: Lessons In Promoting Drug Development And Access. https://doi.org/101377/hlthaff202002273. 2021 Aug 1;40(8):1243–51.

53. Esmail LC, Phillips K, Kuek V, Cosio AP, Kohler JC. Framing access to medicines in developing countries: An analysis of media coverage of Canada's Access to Medicines Regime. BMC Int Health Hum Rights [Internet]. 2010 Jan 4 [cited 2022 Apr 21];10(1):1–15. Available from: https://bmcinthealthhumrights.biomedcentral.com/articles/10.1186/1472-698X-10-1

54. WHO - list of prequalified Active Pharmaceutical Ingredients (APIs) [Internet]. 2021 [cited 2022 Apr 21]. Available from: https://extranet.who.int/pqweb/medicines/active-pharmaceutical-ingredients

55. European Medicines Agency. Defining the strategic vision for the EMA 'Article 58' process [Internet]. 2015 [cited 2022 Apr 21]. p. 49–50. Available from: https://www.ema.europa.eu/documents/other/defining-strategic-vision-ema-article-58-process-final-read-out_en.pdf

56. Holtorf AP, Mueller D, Sousa MSA, Pretorius L, Wijaya KE, Adeyemi S, et al. Pilot approach to analyzing patient and citizen involvement in health technology assessment in four diverse low- and middle-income countries. Int J Technol Assess Health Care [Internet]. 2021 [cited 2022 May 5];37(1):1–9. Available from: https://www.cambridge.org/core/journals/international-journal-of-technology-assessment-in-health-care/article/pilot-approach-to-analyzing-patient-and-citizen-involvement-in-health-technology-assessment-in-four-diverse-low-and-middleincome-countries/F9E8A4AD2DD19409C1C9FA861DF3A4B9

57. Chalkidou K, Claxton K, Silverman R, Yadav P. Value-based tiered pricing for universal health coverage: an idea worth revisiting. Gates Open Res [Internet]. 2020 [cited 2022 Apr 22];4. Available from: /pmc/articles/PMC7059551/

58. Access to Medicine Foundation. Are companies engaging in voluntary licensing to expand access? [Internet]. 2021 [cited 2022 Apr 22]. Available from: https://accesstomedicinefoundation.org/access-to-medicine-index/results/are-companies-engaging-in-voluntary-licensing-to-expand-access

59. Urias E, Ramani S V. Access to medicines after TRIPS: Is compulsory licensing an effective mechanism to lower drug prices? A review of the existing evidence. J Int Bus Policy [Internet]. 2020 Dec [cited 2022 Apr 22];3(4):367. Available from: /pmc/articles/PMC7468182/

60. Kostyak L, Shaw DM, Elger B, Annaheim B. A means of improving public health in low- and middle-income countries? Benefits and challenges of international public–private partnerships. Public Health. 2017 Aug 1;149:120–9.

61. Access to Medicine Foundation. Pharma companies make limited use of the many ways to improve access to antibiotics [Internet]. 2021. [cited 2022 Apr 22]. Available from: https://accesstomedicinefoundation.org/amr-benchmark/results/pharma-companies-make-limited-use-of-the-many-ways-to-improve-access-to-antibiotics

62. Médecins Sans Frontières. Gilead Sciences fails to expand promised access to lifesaving drug for people living with HIV [Internet]. Geneva; 2019 Jun [cited 2022 Apr 22]. Available from: https://www.msf.org/gilead-sciences-fails-expand-promised-access-lifesaving-drug-people-living-hiv

63. World Health Organization. WHO guidelines on technology transfer in pharmaceutical manufacturing [Internet]. 2021 Aug [cited 2022 Apr 26]. Available from:

https://cdn.who.int/media/docs/default-source/essential-medicines/norms-and-standards/qas20-869-transfer-of-technology.pdf?sfvrsn=2a4723bc_5

64. World Health Organization. eEML - Electronic Essential Medicines List [Internet]. 2022 [cited 2022 Apr 26]. Available from: https://list.essentialmeds.org/