Accelerating Access to Medicines in Developing Countries – an Evaluation of EU-Medicines4all (formerly Article 58 procedure)

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät
der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von
Anja Krug
aus Schwandorf

Bonn 2020

Betreuer und Erstgutachter:	Dr. Santiago Figueroa-Pérez
Zweitgutachter:	Prof. Dr. Werner Knöss

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List of Abbreviations

ACT	Artemisinin-based Combination Therapy
CAMR	Canada's Access to Medicines Regime
CHMP	Committee for Medicinal Products for Human Use
CPP	Certificate of Pharmaceutical Product
CRP	Collaborative Registration Procedure
DND*i*	Drugs for Neglected Diseases *initiative*
DRC	Democratic Republic of Congo
EAC	East African Community
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EU-M4all	EU-Medicines4all
gHAT	Human African Trypanosomiasis caused by T. b. gambiense
GSK	GlaxoSmithKline
HAT	Human African Trypanosomiasis
IPM	International Partnership for Microbicides
LMIC	Low- and Middle-Income Countries
LoOI	List of Outstanding Issues
MA	Marketing Authorization
MAGHP	Marketing Authorization for Global Health Products
MMV	Medicines for Malaria Venture
MP	Medicinal Product
MPP	Medicines Patent Pool
N/A	Not Applicable
NECT	Nifurtimox/Eflornithine Combination Therapy
NRA	National Regulatory Authority
NTD	Neglected Tropical Disease
GMP	Good Manufacturing Practice
PDP	Product Development Partnership
PEPFAR	The U.S. President's Emergency Plan for AIDS Relief
PQM	Promoting the Quality of Medicines
PQT	WHO Prequalification Team
PRAC	Pharmacovigilance Risk Assessment Committee

PRIME	Priority Medicines Scheme
rHAT	Human African Trypanosomiasis caused by T. b. rhodesiense
SME	Micro, Small or Medium-sized Enterprise
SOH	Scientific Opinion Holder
SRA	Stringent Regulatory Authority
SSP	Stop Stock Outs Project
TD PRV	Tropical Disease Priority Review Voucher Program
WANECAM	West African Network for Clinical Trials of Anti-Malarial Drugs
WHO	World Health Organization

1. Introduction

Due to limited resources and capacities, regulatory authorities of many countries with low and middle incomes (LMICs) rely on previous review and approval of medicines by stringent regulatory authorities (SRAs). The national regulatory authorities (NRAs) often lack the infrastructure to assess the quality, efficacy and safety of the products, particularly with regard to innovative medicines.[1]

LMICs not only suffer from substandard and counterfeit medicines circulating in their countries, but also from the non-availability of innovative medicines at affordable prices – or at all, either since innovators do not register their products due to small market size and/or revenues, or because access is restricted by the non-functionality of NRAs.[2] Additionally, major health problems differ between low-, middle- and high-income countries.

To stimulate the development of medicines and vaccines for low- and middle-income countries, Article 58 of Regulation (EC) No 726/2004 was implemented into the European Regulation in 2004, providing the European Medicines Agency (EMA) with a mechanism to give tailor-made scientific assessments of medicines to developing countries following the same high standards as for products intended for the European market.

The thesis analyzes the use of the Article 58 procedure up to the present day and examines three case studies in detail. It further investigates trends within the procedure and adaptations made to the mechanism in terms of improvement, and discusses strengths and weaknesses in relation to further potential pathways for LMIC products offered by other highly regulated authorities.

2. EMA's Article 58 procedure (EU-Medicines4all)

2.1. Background

Article 58 was introduced into Regulation (EC) No 726/2004 to foster the development of medicines and vaccines for low- and middle-income countries:

> 1. The Agency may give a scientific opinion, in the context of co-operation with the World Health Organization, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Union. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use may, after consulting the World Health Organization, draw up a scientific opinion in accordance with Articles 6 to 9. The provisions of Article 10 shall not apply.
>
> 2. The said Committee shall establish specific procedural rules for the implementation of paragraph 1, as well as for the provision of scientific advice.[3]

The procedure is not a registration pathway for access to the European market, but serves to obtain a scientific opinion by the Committee for Medicinal Products for Human Use (CHMP) specifically for products intended for markets outside the European Union. This scientific review is performed by applying the same high standards as for medicines intended for the European market, but by taking into consideration the target country's population. Additionally, World Health Organization (WHO) and the respective NRAs are involved in the evaluation process.

After the CHMP opinion is obtained, the pharmaceutical companies need to apply locally in the intended non-EU countries, either by their standard registration procedures or following a collaborative registration procedure (CRP), where possible. The Article 58 procedure is open to innovative as well as generic or biosimilar medicines and vaccines.[4]

Recently, the Article 58 procedure was renamed to "EU-Medicines4all" (short: "EU-M4all") to provide the mechanism with a more appealing name.[5] Throughout the thesis, the procedure's new term will be used for all procedures before and after the name change.

2.2. Procedural aspects

EU-M4all in principle follows the centralized marketing authorization procedure. The fees are the same as for the centralized procedure unless a fee waiver or fee reductions apply, but the latter are only relevant for small and medium-sized enterprises or if granted by EMA upon justified request.[6]

EMA offers a variety of tools to support applicants for EU-M4all, starting with scientific advice at an early stage in development up to EMA's early access tools to accelerate registration. The tools are the same as for centralized procedures but take into account the situation in the target countries and may also involve experts from WHO or NRAs from relevant countries.

Applicants are encouraged to discuss their products and developments in scientific advice or business pipeline meetings. Business pipeline meetings offer the possibility to discuss the respective product portfolio and discover potential issues and need for additional expertise. The support mechanisms for micro, small and medium-size enterprises (SMEs) are applicable for EU-M4all procedures as well, enabling access to fee exemptions or reductions, or additional assistance by EMA.[7]

The full range of early access tools – accelerated assessment, conditional opinions and opinions under exceptional circumstances – can be applied with EU-M4all provided that the respective eligibility criteria on unmet medical need or major public health interest are fulfilled.[7]

EU-M4all products may also fall under the scope of the Priority Medicines scheme (PRIME), the EMA strategy to streamline and accelerate the development of promising new medicines for unmet medical needs.[8]

Starting March 2020, parallel review of medicines or vaccines in the centralized procedure and via EU-M4all has been enabled by EMA.[9] For such cases, the applicant still needs to submit two separate applications, which result in two assessment reports and opinions by the CHMP. On the upside, the assessments will be harmonized as much as possible for the EU and non-EU opinion, as both procedures will have the same (co-)rapporteurs and the assessment reports will be identical except for products where different conditions of use would apply between European and non-European settings. Thus, time and resources are saved obtaining both opinions. On the downside, the fees will be charged as before for each procedure individually.[10]

Before starting an EU-M4all procedure, the eligibility needs to be confirmed by CHMP in consultation with WHO. Eligible are particularly vaccines and medicines that address unmet medical needs, or which are of public health interest.

The following specific examples are listed on the EMA webpage:

Vaccines

- used in the WHO Expanded Program on Immunization
- for protection against a WHO public health priority disease
- that are part of a WHO-managed stockpile for emergency response

Other medicines

- for WHO target diseases such as human immunodeficiency virus (HIV) / acquired immune deficiency syndrome (AIDS), malaria and tuberculosis
- for maternal and newborn healthcare[6]

There are no restrictions in the type of product for EU-M4all. The procedure is open for completely new products as well as new formulations, pharmaceutical forms or routes of administration, or generics of products that are already authorized in the EU.[6] Although the legal basis is Article 58 of Regulation (EC) No 726/2004, the type of application needs to be indicated in analogy with Directive 2001/83/EC. They are the same options as for products intended for the European market (full application, well-established use, fixed-dose combination, informed consent, generic, hybrid and biosimilar).[11]

In contrast to centralized procedures, the following elements are not mandatory under Article 58 of Regulation (EC) No 726/2004:

- Invented name
- Pediatric investigation plan
- Mock-ups and specimens
- Environmental risk assessment (with justification)
- Requirements for location of entities and activities

Elements like the pharmacovigilance system, risk management plans and justifications for accelerated assessment need to be tailored to address the target countries' situation. The product information is reviewed in English, no translations will be part of the evaluation as the final product information needs to be discussed with the NRAs during their national procedure.[8,11]

The validation and evaluation of EU-M4all applications follows the timetable of the centralized procedure up to the adoption of CHMP scientific opinion and assessment report, i.e. a 210-day assessment procedure plus clock-stops for the applicant's responses to the List of Questions/Outstanding Issues on the application. Within two months after the scientific opinion, a Public Assessment Report is prepared.

Unlike for the centralized procedure, experts from WHO or experts or observers from target countries nominated by WHO may participate in the evaluation. These experts/observers may provide their input to the CHMP but are not eligible to vote. The Pharmacovigilance Risk Assessment Committee (PRAC) is involved for assessment of risk management aspects. After adoption of the scientific opinion by the CHMP, the assessment report is shared with WHO for joint elaboration of a public assessment report for EU-M4all.[8,11]

The scientific opinion holder needs to fulfill maintenance and pharmacovigilance obligations (reporting of serious adverse reactions, periodic safety update reports, safety signal detection) to EMA and keep the opinion updated. Variation applications are evaluated by EMA together with WHO.[8,11]

Although no marketing authorization is obtained, EMA can issue certificates of pharmaceutical product (CPP) complying to the WHO certification scheme based on EU-M4all opinions. These may be used to provide evidence and support submissions in countries outside the EU.[12]

Additionally, products positively assessed via EU-M4all are eligible to be included directly in the WHO list of prequalified products.[13]

3. Utilization of EU-Medicines4all

Despite the procedure's effectiveness for more than 15 years, it has only been used a couple of times, as shown in the overview in Figure 1.[4]

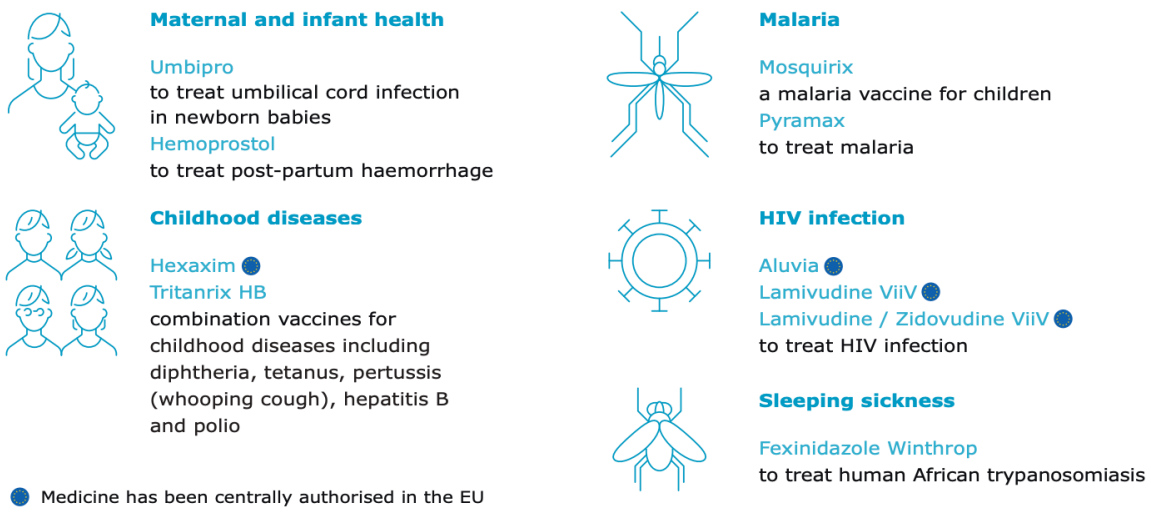

Figure 1: Overview of products reviewed via EU-M4all

Reprinted from European Medicines Agency[4]

All in all, the current situation of the EU-M4all procedure is as follows:

- 6 active opinions (Umbipro, Hexaxim, Mosquirix, Pyramax, Aluvia, Fexinidazole Winthrop)
- 4 withdrawn opinions (Hemoprostol, Tritanrix HB, Lamivudine ViiV, Lamivudine / Zidovudine ViiV)
- 1 withdrawn application (Globorix)
- 1 on-going application (dapivirine vaginal ring)[14]

According to Cavaller Bellaubi et al. there have been four applications that were either withdrawn before receiving an opinion or received a negative opinion.[15] The only published case is the one of Globorix, the other three cases are not listed on the EU-M4all website.[14]

An overview of the reviewed products, their formal aspects and their background on development is provided in Table 1 to Table 6 on the next pages.

Table 1: Overview of active EU-M4all opinions – formal aspects

Brand name	SOH	Medicinal Product	Scientific advice	Accelerated assessment	Submis-sion date	Date of opinion	Application type[a]	No. of appro-vals[b,15]
Aluvia[16–18]	AbbVie	Lopinavir / ritonavir (1) 200 mg/50 mg film-coated tablets (2) 100 mg/25 mg film-coated tablets	N/A	N/A	(1) 6 Jul 2006 (2) not published	(1) 21 Sep 2006 (2) 24 Jan 2008	Art. 8(3), cross reference to centrally authorized product Kaletra	73
Fexinidazole Winthrop[19]	Sanofi-Aventis	Fexinidazole 600 mg tablets	2 x (2011, 2014)	Granted, converted to standard TT	14 Dec 2017	15 Nov 2018	Art. 8(3)	1
Hexaxim[20]	Sanofi Pasteur	Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed).	N/A	N/A	23 Jun 2011	21 Jun 2012	Art. 8(3)	22
Mosquirix[21]	GSK Biologicals	Vaccine against plasmodium falciparum and hepatitis B (recombinant, adjuvanted)	6 x (2007 - 2012)	N/A	26 Jun 2014	23 Jul 2015	Art. 8(3)	3
Pyramax[22–25]	Shin Poong Pharma-ceutical Co., Ltd	Pyronaridine / artesunate (1) 180 mg/60 mg film-coated tablets (2) 60 mg/20 mg granules for oral suspension	N/A	N/A	(1) 09 Apr 2010 (2) 10 Oct 2014	(1) 16 Feb 2012 (2) 19 Nov 2015	(1) Art. 8(3) (2) extension application	26

Brand name	SOH	Medicinal Product	Scientific advice	Accelerated assessment	Submis-sion date	Date of opinion	Application type[a]	No. of appro-vals[b,15]
Umbipro[26]	GSK	Chlorhexidine digluconate 7.1% w/w gel	2 x (2013, 2014)	Granted	07 Oct 2015	28 Apr 2016	Art. 8(3)	13

Note. GSK = GlaxoSmithKline, N/A = not applicable, SOH = Scientific Opinion Holder, TT = timetable

[a] legal basis is Article 58 of Regulation (EC) No 726/2004, application type indicated in analogy to Dir. 2001/83/EC

[b] worldwide approvals based on EU-M4all opinion, as per April 2019

Table 2: Overview of active EU-M4all opinions – background on development

Brand name	Indication	Background on development	Partnership
Aluvia[17]	Antiretroviral combination therapy for the treatment of HIV/AIDS, for adults and children above 2 years	Identical indication but different appearance of the tablet for the use outside of Europe vs. product for EU market (red/pale pink tablets for non-EU, yellow/pale yellow tablets for EU, different embossing). Details are provided in section 4.1.	N/A
Fexinidazole Winthrop[19,27]	Treatment of human African trypanosomiasis due to *Trypanosoma brucei gambiense*, for adults and children ≥ 6 years and ≥ 20 kg	Fexinidazole had already been discovered but abandoned as an anti-infective agent in the 1970s. It has been repurposed for sleeping sickness, a neglected tropical disease (NTD). Details are provided in section 4.3.	Sanofi / Drugs for Neglected Diseases *initiative*
Hexaxim[20]	Vaccine against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and Haemophilus influenzae type b, for infants and toddlers from 6 weeks of age	Prevention of diseases of major public interest, following the immunization schedules of developing countries and WHO's Expanded Program on Immunization. Basis for the hexavalent vaccine was the pentavalent vaccine Pentavac/Pentaxim adding the hepatitis B antigen. All clinical trials were conducted outside the EU (Argentina, Peru, Mexico, Turkey, Thailand, South Africa). Later, the product was centrally approved in Europe as Hexacima/ Hexyon (CHMP opinion on 21 February 2013).	N/A
Mosquirix[21,28–30]	Vaccine against malaria caused by *Plasmodium falciparum* and against hepatitis B for children aged 6 weeks up to 17 months	Development of the vaccine against the NTD malaria started already in 1984. The EU-M4all opinion was based on 11 clinical trials involving over 19,000 trial participants. Phase II and III trials were conducted in several sub-Saharan African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, Tanzania). Despite only moderate efficacy, the benefits were considered particularly important for the severely affected	GSK / PATH Malaria Vaccine Initiative

Brand name	Indication	Background on development	Partnership
		children in high-transmission areas. Implementation of the vaccine has started in Ghana, Malawi and Kenya coordinated by WHO and in collaboration with GSK and PATH.	
Pyramax[22–25]	Acute, uncomplicated malaria infection caused by *Plasmodium falciparum* or *Plasmodium vivax* (1) Tablets: adults / children from 20 kg body weight (2) Granules: children / infants from 5- 20 kg body weight	Development of a new oral combination medicinal product for the treatment of the NTD malaria following the WHO recommendation to use artemisinin derivates in combination therapy with a compound of longer half-life to avoid resistances. Details are provided in section 4.2.	Shin Poong / Medicines for Malaria Venture
Umbipro[26,31,32]	Antiseptic gel to prevent umbilical cord infections (omphalitis) in newborn infants	Chlorhexidine solution was already available as mouthwash and topical antiseptic. WHO treatment guidelines for umbilical cord care for home births recommended Chlorhexidine in regions with high neonatal mortality. GSK reformulated their mouthwash as a gel, which it is easier to apply and to retain at site of application than a solution. A complete dossier was submitted for a known active substance: • mainly literature based on solution (clinical/non-clinical data), clinical trials were conducted in Nepal, Bangladesh and Pakistan • bridging efficacy/safety to the literature on the Chlorhexidine solution via *in vitro* antibacterial equivalence and skin-irritancy studies	GSK / Save the Children

Note: GSK = GlaxoSmithKline, N/A = not applicable

Table 3: Overview of pending EU-M4all applications

Medicinal Product	SOH	Intended indication	Procedural steps	Scientific opinion	Background on development	Partnership
Dapivirine vaginal ring[33–39]	IPM	Reducing the risk of HIV-1 infection via vaginal intercourse in sexually active HIV-uninfected women	Start of procedure: July 2017 List of Question (d120) 19.11.2017 Lists of Outstanding Issues: 18.10.2018, 26.04.2019 and 25.07.2019	Expected: mid 2020	Development of a long-acting HIV prevention method for women who cannot use daily oral pre-exposure prophylaxis	IPM holds an exclusive worldwide license for dapivirine from Janssen Sciences Ireland UC

Note: IPM = International Partnership for Microbicides

Table 4: Overview of withdrawn EU-M4all applications

Brand name	SOH	Intended indication	With-drawal	Background on development	Reason for withdrawal of application
Globorix[40–42]	GSK Biologicals	Vaccine against diphtheria, tetanus, pertussis, hepatitis B, invasive disease caused by Haemophilus influenzae type b and Neisseria meningitidis serogroups A and C.	Oct 2007 (after d120)	Intended for the "Expanded Programme on Immunization", mainly for use in sub-Saharan Africa.	The developed product was considered not to fit the WHO vaccination strategy for meningococcal disease after change of strategy.

Table 5: Overview of withdrawn EU-M4all opinions – formal aspects

Brand name	SOH	Medicinal product	Indication	Date of opinion	With-drawal	Application type[a]
Hemoprostol [43,44]	Linepharma International	Misoprostol 200 micrograms sublingual tablets	Post-Partum Hemorrhage	23 Jan 2014	Apr 2017	Art. 8(3)
Lamivudine ViiV[45–47]	ViiV Healthcare (until 06/2010: GSK Group)	Lamivudine 150 mg film-coated tablets	Antiretroviral combination therapy for the treatment of HIV/AIDS	17 Nov 2005	Dec 2015	Art. 8(3), cross reference to non-/clinical data of centrally authorized products Epivir (GSK) or Combivir (GSK), respectively
Lamivudine / Zidovudine ViiV[48–50]		Lamivudine/zidovudine 150/300 mg film-coated tablets				
Tritanrix HB[51,52]	GSK Biologicals	Diphtheria (D), tetanus (T), pertussis (whole cell) (Pw) and hepatitis B (rDNA) (HBV) vaccine (adsorbed)	Active immunization against diphtheria, tetanus, pertussis and hepatitis B (HBV)	19 Dec 2013	Aug 2019	Art. 10c referring to Tritanrix HepB

[a] legal basis is Article 58 of Regulation (EC) No 726/2004, dossier structure indicated in analogy to Dir. 2001/83/EC

Table 6: Overview of withdrawn EU-M4all opinions – background on development and withdrawal

Brand name	Indication	Background on development	Reason for withdrawal of opinion
Hemoprostol[43,44]	Post-Partum Hemorrhage	Re-purposing of existing product: Identical product was already marketed in France for termination of early pregnancy and preparation for surgical termination of pregnancy. Clinical trials were conducted in a product development partnership with Gynuity Health Projects (sponsored by the Bill and Melinda Gates Foundation), while the tablets were supplied by Linepharma.	Inability to obtain national MAs or commercialize the product since the issuance of the CHMP scientific opinion (2014 - 2017).
Lamivudine ViiV[45–47]	Antiretroviral combination therapy for the treatment of HIV/AIDS, for adults and children	Identical indication but different appearance of the tablets for the use out outside of Europe vs. product for EU market (red tablets for non-EU, white tablets for EU, different embossing)	Stop of the manufacture of the HIV medicine Lamivudine ViiV (mono and combination product) for commercial reasons.
Lamivudine / Zidovudine ViiV[48–50]			
Tritanrix HB[51,52]	Vaccine against diphtheria, tetanus, pertussis and hepatitis B (HBV), for infants from 6 weeks of age	The centrally authorized quadrivalent vaccine Tritanrix HepB was abandoned in the EU in favor of a pentavalent vaccine. The EU authorization was to expire due to Sunset Clause by the end of 2013. By using EU-M4all, the product could be made available for use outside of Europe avoiding interruption of supply.	Withdrawal due to commercial considerations in August 2019. The intention to discontinue production of Tritanrix HB had already been communicated in March 2014.

4. Case Studies

4.1. Case Study: Aluvia Film-Coated Tablets for HIV treatment

4.1.1. Developmental Aspects

Kaletra soft capsules and oral solution, containing the combination of lopinavir/ritonavir, were approved via the centralized procedure in EU in March 2001. In 2006, the soft capsules were replaced by a film-coated tablet formulation to reduce the pill burden and improve storage conditions (room temperature instead of refrigerated storage). The additional strength 100 mg/25 mg film for pediatric use as alternative to the solution was approved in March 2008 for Kaletra.

With Aluvia, Abbott developed a differently looking formulation of the Kaletra tablets by using a differently colored coating (red instead of yellow for 200 mg/50 mg, pale pink instead of pale yellow for 100 mg/25 mg) and different embossing (Abbott logo + AL instead of Abbott logo + KA for 200 mg/50 mg, Abbott logo + AC instead of Abbott logo + KC for 100 mg/25 mg) as exemplarily shown for the 200 mg/50 mg tablets in Figure 2.

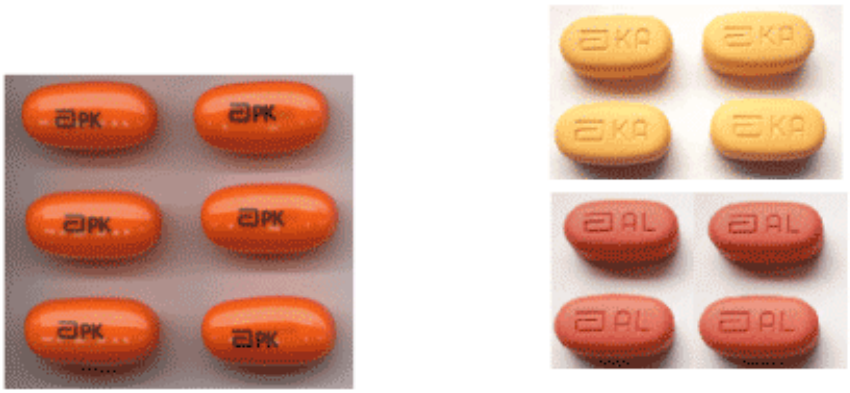

Figure 2: Appearance of Kaletra and Aluvia

Kaletra soft capsules (left), Kaletra 200 mg/50 mg tablets (top right), and Aluvia 200 mg/50 mg tablets (bottom right). Reprinted from Levin.[53]

Both Kaletra and Aluvia are indicated "in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infected children above the age of 2 years, adolescents and adults" and are based on the same clinical and non-clinical data.[16,17]

The reasoning to develop alternative formulations was to combat the reimportation of the lower-priced products from LMIC's markets.[54]

4.1.2. Regulatory Aspects

As Kaletra, AbbVie's product had already been registered by many core SRAs (US FDA, Health Canada, central registration in EU).[55] Subsequently, AbbVie used the EU-M4all pathway to obtain the scientific opinion for its differently colored version Aluvia by cross reference to the non-clinical and clinical data of Kaletra in 2006 (200 mg/50 mg strength) and 2009 (100 mg/25 mg strength). Due to the available scientific assessment of Kaletra and limited changes of the quality part, the initial EU-M4all opinion for Aluvia was issued only two months after the start of the procedure.[16]

Until 2013, Abbot was the holder of the marketing authorization and scientific opinion for Kaletra/Aluvia respectively. After split of Abbott into two companies, lopinavir/ritonavir was transferred to the AbbVie portfolio.[56]

Based on the EU-M4all opinion, the LMIC-specific version Aluvia was approved in several important LMIC countries, e.g. Indonesia, Kenya, India, South Africa and Thailand.[55]

According to an assessment by Cavaller Bellaubi et al. reflecting the situation up to April 2019, approvals based on the EU-M4all opinion for Aluvia have been obtained in 73 countries.[15] This makes Aluvia not only the oldest EU-M4all product that is still active, but also the one with the highest number of worldwide registrations by far.

4.1.3. Implementation

Due to the high medical need for HIV medication, pricing is of high relevance for LMIC countries. On the other hand, there is the ambition by the developing company to return their invest. Therefore, innovative companies protect their innovation via patents against generic competition, which leads to monopoly position until the expiry of these patents. The decision, in which countries registration is sought and which prices are offered for which countries, rests in the hand of that company as well.

The Medicines Patent Pool (MPP) is a public health organization backed by the United Nations to increase access to affordable and effective medicines for a certain set of products (initially HIV, tuberculosis and hepatitis C, expansion to further essential medicines planned). By negotiating voluntary licenses with the innovator companies, the MPP sets the basis for generic competition. This leads to a reduction of prices in the countries in scope of the license. In exchange for their loss of exclusivity, the patent holders receive royalties from the generic manufacturers.[57]

In contrast, compulsory licenses may be issued temporarily without the consent of the patent holder, often at a defined royalty rate, and allow the introduction of generics in spite of valid patents.[58]

In the following, the access situation of Aluvia is exemplarily discussed for Thailand and South Africa as well as the development during the COVID-19 pandemic.

Thailand

Due to the high prices of Kaletra (still the non-heat-stable soft capsule formulation), Thailand issued a compulsory license in January 2007 to enable more affordable access to lopinavir/ritonavir via generic competition, which caused a lot of resistance from developed countries and international pharmaceutical companies.[56]

Reacting to that, Abbott withdrew all pending applications for new products in Thailand in March 2017, among them the one for Aluvia, the urgently needed heat-stable tablet formulation of lopinavir/ritonavir reviewed via EU-M4all. This provoked international criticism and activists initiated a global boycott of Abbot products as well as demonstrations in many countries worldwide. After WHO appealed to Abbot, they agreed to reduce the prices for Kaletra/Aluvia capsules and tablets for more than 40 low- and low-middle-income countries ($1,000 per person per year from previous $2,200).[59,60]

Thailand's Food and Drug Administration declined this offer for Aluvia since it was provided under the condition that no compulsory license would be granted for Aluvia in Thailand. In September 2007, the first generic version of Aluvia was registered in Thailand, manufactured by the Indian company Matrix Laboratories and offered at a lower price of $695 per person per year than Abbott's already reduced offer.[61,62]

South Africa

For South Africa, AbbVie is the single supplier of lopinavir/ritonavir (brand name Aluvia), since multiple patents valid until 2026 prevent generic alternatives from entering the market. Since the combination is a preferred second-line treatment option for adults (i.e. after development of resistances to first-line therapy), recurring nationwide stockouts for Aluvia in South Africa resulting from insufficient supply triggered a severe health care problem in 2015, with an estimated 160,000 people using this combination at that time.[63]

To resolve the situation, the members of the consortium Stop Stock Outs Project[1] (SSP) requested the South African government to issue a compulsory license overruling the patent protection for Aluvia and to allow for production or import of generic alternatives in October 2015.[64]

The National Department of Health pointed to the innovator company to preferably issue a voluntary license rather than applying a compulsory one. Eventually, AbbVie agreed on a voluntary licensing agreement with the Medicines Patent Pool (MPP) for all African countries in December 2015. Although there were locally registered and WHO-prequalified generic suppliers for lopinavir/ritonavir, this measure did not have the desired short-term effect. Finally, in July 2016, three manufacturers signed the voluntary license.[56,58,65]

Several reasons are discussed for this slow uptake of generic supply:

- Restricted scope of the MPP license (Africa only) resulting in low attractiveness as no broad market or high-income countries were involved.
- Generic competition was undermined by AbbVie's policy of prices lower than production costs. Thus, creating manufacturing capacities was not attractive to generic suppliers and the interest from the Department of Health to secure the supply with the higher priced alternatives was limited.

Additional recommendations by the SSP to overcome such situations in South Africa were to expedite the pending reform of intellectual property legislation, to ensure clear regulations and transparent regulatory procedures and to include an additional second-line therapy option for HIV treatment to diversify the supply .[58,63]

[1] The Stop Stockouts Project is a consortium monitoring and reporting on shortages and stockouts of essential medicines, childhood vaccines and chronic medicines in South Africa (member organizations: Doctors Without Borders (MSF), the Rural Doctors Association of Southern Africa (RuDASA), the Rural Health Advocacy Project (RHAP), the Treatment Action Campaign (TAC), SECTION27 and the Southern African HIV Clinicians Society (SAHIVSoc)).

COVID-19 pandemic

Lopinavir/ritonavir is regarded a potential candidate for the treatment of COVID-19 and is tested in clinical trials.

On 17 March, the parliament of Chile declared that they would consider the coronavirus pandemic an appropriate justification to issue compulsory licenses to any potential instrument to combat the virus. On 19 March 2020, Israel issued compulsory patent licenses for lopinavir/ritonavir allowing the import of generic products that are already available in other countries in order to ensure the supply for clinical trials.

Following the Israeli announcement, the innovator company AbbVie notified the MPP on the same day that they would not enforce their patent rights for both the adult and the pediatric formulations given the COVID-19 pandemic situation. This waiver was declared to be effective worldwide and immediately. However, AbbVie did not proclaim this move openly but rather seems to follow a strategy to prevent further compulsory licenses in other countries.[66,67]

From April 2020, the French NRA formally allowed the exceptional and temporary import of the EU-M4all version (i.e. not having marketing authorization in Europe) Aluvia 200 mg/50 mg tablets to overcome the coronavirus-related shortage of the centrally registered version Kaletra.[68]

In summary, the described cases show the relevance of patents for the protection of the innovator's rights and commercial strategy. On the downside, they prevent generic competition and thus lower prices and alternative medicines to stabilize supply. Voluntary or compulsory licenses are a tool to improve the pricing/supply situation for LMICs or for special situations like the COVID-19 pandemic.

4.2. Case Study: Pyramax Film-Coated Tablets and Granules for Malaria

4.2.1. Developmental Aspects

Pyramax is a new fixed-dose combination of pyronaridine tetraphosphate and artesunate and indicated for "acute, uncomplicated malaria infection caused by *Plasmodium falciparum* or *Plasmodium vivax*" in adults and children from 20 kg body weight (film-coated tablets) or children and infants from 5 to 20 kg body weight (granules for oral suspension).

Malaria is a major public health issue in Africa and severely affects young children below the age of 5, especially those under 12 months of age, in endemic countries. Resistance of *Plasmodium falciparum* reduced the efficacy of available monotherapies like chloroquine or sulfadoxin/pyrimethamine, creating the need for medicines without resistance.

In order to approach the risk of developing resistances, WHO recommended the use of artemisinin derivates, which are commonly used against malaria, for combination therapy in areas where *P. falciparum* is the prevailing infecting species. By adopting a combination regimen with an agent of a longer half-life, the disadvantage of the relatively short half-life of the artemisinin derivates is compensated.

Pyramax is in line with this recommendation on combination therapy as artesunate is the most commonly used artemisinin derivate, while pyronaridine is a suitable combination agent due to its longer half-life and has been in clinical use as a monotherapy for malaria in China since the 1980s.[22,25,69]

The development comes from a public-private partnership between Shin Poong Pharmaceutical Co. Ltd., a company based in South Korea and originally focused on manufacturing and distribution of generics, and the Medicines for Malaria Venture (MMV)[2], providing their knowledge of malaria and clinical development. Additionally, the University of Iowa contributed their expertise in pharmacokinetics and -dynamics. The co-development was triggered by WHO, who contacted Shin Poong on their willingness to support the development of a new artemisinin-based combination therapy (ACT) in 1999. After involving the MMV, the collaboration started in 2001.[70]

[2] The MMV is a Swiss foundation, established in 1999 and the leading product development partnership for research and development of antimalarial drugs.

The product was developed as an oral formulation and needs to be taken once daily for three days.

Pyramax tablets

The pivotal clinical trials for the initial tablet application were designed to demonstrate non-inferiority to the respective standard therapies.

P. falciparum:

Two phase III trials on acute uncomplicated *P. falciparum* malaria were conducted in adults and children (≥ 20 kg body weight). Comparators were other artemisinin combinations (artesunate plus mefloquine or artemether/lumefantrine, respectively). Clinical data using the pediatric granule formulation for acute uncomplicated *P. falciparum* malaria (study SP-C-007-07) were already included and assessed in the initial application of the tablets. The *P. falciparum* studies were conducted in sub-Saharan Africa and South East Asia.

P. vivax:

Non-inferiority for acute uncomplicated *P. vivax* malaria was evaluated in comparison to chloroquine treatment, in adults and children (≥20 kg body weight). One study was conducted in South East Asia; another conducted in Korea was terminated prematurely due to slow recruitment.[22]

Pyramax granules for oral suspension

The later pediatric extension application was based on the following studies:

- Relative bioavailability study comparing the granule to the tablet formulation
- Study SP-C-007-07, which was already part of the tablet application
- WANECAM (West African Network for Clinical Trials of Anti-Malarial Drugs) study: a longitudinal trial in three West African countries observing subsequent malaria episodes over a two-year period. It was designed as a three-arm study comparing the safety and efficacy of repeated treatments of two innovative ACTs, Pyramax (both tablets and granules) and dihydroartemisinin-piperaquine, to the local first line ACT therapies.[23]

The WANECAM study was also basis for the extension of indication to remove the restrictions from the initial tablet procedure. Details are described on the next pages.[25]

Pyramax is the first ACT approved by a SRA for treatment of blood-stage malaria by both *P. falciparum* and *P. vivax*. Additional benefits include that it can be taken with or without food, since malaria is frequently accompanied by loss of appetite, and may also be used concomitantly with Primaquine, which is crucial for the treatment of *P. vivax* malaria.[71]

4.2.2. Regulatory Aspects

EU-M4all

It is notable that the applicant and Scientific Opinion Holder Shin Poong Pharmaceutical Co., Ltd. is based in South Korea. A contact point in the European Economic Area (EEA) is also not mentioned.[24] Apparently, this was accepted since the opinion is not granting market access in Europe, although the procedural advice on Article 58 states that the applicant or their contact point must be established in the EEA.[11]

Pyramax tablets

After confirmation of the eligibility for Article 58 by WHO in June 2006, the application for Pyramax film-coated tablets was submitted in April 2010.

The dossier submitted for the fixed combination product was a full application by analogy to Article 8(3) of Directive 2001/83/EC and contained complete information on quality, non-clinical and clinical data from own tests/studies as well as bibliographic references.

The CHMP issued the List of Questions in May 2011 and two Lists of Outstanding Issues in July 2011 and January 2012, respectively. Following an oral explanation on the remaining outstanding issues before the CHMP, the procedure was closed with a positive scientific opinion in February 2012.[22]

During the initial procedure, the CHMP raised concerns about potential hepatotoxicity and on increased liver transaminases after repeated administration. These findings were attributed to pyronaridine as no such effects had been reported for artesunate so far. After consultation of an Ad-Hoc Expert Group consisting of WHO advisors and an observer from an African NRA, the CHMP concluded the benefit-risk balance to be positive only for use as a single 3-day treatment course. Furthermore, imposed conditions were monitoring the liver function, use restricted to areas with low malaria transmission and with evidence of resistance to ACTs. As part of the RMP, Shin Poong was obliged to conduct repeated dosing studies to evaluate the safety regarding hepatotoxicity and repeated use in endemic areas in order to lift the restrictions.[22,69]

The granted indication at that time point was:

> Treatment of acute, uncomplicated malaria infection caused by Plasmodium falciparum or by Plasmodium vivax in adults and children weighing 20 kg or more, in areas of low transmission with evidence of artemisinin resistance.
> Pyramax is to be used only as a single treatment course in any given patient (see section 4.2 and 4.4.)
> Consideration should be given to official guidance on the appropriate use of antimalarial agents (see section 4.4).[22]

Although the initial application already contained some clinical data using the pediatric granule formulation, the data was not accepted for extrapolation to the tablets as bioequivalence was not demonstrated. Therefore, the indication was restricted to children weighing 20 kg and more and Shin Poong committed to conduct an additional clinical study with the granules in the pediatric population.[22]

Type II variation on extension of indication / extension application for Pyramax granules for oral suspension

A type II variation was submitted in March 2014 to extend the indication also to repeated treatments with Pyramax and to remove the initial restriction to areas of low transmission with evidence of artemisinin resistance. Altogether, four requests for supplementary information were issued during the course of the type II variation.[25]

In parallel, an extension application was filed in October 2014 to add the pediatric dosage form granules for oral suspension targeting at children from 5 kg to under 20 kg body weight.[23] Both applications were reviewed simultaneously.

The submitted relative bioavailability study in the granule application was not sufficient to establish bioequivalence of the tablet and granule formulation for the artesunate component. Therefore, the evaluation of efficacy relied on the data from the submitted clinical studies on the granules only.[23]

Systematic liver monitoring was not considered feasible as a routine test in the intended clinical setting and the product would be applied to a broader population than in the clinical trials. Hence, the risk management plan was aligned to include appropriate pharmacovigilance measures and the commitment to conduct a phase IV safety study on the topics in question. Uncertainties in the pediatric population below 1 year of age were considered to be addressed by a study comparing safety and efficacy of the Pyramax granules to artemether-lumefantrine in children from 6 months to 12 years.[23,25]

In the end, the positive scientific opinion on both the granules and the type II variation was issued in November 2015.

The indication for the tablets was revised as follows:

> Pyramax tablets are indicated in the treatment of acute, uncomplicated malaria infection caused by Plasmodium falciparum or by Plasmodium vivax in adults and children weighing 20 kg or more~~, in areas of low transmission with evidence of artemisinin resistance~~.
> ~~Pyramax is to be used only as a single treatment course in any given patient (see section 4.2 and 4.4.)~~
> Consideration should be given to official guidance on the appropriate use of antimalarial agents (see section 4.4).[23]

The indication granted for the new granule dosage form was identical apart from the different target group (children and infants weighing 5 kg to under 20 kg).[23,25]

The tablets were listed on the WHO list of prequalified medicines in May 2012, three months after the EMA scientific opinion, the granules in March 2016, four months following the opinion.[72,73]

Worldwide regulatory status

Approval for Pyramax tablets was already obtained in South Korea as manufacturing country of origin in August 2011, even before the EU-M4all opinion.

The increase of worldwide approvals was slow in the beginning; in mid 2017 only ten approvals were obtained, showing limited trust of the developing countries in the EU-M4all procedure.[74]

After the inclusion of artesunate-pyronaridine in the WHO's Essential Medicines lists in 2017, the registration situation of Pyramax is as follows as per May 2020: 28 approvals for Pyramax tablets and 19 approvals for the granules have been obtained in endemic countries.

The tablet formulation has been approved in 22 African and 6 Asian countries as shown in Figure 3:

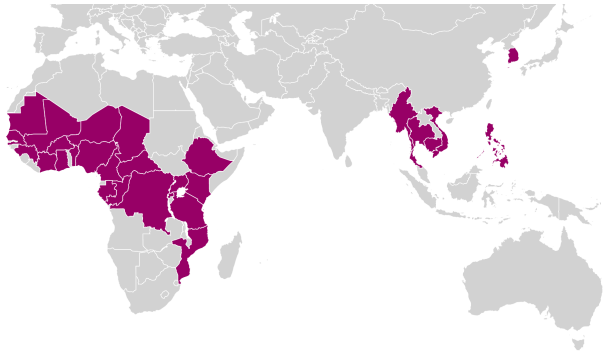

Figure 3: Countries where Pyramax tablets are registered (situation as of May 2020)
Reprinted from Medicines for Malaria Venture[75]

For the more recent granule formulation, 19 approvals have been received, 18 in Africa, and one in the country of origin, Korea. In contrast to the tablet formulation, no approvals have been granted in South East Asia. The worldwide distribution of registrations is shown in Figure 4:

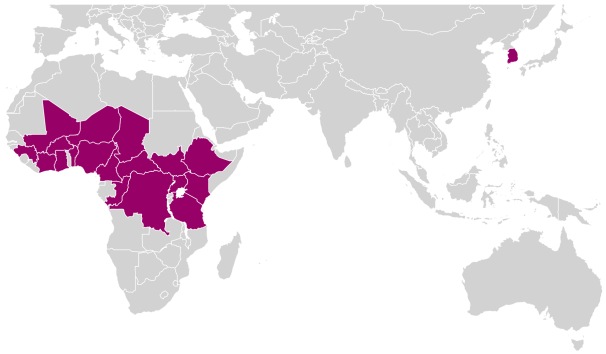

Figure 4: Countries where Pyramax granules are registered (situation as of May 2020)
Reprinted from Medicines for Malaria Venture[76]

Shin Poong also made use of the WHO SRA collaborative registration pilot to obtain accelerated approvals in Africa. This registration pathway is intended to lead to accelerated registration in the participating NRAs on basis of previous evaluations performed by SRAs, the target for decision making is 90 days.[77] In a presentation by WHO from November 2017, ten applications were indicated for the granules (1 approved, 9 pending) and five for the tablets (1 approved, 4 pending).[78] Still, according to the WHO Excel list on SRA approved products (last update on 10 Oct 2018), only three approvals have been obtained: Tanzania approved both tablets and granules, Cameroon only the granules.[79]

This stands in contrast to the information given by the MMV in the figures above, where approvals have been obtained in several African countries. Cavaller Bellaubi et al. also state that the WHO collaborative registration procedure was used for Pyramax in South-East Asia and Africa.[15] Therefore, the information on the outcomes apparently has not been updated on the WHO website or has not been provided accordingly to WHO for publication.

4.2.3. Implementation

Upon application by Shin Poong and supported by Doctors without Borders, the fixed-dose combination artesunate/pyronaridine was introduced in both the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children in June 2017.[80]

While the EMA review had already been finished in 2012 for the tablets, only the introduction into the Essential Medicines Lists built the necessary confidence and finally kicked off the export of the malaria drug into 17 countries in Africa and Southeast Asia. Shin Poong announced in March 2018 to have signed agreements with distributors to supply Pyramax in Kenya and 16 countries in West Africa.[74]

After that, the first procurement took place in Cambodia in June 2018, which was funded via the Global Fund[3].[81] Launches of Pyramax took place in sub-Saharan Africa from 2018[71] (for both adult and pediatric formulation, e.g. in Kenya in June 2018[82], in Cote d'Ivoire in July 2018[83] and in Uganda in April 2019[84]), additional launches are still planned for Africa.

In October 2019, WHO issued an information note encouraging the inclusion of artesunate-pyronaridine into national treatment guidelines along with procurement of the medicine where an effective monitoring system for safety and efficacy is in place. The note was intended to close the gap between the WHO list of prequalified medicines for malaria and the Model List of Essential Medicines recommending the combination, and the WHO Guidelines for the treatment of malaria from 2015, where the medicinal product was not recommended due to the hepatic safety concerns still present at that time. Revision of the Guidelines for the treatment of malaria is planned.[85]

[3] The Global Fund is a partnership investing in programs to combat HIV, tuberculosis and malaria, based in Switzerland.

Although the product is still not formally included in the WHO Malaria Treatment Guidelines, a few national guidelines by African countries already recommend Pyramax as of 2020 (e.g. Benin, Cameroon, Niger).

To support the safe use of the medicine, the MMV and Shin Poon conducted field tests in Kenya, India and Senegal to confirm that packaging and dosing instructions are suitable, accepted and understood.[71] The pictograms on correct posology are shown in Figure 5.

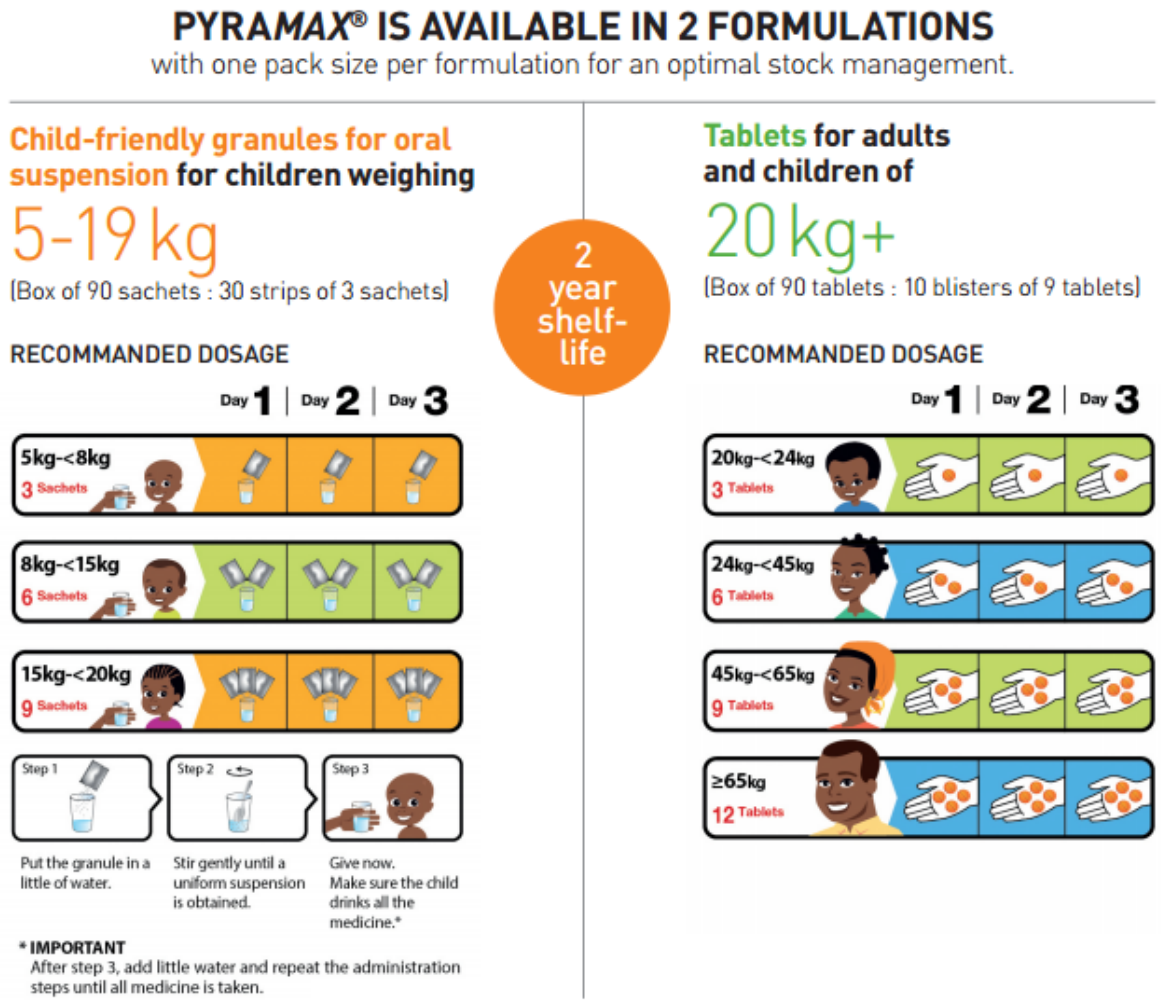

Figure 5: Instructions for use for Pyramax granules and tablets

Simple pictograms were developed to demonstrate the correct dosing. The pictograms are printed on the dispensing envelopes coming with the product.
Reprinted from Shin Poong Pharmaceutical Co. Ltd[86]

Figure 6 shows the pack of Pyramax blisters. The secondary packaging was designed to facilitate the correct use of the product by depicting the correct posology and contains dispensing envelopes for improved dispensing by healthcare professionals. A pack of 90 tablets consists of ten blisters of nine tablets each.[87]

Figure 6: Pyramax tablets pack, dispensing envelope and blisters

Reprinted from Shin Poong Pharmaceutical Co. Ltd[87]

The granules pack, too, brings envelopes for dispensing of the 30 strips consisting of three sachets each. The pack is shown in Figure 7.

Figure 7: Pyramax granules pack, dispensing envelope and strips Reprinted from Shin Poong Pharmaceutical Co. Ltd[87]

4.3. Case Study: Fexinidazole Winthrop Tablets for Sleeping Sickness

4.3.1. Developmental Aspects

Fexinidazole is the case of a repurposed molecule, that had already been discovered as an anti-infectant in the late 1970s by Hoechst AG (now Sanofi Aventis), but was discontinued due to strategic reasons at the time. Searching for potential anti-parasitic candidates for neglected diseases, the Drugs for Neglected Diseases *initiative* (DND*i*), a non-profit research and development organization, identified fexinidazole in 2005 and went into an agreement with Sanofi in 2009. The DND*i* took care of the clinical, pre-clinical and pharmaceutical development, while Sanofi was responsible for industrial development, registration, manufacturing and distribution of the product. Additionally, several public and private donors like the Bill and Melinda Gates Foundation or the UK Department for International Development were involved in the funding.[88,89] Sanofi contributes Fexinidazole Winthrop for free to WHO for distribution by Doctors Without Borders and funds projects to tackle the disease like capacity building or screening of patients.[27,90]

Fexinidazole Winthrop 600 mg tablets were developed as an oral formulation for human African trypanosomiasis (HAT). The disease is also known as sleeping sickness and is a typical neglected tropical disease, which occurs in sub-Saharan Africa, particularly in the Democratic Republic of the Congo. It is caused by the parasites Trypanosoma brucei gambiense (gHAT) and the less frequent T. b. rhodesiense (rHAT, only accounting for 3 % of the cases), which are transmitted by the tsetse fly.[19] Without treatment the disease is usually fatal.

Due to global initiatives and national sleeping sickness control programs in endemic countries leading to improved screening and control, a decline in HAT cases has already been achieved over the last 20 years. WHO set the target dates of 2020 for global elimination of gHAT as a public health problem and 2030 for the complete stop of transmission in Africa.[91]

Before fexinidazole, there were already treatments available for both stages of HAT. Still, their practical relevance was limited by logistical obstacles, their parenteral application routes requiring hospitalization, long administration duration, toxicity and/or the requirement for lumbar puncture to differentiate between stage 1 and 2 of the disease. These factors often hampered or prevented treatment in resource-constrained countries

and their remote or possibly even politically unstable regions. Hence, there was a high unmet medical need for an all-oral treatment covering both stages.[89,92]

The oral administration once daily over ten days is a major achievement in terms of facilitated distribution. The blister packs significantly reduce the effort for transport and storage, as further explained in section 4.3.3. Additionally, fexinidazole allows for home-based therapy and the elimination of the mandatory identification of the stage of gHAT by lumbar puncture.[27]

The great advantage of oral administration for access in the target countries was also taken into account for the design of the comparative pivotal phase II/III clinical trials. A non-inferiority design with a 13 % inferiority window was accepted for success rates when compared to the available standard therapy for late stage 2 HAT (NECT, nifurtimox/eflornithine combination therapy).[93]

Additional studies were conducted as plug-in to the pivotal study to demonstrate efficacy and safety in adult patients with stage 1 or early stage 2 gHAT and in children for both stages.[27]

While the first-in-human clinical trials were still conducted in France in healthy males of African origin, the phase II/III trials took place at 10 sites in the DRC and Central African Republic. Thus, local infrastructure in remote regions was established along with training of staff on Good Clinical Practice and examination and treatment procedures.[27]

Fexinidazole is currently also being tested in clinical trials for the treatment of HAT caused by T. b. rhodesiense (phase II/III trial)[94] and for the treatment of chronic Chagas disease (proof of concept trial).[95]

4.3.2. Regulatory Aspects

The eligibility of an application under Article 58 of Regulation 726/2004 was already confirmed in April 2010 and reinforced in April 2015. Two scientific advices were conducted in 2011 and 2014 on clinical development. The regulatory application was submitted for accelerated assessment in December 2017.

Accelerated assessment was granted because of major public health interest, but needed to be converted to a standard timetable during the assessment in light of major objections. These required redefinition of a starting material of the active substance, which could be resolved by introducing a post approval change management protocol and commitments

by the applicant, along with related adaptions of impurity limits and validation of analytical procedures of the starting materials.

The dossier was presented as a full application by analogy to Article 8(3) of Directive 2001/83/EC and contained complete information on quality, non-clinical and clinical data from own test/studies as well as bibliographic references.[19]

The indication granted for Fexinidazole Winthrop tablets is:

> Treatment of both first-stage (haemo-lymphatic) and second-stage (meningo-encephalitic) of human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense in adults and children ≥ 6 years old and weighing ≥ 20 kg. Fexinidazole should be used in line with official recommendations.[19]

Fexinidazole was less effective than NECT treatment for late stage 2 patients with higher severity of disease. For cases where other treatments are not available or tolerated, the use of fexinidazole was still considered favorable under close monitoring via hospitalization.[19]

Drawbacks of the product are the mandatory intake with food to achieve good absorption, and frequent side effects like vomiting or nausea, potentially compromising compliance. Therefore, EMA imposed additional risk minimization measures to be implemented prior to launch after alignment with the National Competent Authority. These measures include a controlled access program and controlled distribution system together with an educational program to ensure that the patients are instructed on the safe use of the medicine. The use of fexinidazole may only take place under supervision of trained health care personal and patients require a follow up after 12 and up to 24 months at recurrence of symptoms to discover relapses. Additionally, Sanofi was requested to perform a post-authorization safety study on fexinidazole as part of the risk management plan.[19,96]

Specific to the EU-M4all procedure, WHO and the endemic countries Democratic Republic of Congo (DRC) and Uganda were involved in the CHMP evaluation.[97] The positive scientific opinion was adopted in November 2018.[19]

Facilitated by the fact that the country was already participating in the CHMP evaluation procedure, Fexinidazole Winthrop was already approved in the DRC a month after adoption of the EU-M4all opinion in December 2018.[27] As of May 2020, registration of Fexinidazole Winthrop is still pending in Uganda.[98]

By the EU-M4all opinion, Fexinidazole Winthrop was eligible to be listed on the WHO list of prequalified medicines, where it was added by March 2019.[27]

4.3.3. Implementation

Fexinidazole was added to the WHO's Essential Medicines List in July 2019 as the first all-oral option for the treatment of both stages of sleeping sickness[99] and included in the WHO interim treatment guidelines for the treatment of gHAT.[100]

The roll-out of fexinidazole was prepared via WHO trainings of health care staff in the proper use, starting in DRC and continuing in other HAT-endemic African countries during 2019. Also, the DND*i* works on the access and supports pharmacovigilance activities in DRC and further countries like Guinea, Central African Republic, Angola and South Sudan. The drug is donated to WHO by Sanofi for the purpose of national sleeping sickness control programs in endemic countries. In January 2020, DRC was the first country where distribution was started.[101]

Figure 8 on the next page shows a comparison between the old standard therapy NECT and the fexinidazole tablet wallets and illustrates the benefits of the all-oral therapy in terms of logistics and practicability.

Figure 8: Comparison of NECT kit and Fexinidazole Winthrop tablets.

Fexinidazole as an all-oral therapy has added value with regard to logistical aspects, especially in remote settings of developing countries. (**A**) A treatment kit as distributed by WHO containing four treatments of NECT is transported by health workers. The box weighs 36 kg and requires significant efforts for transportation.[102] (**B**) NECT therapy needed for one patient, consisting of nifurtimox tablets and eflornithine for i.v. infusion. Both medicines are supplied in glass bottles. Eflornithine must be stored refrigerated after dilution.[102] (**C-F**) In contrast, Fexinidazole Winthrop tablets come in wallets that can easily be transported and allow for home use. Pictures C and D depict the pediatric wallet for one treatment cycle, pictures E and F the adult wallet for one treatment cycle.[27] The figure is reprinted from Neau et al.[27]

5. Prequalification status of EU-M4all products

The purpose of WHO prequalification of medicines is to improve access to high-quality, safe and efficacious products at low costs in developing countries. Prequalification status can be applied to finished products, active pharmaceutical ingredients and quality control laboratories. Prequalification (PQ) is not a marketing authorization, but basis for national registration in LMIC or for the purchase of medicines supplied by UN agencies for distribution in resource-limited countries. The scope is limited to finished products and active pharmaceutical ingredients with an "Invitation to Manufacturers to Submit an Expression of Interest for Product Evaluation" issued by WHO. Generally, this is the case for products on the WHO Model Lists of Essential Medicines or in WHO treatment guidelines.[103,104]

WHO is already involved for both confirmation of eligibility for EU-4all as well as during the evaluation process, and the CHMP scientific opinion considers the clinical context in the target countries. Therefore, products that were reviewed via EU-M4all can be co-listed on the WHO List of Prequalified Medicinal Products based on the review by the CHMP for medicines.[13] Requalification is required every five years afterwards.[105]

For EU-M4all vaccines, a specific simplified PQ procedure was published in 2010. After submission of the EU-M4all application, the intention for prequalification including all relevant technical information should be notified not only to WHO but also to the UN purchasing agency. Most aspects are reviewed during the EU-M4all procedure, but for the PQ specific additional aspects are of relevance like conformance to UN tender specifications or an international shipment validation. The PQ status for vaccines is usually given for two years and may be extended for up to five years in certain cases.[106]

Remarkably, not all EU-M4all opinions have PQ status, as can be seen in Table 7. Two of the six active opinions have not been prequalified. For Umbipro, this may be due to the manufacturer's plans to preferably foster the production of generic products instead of commercializing the product (please refer also to section 7.2). For Mosquirix, prequalification had been intended in the beginning[107], but has not been granted so far.[108] This is presumably related to the additional requirements for prequalification of vaccines as described above, that are not yet met.

Table 7: WHO prequalification status of active EU-M4all opinions[27,71,72,109,110]

Type	Brand name	EU-M4all opinion	Prequalified	PQ date
Medicine	Aluvia	(1) Sep 2006 (2) Jan 2008	Yes	not published
Medicine	Fexinidazole Winthrop	Nov 2018	Yes	Mar 2019
Vaccine	Hexaxim	Jun 2012	Yes	Dec 2014
Vaccine	Mosquirix	Jul 2015	No	N/A
Medicine	Pyramax	(1) Feb 2012 (2) Nov 2015	Yes	(1) May 2012 (2) Mar 2016
Medicine	Umbipro	Apr 2016	No	N/A

Since prequalification is well-recognized and very common especially for (locally manufactured) generics, the prequalification status provides the target countries a certain level of credibility to grant national authorization, whereas awareness of EU-M4all might still be limited.

On the other hand, prequalification alone does not guarantee success, since the manufacturer of the EU-M4all product Hemoprostol was not able to obtain approvals or commercialize the product, although PQ status had been received.[111]

As already discussed in section 4.2.2, there is a pilot collaborative registration procedure (CRP) for SRA-approved products leading to expedited national authorizations in the participating LMICs (decision making by the NRA within 90 days based on the SRA assessment).[77] According to the information published on the WHO website, this pathway has only been used for Pyramax from all EU-M4all products, in Tanzania for both Pyramax granules and tablets as well as in Cameroon for the granules. The last update of the product list for this pathway on the WHO website is from October 2018, however, so the information might not be exhaustive.[79]

In general, this CRP might offer an attractive option to expedited approvals in the target countries based on the EU-M4all opinion, which is tailor-made for the settings in these countries.

6. Approvals based on EU-M4all in Target Countries

In an article published in February 2020, EMA conducted a study on the approvals obtained for all EU-M4all medicinal products reflecting the situation as of April 2019 with the target to evaluate the public health impact resulting from the EU-M4all procedure. It is emphasized, however, that a direct assessment of patient access and affordability in non-EU countries is complex and not transparent to EMA. Therefore, the number of approvals obtained in non-EU countries based on EU-M4all was considered the best available surrogate to start with. Further analysis of data on patient level would need to follow.[15]

For the six active opinions, 138 approvals were granted based on EU-M4all in 90 non-EU countries as per April 2019. The worldwide distribution and number of approvals per country is broken down in Table 8 and visualized in Figure 9 on the next page.[15]

Table 8: Number of countries and approvals per region based on EU-M4all (as of April 2019)

Region	Number of countries	%	Number of approvals	%
Africa	39	43	75	54
Middle East and Asia	17	19	24	17
Central and South America	20	22	23	17
Europe (non-EU) and Central Asia	14	16	16	12
Total	90	100	138	100

Note: Reprinted from Cavaller Bellaubi et al.[15]

The majority of countries (39 out of 90) is located in Africa. These countries frequently have more than one product registered.

Further focus areas are Central and South America, where most countries have one and only a few countries have two medicines registered, and Asia, where the number of approvals per country varies between one and three.

The distribution of registrations can be related to the fact that several of the opinions are for neglected tropical diseases (Fexinidazole Winthrop, Pyramax, Mosquirix), which mostly and most severely affect sub-Saharan Africa.

The approvals granted in non-EU European, Middle East and Central Asian countries are likely for HIV treatment (Aluvia) or the hexavalent vaccine Hexaxim. Unfortunately, the exact distribution is not disclosed in the article by Cavaller Bellaubi et al.

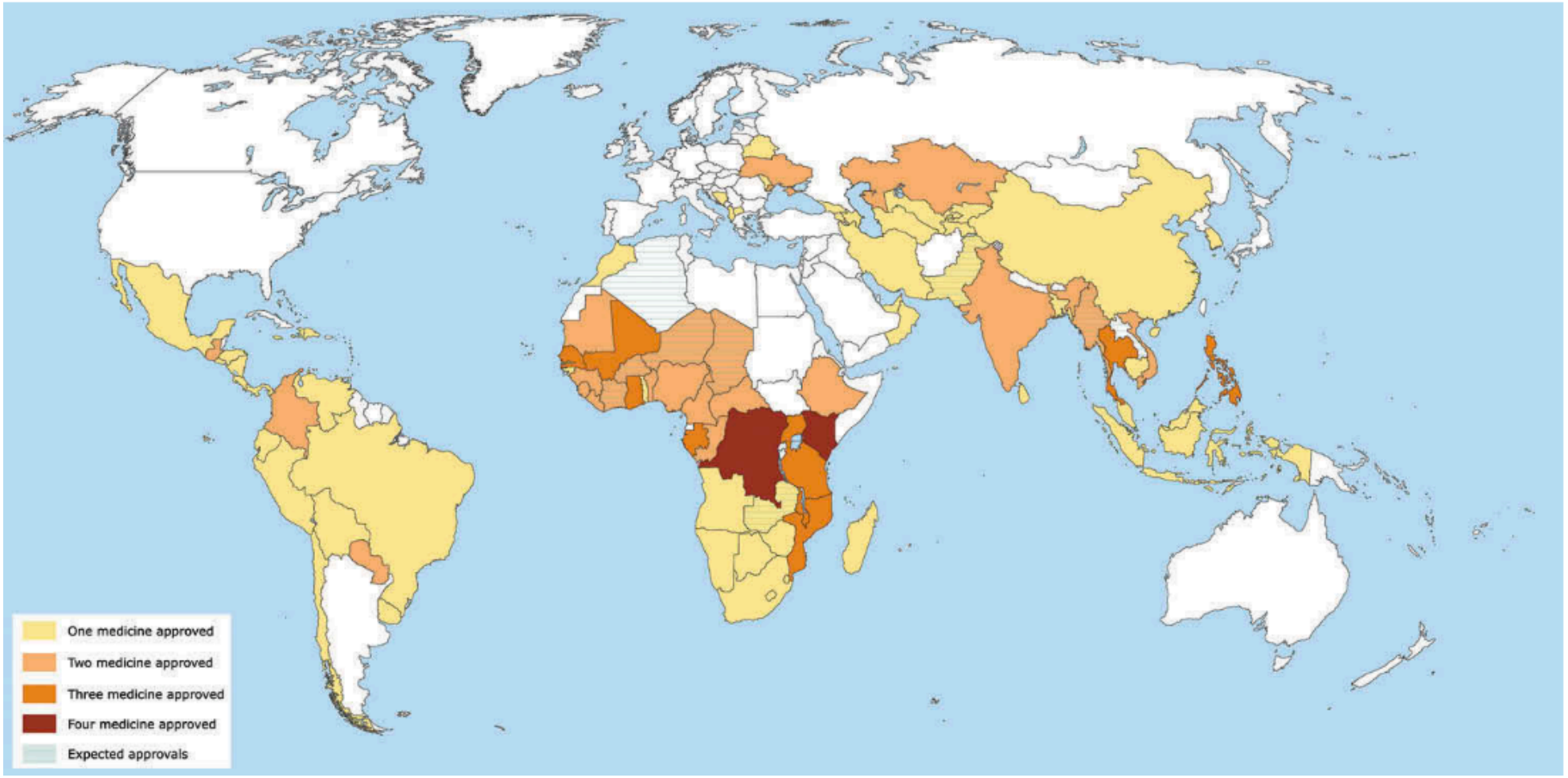

Figure 9: Approvals based on Article 58 opinions (as of April 2019)

Reprinted from Cavaller Bellaubi et al.[15]

Considering that the evaluation only includes the six active opinions, it is remarkable that there are two African countries (the DRC and Kenya) where four out of the six EU-M4all medicines are approved.

The individual worldwide number of authorizations per product is shown in Table 9:

Table 9: Number of worldwide approvals per EU-M4all opinion (as of April 2019)

Brand name	EU-M4all opinion	No. of approvals[15]
Aluvia	(1) Sep 2006 (2) Jan 2008	73
Fexinidazole Winthrop	Nov 2018	1
Hexaxim	Jun 2012	22
Mosquirix	Jul 2015	3
Pyramax	(1) Feb 2012 (2) Nov 2015	26
Umbipro	Apr 2016	13

Aluvia is by far the oldest still active opinion and also has the most approvals worldwide. All in all, 73 registrations have been obtained since 2006. Pyramax and Hexaxim are the oldest opinions after Aluvia (both issued in 2012) and have received 26 and 22 approvals, respectively.

Evidently, it takes time to have the products registered worldwide. Only a limited number of approvals has been obtained for the more recent procedures Mosquirix (2015, 3 approvals), Umbipro (2016, 13 approvals) and Fexinidazole Winthrop (2018, 1 approval). This fact is also linked to the complexity of implementation of these products, which requires structural support by non-governmental organizations and WHO.

As of yet, Mosquirix is registered in Ghana, Kenya and Malawi, the three countries chosen for the pilot implementation of the vaccine in sub-Saharan Africa.[112] Fexinidazole Winthrop is currently only registered in the DRC.[89]

One EU-M4all opinion, Hemoprostol, even was withdrawn because the scientific opinion holder was not able to register and commercialize the product at all.[44] This was attributed to the low awareness of the EU-M4all procedure at the NRAs in the LMICs.[55]

7. Discussion

7.1. Types of products in EU-M4all

7.1.1. Different appearance for same product

The first products going through EU-M4all in 2005 and 2006 were differently colored variants of already centrally approved medicines. Out of the eleven opinions for EU-M4all, three were for modified appearances of centrally registered products. These three products were oral tablet formulations for the treatment of HIV (Aluvia, Lamivudine ViiV, Lamivudine/Zidovudine ViiV). The purpose of the alteration was to prevent EU reimportation of the lower-priced products placed on the LMIC's markets.[54]

While 73 approvals based on the EU-M4all opinion were obtained for Aluvia (lopinavir/ritonavir) as of April 2019, the opinions for the Lamivudine mono and combination products were withdrawn due to commercial reasons after 10 years at the end of 2015.[15,47,48] A possible reason could be that the patent protection already ended in 2010 for the Lamivudine products, whereas there are still active patents for lopinavir/ritonavir, which prevent generic competition and keep the product commercially viable.[56]

Another difference is that Combivir/Epivir were already registered in several countries before the EU-M4all version was available. In contrast, Abbott used the EU-M4all pathway to introduce two different versions of the heat-stable tablet formulation when replacing the previous soft capsule, which before had uniformly been registered as Kaletra in high- as well as low- and middle-income countries. The yellow colored tablet has been offered to high income countries as Kaletra and the red colored one to developing countries as Aluvia.[55]

Lamivudine and Lamivudine/Zidovudine tablets were already prequalified in 2002 based on the EMA approval for Epivir and Combivir.[113,114] The WHO prequalification is a widely recognized pathway to obtain subsequent approval in LMICs. Since after patent expiry the need for protection against reimportation vanishes due to the generic market entry, and competitive pricing becomes crucial for the innovator, too, it might be preferable for the manufacturer to use only one, in this case the original formulation of Epivir/Combivir, for all markets. Additionally, the annual fees for the EU-M4all opinion and maintenance can

be omitted by withdrawal of the opinion. Of course, this implies either cessation or switch from the EU-M4all formulation to the EU CP formulation in all affected countries.

After the three initial examples, there were no further cases of products with different appearance going through EU-M4all. This indicates that the benefits related to the reduced risk of reimportation are not worth the effort and costs due to double maintenance of the centrally registered and the EU-M4all product as well as the higher complexity for manufacturing and stock-keeping.

7.1.2. Vaccines

Of the eleven applications for EU-M4all in total, four were for vaccines:

- withdrawn during EU-M4all procedure: Globorix (application in 2007)
- withdrawn in 2019: Tritanrix HB (opinion in 2013)
- active in 2020: Hexaxim (opinion in 2012), Mosquirix (opinion in 2015)

There have consistently been cases for vaccines in EU-M4all over time, but the success and thus the fate of the vaccines strongly depend on the development of immunization schedules. Therefore, the individual circumstances were completely different for each of the products.

Globorix

Due to a guideline update and change in WHO meningococcal disease strategy, the applicant GSK Biologicals withdrew the application at d120 of the procedure. The developed product was considered not to fit anymore in the WHO vaccination strategy for meningococcal disease.[40,42]

Tritanrix HB

The opinion for the quadrivalent vaccine was obtained for CPP purposes in 2013 to continue supply for developing countries while the centrally registered product was abandoned in Europe in favor of a pentavalent vaccine. The decision to discontinue the production was already communicated in March 2014 and the EU-M4all opinion eventually withdrawn in August 2019.[51,52]

Hexaxim

The hexavalent combination vaccine against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B and invasive infections caused by Haemophilus influenzae type b was initially

only targeted at LMICs but also registered centrally in Europe a year after the EU-M4all opinion.[55]

Mosquirix

The malaria vaccine was the first EU-M4all vaccine developed in partnership between GSK and the PATH Malaria Vaccine Initiative. Despite only moderate efficacy, the benefits were considered outweighing the risks to address the disease particularly in high-transmission areas and to reduce mortality in young children.

After the issue of the positive EU-M4all opinion, WHO recommended a phased introduction of Mosquirix in sub-Saharan Africa. Ghana, Malawi and Kenya were chosen as the first three countries for the six-year implementation program due to their high burden of disease and existing working malaria and immunization programs.[108,112] This pilot is intended to evaluate the adherence to the four doses of Mosquirix given over the children's first two years and to assess the effects on prevention.[115] This will later form the basis for WHO's decision on the recommendation of a potential broader use of the vaccine in Africa.[108]

Since vaccines are a powerful tool in prevention of severe diseases, it can be expected that additional vaccines will go through EU-M4all. This will depend on the future attractivity of the EU-M4all procedure vs. alternative pathways. Please refer also to the discussion of the Ebola vaccine case in section 7.5.

7.1.3. Repurposing of existing products / known molecules

Repurposed product

Since 2004 Hemoprostol 200 µg sublingual tablets have already been marketed as Gymiso in France for the indications medical termination of early pregnancy in combination with mifepristone and preparation of the cervix for surgical termination of pregnancy. The EU-M4all application for the 200 µg tablet submitted in 2012 was approved for a different indication, "treatment of post-partum hemorrhage due to uterine atony in situations where intravenous oxytocin is not available".[43]

Since the scientific opinion holder was not able to obtain national marketing authorizations and commercialize the EU-M4all product, the opinion was withdrawn three years after the grant.[44]

Repurposed molecules

New formulation

Basis for Umbipro was the already available chlorhexidine solution, which has been used as mouthwash and topical antiseptic. In partnership with Save the Children and following a call by the United Nations made in 2012, the applicant GSK developed an alternative gel formulation of the product for the use as umbilical cord care for home births.[31] The gel formulation should facilitate the use and retention of the active agent at the site of application.[26]

New fixed dose combination

As described in section 4.2, Pyramax is a new fixed dose combination of the well-known molecule artesunate with pyronaridine, which has been used for malaria in China since the 1980s. This combination was in line with the WHO recommendation on artemisinin derivates for malaria.

7.1.4. Development of innovative molecules

Fexinidazole had already been discovered as an anti-infective drug in the late 1970s, but the development was stopped at that time due to commercial reasons. After a systematic screening for potential candidates for neglected tropical diseases, fexinidazole was re-discovered and developed for gHAT in a public-private partnership between Sanofi and the DND*i*. The structure was selected as a set of non-clinical tests was already available to designate fexinidazole as a promising candidate.[27] Please refer to section 4.3 for details.

The non-nucleoside reverse transcriptase inhibitor dapivirine was initially developed as an oral treatment for HIV by Janssen Sciences Ireland (previously Tibotec). Janssen granted a license to the International Partnership for Microbicides (IPM) for development and commercialization of the agent as a microbicide for use in resource-limited countries.[116] The EU-M4all procedure is still ongoing and expected to close in Q2/2020.

7.2. Product development partnerships

Product development partnerships (PDP) are non-for-profit organizations driving the development of products for poverty-related and neglected diseases in collaboration with different external partners. The costs and risks for research and development are high and return of investment is low for diseases that mainly occur in resource-constrained LMICs, although the need for affordable medicines is high. Therefore, pharmaceutical

companies have hardly invested in such diseases in standalone programs. PDPs have been closing this gap and thus accelerated the development of such products by coordinating between the different partners as shown in Figure 10. Thus, costs and risks are shared between the partners. The projects are usually financed either via philanthropic or governmental funding. PDPs commonly focus on a specific disease or a disease area following a portfolio approach and take over the selection of the most promising strategies.[117,118]

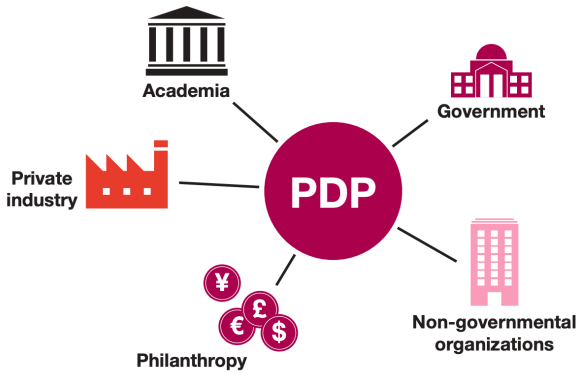

Figure 10: Parties involved in Product Development Partnerships

Reprinted from Medicines for Malaria Venture[118]

The foundation of such PDPs has started in the 1990s with many of them being established in the early 2000s. These PDPs have shaped and improved the situation for neglected diseases.[119] While the first EU-M4all product were still developed and commercialized by standalone companies, all of the more recent procedures were the result of product development partnerships between companies and non-profit organizations as shown in Table 10.

Table 10: Product development partnerships for EU-M4all

Brand name	EU-M4all opinion	PDP	Mission of the PDP
Pyramax	2012	Medicines for Malaria Venture	Treatment and protection up to eradication of malaria[120]
Hemoprostol	2014	Gynuity Health Projects	Scientifically based development of reproductive and maternal health[121]
Mosquirix	2015	PATH Malaria Vaccine Initiative	PATH: improvement of health outcomes in low-resource settings, with malaria as one of the focus areas[122]

Brand name	EU-M4all opinion	PDP	Mission of the PDP
Umbipro	2016	Save the Children	Saving and improvement of children's lives worldwide[123]
Fexinidazole Winthrop	2018	Drugs for Neglected Diseases *initiative*	Development of new treatments for neglected diseases[124]
Dapivirine vaginal ring	Expected Q2/2020	International Partnership for Microbicides	Development of HIV prevention products for resource-limited settings[125]

In this setup, the clinical and pharmaceutical development is driven by the PDP, while the pharmaceutical companies usually take care of supply and registration activities. In the end, affordable pricing is crucial to enable access in the developing countries. PDPs are ideal to tackle neglected diseases as their motivation is the improvement of public health rather than commercial viability.[119]

As an example, GSK also committed to offer Umbipro gel at a non-profitmaking price and, in addition, to transfer the knowledge about the product and manufacturing to the Promoting the Quality of Medicines (PQM) Program. The PQM will support to establish the know-how for local manufacturing of the chlorhexidine gel. Thus, quality-assured product will be made available to the local markets in a cost efficient way.[32,126]

In contrast, conflicting interests between the medical need and the manufacturer's interest in patent protection and commercially attractive pricing have been observed for individually marketed products like described for Aluvia in section 4.1.

An important pillar for the success of a product for resource-constrained countries is an implementation concept that considers local needs like appropriate training of healthcare staff or a distribution set-up ensuring access also in remote locations.

PDPs have proven to be successful in bringing products to the market in LMICs due to their non-for-profit nature and by going beyond the step of obtaining marketing authorization. It can be expected that further PDP products will use the EU-M4all pathway unless other procedures are more beneficial to the respective candidate.

7.3. Trends and Tendencies in EU-M4all

Figure 12 on the next page visualizes the distribution of the EU-M4all opinion over time. It can clearly be seen that the focus of EU-M4all were HIV/AIDS medicines in the beginning, from 2005 to 2011 the only scientific opinions obtained were for Lamivudine ViiV, Lamivudine/Zidovudine ViiV and Aluvia. The success of the strategy to combat reimportation may be questioned since there were no similar cases later on, and the opinions for Lamivudine and Lamivudine/Zidovudine were withdrawn after 10 years.

In the 2010s, a broader variety of different products underwent the EU-M4all procedure, ranging from products for neglected tropical diseases over vaccines for different conditions to products for maternal and newborn care. Currently, an innovative product for prevention of HIV/AIDS is under review, the dapivirine vaginal ring. It is striking that almost all newer opinions were developed in public-private partnerships.

The detailed indications of the EU-M4all medicines are listed in Table 2, Table 3 and Table 6 in section 3. HIV/AIDS medicines and vaccines for various indications each account for a third of the EU-M4all opinions. Due to the overall low number of EU-M4all opinions, it is not reasonable to assume that any of the indications prevails, however. The distribution is shown in Figure 11.

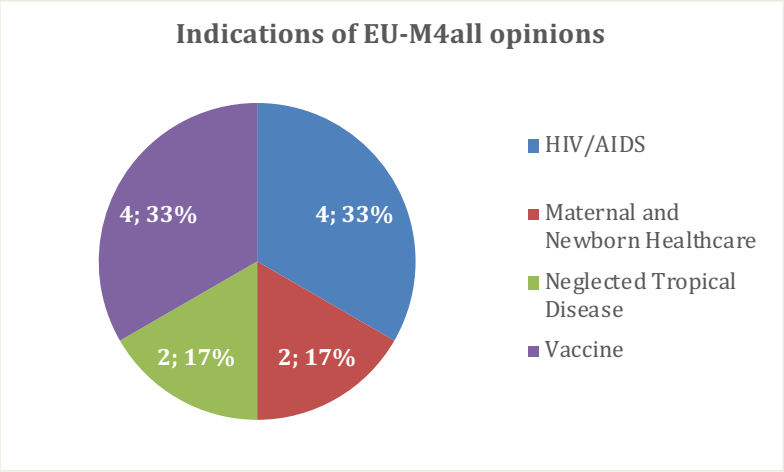

Figure 11: Indications of EU-M4all opinions (n=12)

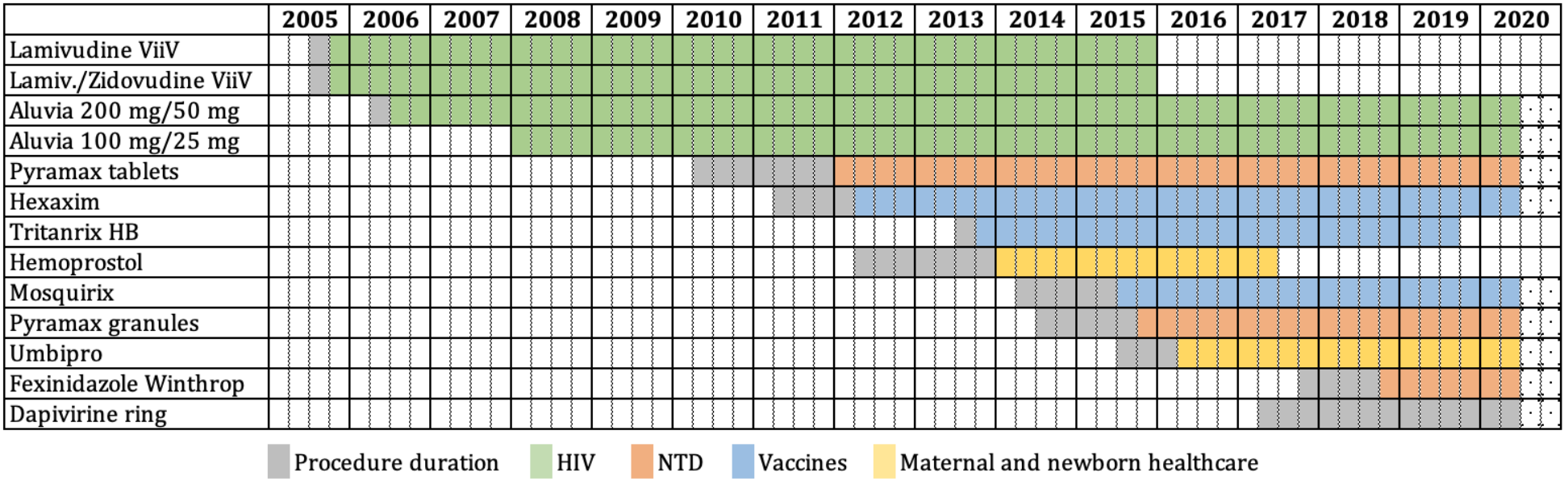

Figure 12: Distribution of EU-M4all opinions over time (as of May 2020)
Each box represents a quarter of a year. The colored bars depict the time of issue of the scientific opinion and, where applicable, the withdrawal.

Interestingly, the products are distributed evenly between prevention and treatment, as visualized in Figure 13. Prevention is of major relevance to combat major health problems and child mortality in the settings of developing countries, mainly in the form of vaccines, but also with medicinal products like Umbipro for the prevention of umbilical cord infections and the potential new EU-M4all product dapivirine vaginal ring for the prevention of HIV-infections in women.

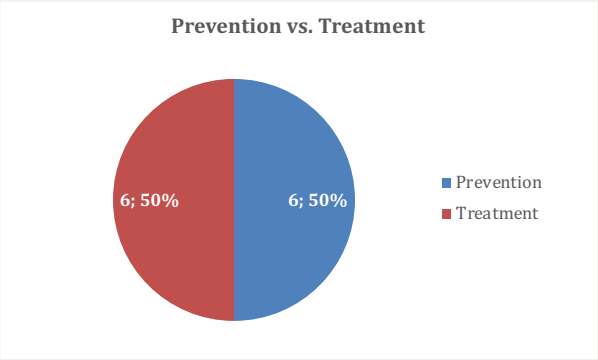

Figure 13: Distribution of EU-M4all between prevention and treatment (n=12)

The different types of products have been discussed in section 7.1 and are depicted in Figure 14. Half of the EU-M4all products have so far been developed in PDPs. The initial EU-M4all products for HIV treatment and the vaccines were standalone developments, but with Mosquirix there is also a recent case of a collaboratively developed vaccine. Standalone developments have only been observed for the earlier EU-M4all procedures and the EU-M4all way has proven appropriate and beneficial for PDP products. Therefore, it is very likely that potential new products undergoing EU-M4all will also be the result of PDPs, unless changes to the EU-M4all procedure will increase the attractiveness to other kinds of products.

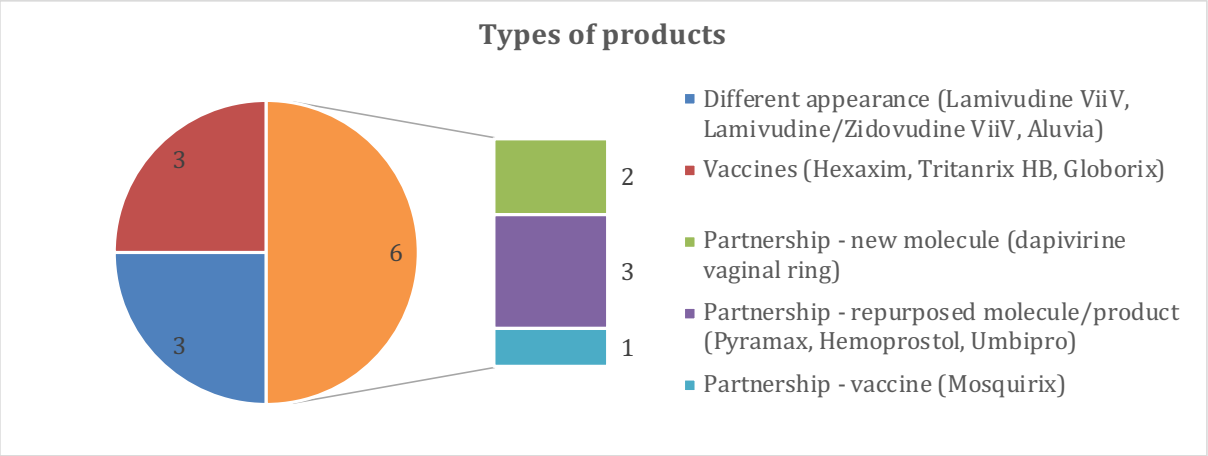

Figure 14: Types of product in EU-M4all (n=12)

7.4. Procedural Aspects

Scientific Advice

Scientific advice has been used several times with EU-M4all procedures. It was sought for four of the EU-M4all products, and for each of these products more than once (Fexinidazole Winthrop 2x on clinical aspects, Mosquirix 6x on clinical and quality aspects, Umbipro 2x on quality, non-clinical and clinical aspects, Globorix 2x with national regulatory agencies, please also refer to Table 1 in section 3).[19,21,26,42]

Whereas scientific advice was hardly used for the EU-M4all products in the beginning, it is quite frequent for newer applications. This is plausible seeing that the applications have turned from the use of available clinical evidence (e.g. for modifications in the appearance of tablet formulations) more and more to new clinical development programs requiring increased scientific consultation with EMA.

Potential applicants appreciate the support in the development of the non-clinical and clinical program via EMA scientific advice.[54] Additionally, WHO and experts from the NRAs in the developing countries can be involved in the procedure and thus provide added value in shaping the development appropriately for the targeted markets.[11]

Pediatric development

In contrast to centralized procedures, a pediatric development plan (PIP) covering the different age groups from newborn to adolescent is not required for EU-M4all procedures.[11] Nevertheless, nine of the ten EU-M4all opinions are indicated exclusively or also for the pediatric population as can be seen in detail in Table 2 and Table 6 in section 3.

The vaccines Hexaxim, Mosquirix and Tritanrix HB and the Umbipro gel were exclusively developed for newborn and infants. Aluvia, Fexinidazole Winthrop, Pyramax, Lamivudine ViiV, Lamivudine/Zidovudine ViiV are indicated for both adults and (parts of) the pediatric population.

This reflects the unmet medical need of many LMICs, where child mortality is still high, especially for children under five. Even if significant improvement has been made over the last 20 years, the highest under-five mortality rates still prevail in sub-Saharan Africa, where simultaneously the most approvals were obtained based on EU-M4all.[127]

Early Access Tools

From the early access tools offered by EMA, only accelerated assessment has been used in two cases so far: the opinion for Umbipro was granted in an accelerated procedure in 2016, while the timetable for Fexinidazole was converted to a standard timetable during the procedure due to major concerns (opinion issued in 2018).[19,26]

Considering that EU-M4all products already need to demonstrate their use for public health priority diseases to be eligible for this pathway, they have a high likelihood to fall within the scope of EMA's early assess tools. This again is related to the type of products undergoing EU-M4all procedure as the newer products tend to be addressed more particularly to non-EU countries and their public health issues, whereas the initial procedures were often copies or modifications of products already available on the European market.

There have been no cases for conditional MAs or MAs under exceptional circumstances. It has been criticized, however, how these concepts should be handled in target countries without a corresponding legislation.[128]

Application type

The same application types are applicable to EU-M4all procedures as to medicines intended for the European market. Although the legal basis for EU-M4all is Article 58 of Regulation (EC) No 726/2004, the application type needs to be indicated in analogy to Directive 2001/83/EC.

Tritanrix HB is the only EU-M4all product where the scientific opinion was sought for a product completely identical to one already registered for the European market, opening the option to use informed consent (Article 10c). All other procedures were full applications in analogy to Article 8(3) as can be seen in Table 1 and Table 5 in section 3.

Alternative application types might have been possible for Umbipro, Hemoprostol, Aluvia or Lamivudine ViiV, where a different indication and/or pharmaceutical form were sought for products already approved in the European Union. Since the clinical and non-clinical data used for the applications were either owned by the respective applicant or publicly available and not protected, the reference of this data in a mixed application via Article 8(3) was possible and provided full flexibility for the applicant. Other aspects that might render alternative application types attractive, like the necessity for an approved pediatric investigation plan for full applications, are not applicable for EU-M4all.

Despite the formal option, EU-M4all has not been used for generic or biosimilar medicines. The EU-M4all opinion involves considerable costs, but is not a marketing authorization and has not been very recognized in many target countries. Therefore, it is cheaper and more established to seek authorization for the European market and use CPPs for applications in developing countries afterwards. Alternatively, WHO prequalification status is a common pathway for generics ahead of registration in developing markets. Additionally, regulatory reference products might not be available on all target markets leaving the question if the countries accept foreign reference products as sole basis for their generic applications.

Procedure duration

Although the procedures in general follow the timetable of the centralized procedure, the observed duration of EU-M4all applications was quite variable as shown in Figure 12. Procedures for products already reviewed and approved in an identical (Tritanrix HB) or similar form (Aluvia, Lamivudine ViiV, Lamivudine/Zidovudine ViiV) took only two to three months. Other products like Hexaxim, Fexinidazole Winthrop or Mosquirix followed standard timelines of about a year, while Umbipro was the first product where the opinion was granted within seven months, due to accelerated assessment. Some procedures took considerably longer than usual, like the initial application for Pyramax (almost two years) or the Dapivirine vaginal ring application, which was submitted in July 2017 and is still on-going in May 2020. In these cases, new clinical data was generated and submitted in prolonged clock-stops.

Sunset Clause

EU-M4all offers the advantage of not being subject to the European Sunset Clause rule, which results in the loss of a registration if a medicine was not marketed for 3 years in the EU. This is of relevance for all products that want to use a CPP for registration in the target markets in LMICs, but are not attractive for marketing in Europe. Examples are Tritanrix HB, where an EU-M4all opinion was obtained to maintain the CPP for LMICs while phasing out the product on the European market, and Hexaxim, which was initially only intended for markets outside the EU.[55]

7.5. Alternative pathways vs. EU-M4all

There are several potential regulatory strategies for products targeted at LMICs. The most suitable strategy depends massively on the characteristics and objectives for the respective product, the location of the manufacturer and manufacturing sites and financial limitations. Manufacturers always have the option to directly head for registration in the LMICs based on CPPs obtained from SRAs. WHO prequalification has been established as a vastly recognized pathway for the registration of high quality generics in LMICs as already discussed in the master's thesis on the WHO collaborative registration procedure by Stefanie Haas.[129] The following sections discuss potential alternative pathways offering some additional benefit for the MAH and/or receiving NRAs in comparison with the EU-M4all procedure.

7.5.1. Centralized procedure

For certain potential candidates for EU-M4all, EMA itself might offer an attractive alternative pathway: the centralized procedure leading to marketing authorization in the EU combined with the benefits of orphan status. Even for diseases that mainly affect markets outside of the EU there is a certain market potential inside the EU, e.g. with regard to travelers, healthcare workers, military, or for stockpiling.[54] Related to that, the diseases might easily qualify for orphan designation, which takes into account solely the epidemiology in the EU. Orphan designation and status allow access to the benefits and incentives of orphan status like protocol assistance (scientific advice for designated orphan products at reduced costs), fee reductions for the activities related to the authorization of the product and orphan market exclusivity (preventing competition by similar medicines with similar indications after approval of the orphan medicine).[130] The lack of specific fee reductions and incentives is a major point of criticism for EU-M4all.

Pyramax and Eurartesim are both Artemisinin-based combination therapies for the treatment of malaria and were developed by the PDP Medicines for Malaria Venture.[131] However, different pathways were used for the applications at EMA: Pyramax was assessed according to Article 58 of Regulation (EC) No 726/2004 (scientific opinion issued in 2012) and Eurartesim via the centralized procedure after orphan designation (approval in 2011). The most significant difference in the evaluation by the CHMP is the different target population: while the EU-M4all opinion considers the targeted populations outside the EU, the centralized applications needs to demonstrate a positive benefit-risk balance for the EU community, where the setting for malaria-naïve travelers

is different from patients in malaria endemic areas, where a certain level of immunity has built up. For Eurartesim, the clinical data was bridged by comparing the pharmacokinetics between different ethnic origins (Caucasian versus Asian).[69]

Users of the centralized procedure need to consider the mandatory pediatric investigation plan including a potential development of a separate pediatric formulation and additional clinical trials, an environmental risk assessment and most importantly, the requirement to market the product in the European Union in order not to lose the MA due to Sunset Clause after 3 years, as discussed in sections 2.2 and 7.2.

Prequalification by WHO can be obtained via both pathways, although it is easier for EU-M4all products that are directly eligible for listing in the WHO list of prequalified products without an additional procedure.[13] The WHO collaborative procedure for SRA-approved products is open to products of both pathways as well.[132]

Alternatively, CPPs can be obtained for both EU-M4all and centrally registered products as basis for registration in the LMICs. The EU-M4all opinion already offers a targeted evaluation, but has been less accepted as "standard" CPPs for products registered and approved for the EU community.[54] Due to the lack of a marketing authorization for EU-M4all, CPPs with the status "marketed", which is required or of advantage in many LMICs, can only be issued for centrally registered products.

Another interesting case is the Ebola vaccine Ervebo. The indication could be regarded as a classic candidate for the EU-M4all procedure, since outbreaks of the Ebola virus disease have been restricted to African countries, with only a few cases outside of Africa, related to travel or secondary infections.[133] Nevertheless, Ervebo was assessed via the centralized procedure under accelerated assessment and the PRIME scheme, and received EU conditional approval in November 2019.[134] Not even two days after approval in the EU, the vaccine was already prequalified by the WHO to allow for procurement via the United Nations agencies and the vaccine alliance GAVI as well as fast local registration and implementation of the product in African countries affected from Ebola outbreaks.[135]

Due to the urgent and high unmet medical need, there was a lot of flexibility by all involved parties. The evaluation covered both EU and non-EU populations, and the application was assessed in parallel by EMA, the FDA and African countries. Involving the African regulators has the potential to reduce local registration times tremendously. WHO committed to an accelerated approach for prequalification by conducting the review on a rolling basis.[135]

In contrast to the previous examples, Hexaxim is the sole example for a product that was centrally registered following the EU-M4all opinion.[136]

In summary, the centralized procedure combined with orphan status may offer advantages over the EU-M4all procedure for some products targeted at LMICs despite the missing assessment for populations outside the European Union. Even if the case of Ervebo is exceptional in regard to the urgency and extent of unmet medical need, it demonstrated the suitability of the centralized procedure for a parallel review for both EU and non-EU population.

Starting March 2020, CHMP offers simultaneous review of centralized and EU-M4all applications.[10] This might be of particular relevance for products that are equally interesting for both EU and non-EU markets. With this change, EU-M4all might become more attractive for products that have only been targeted for the EU market so far and for which a separate non-EU assessment would be beneficial due to different conditions in the clinical use. Thus, the availability of a tailor-made assessment for LMICs and WHO prequalification status could be accelerated. For cases where clinical conditions are similar for EU and non-EU markets, national submissions with CPP or the use of the WHO collaborative procedure for SRA-approved products after central registration at EMA might still be more attractive due to the high costs related to the EU-M4all procedure.

Therefore, it is questionable if the simultaneous assessment will indeed represent a major advance, since the high fees for a centralized procedure and its maintenance still need to be borne for each application individually.[10] This will continue to be a huge obstacle for companies not profiting from fee reductions, e.g. due to SME status. It will become evident after the first cases if and how much impact the parallel review will have on the popularity of EU-M4all.

7.5.2. Dedicated pathways for LMIC products

SRAs have come up with different dedicated pathways for accelerating and improving the situation for medicines disproportionally affecting LMICs.

Main aspects of procedures established by FDA, Health Canada and Swissmedic are compared to EU-M4all in Table 11. Most of them were already established in the 2010s, only the Marketing Authorization for Global Health Products (MAGHP) by Swissmedic is a more recent procedure and still in pilot phase.

Table 11: Dedicated pathways for LMIC products by SRAs

	PEPFAR[137,138]	**EU-M4all**	**CAMR**[139]	**TD PRV**[140–142]	**MAGHP**[143–145]
SRA	FDA	EMA	Health Canada	FDA	Swissmedic
Established in	2003	2004	2005	2007	2017
MA granted	Yes	No	No	Yes	Yes (Swiss or export registration)
Type of product	Innovative/generic	Innovative/generic	Generic	Innovative	Innovative/generic
Scope of indication	HIV/AIDS	Public health priority diseases	Patented drugs	List of approved tropical diseases	Not restricted, focus on diseases disproportionally affecting LMICs
Principle	Expedited review process for antiretroviral therapies for procurement in PEPFAR countries	Scientific opinion by the CHMP for medicines for use outside the European Union	Compulsory license application	Applications for tropical diseases qualify for a priority review voucher that can be sold or used for other applications. Applications must be for new active substances and new clinical data, and qualify for priority review themselves.	Assessment involves NRAs and WHO as active participants or observers, pilot focusses on sub-Saharan Africa. Review for Swiss market but considering input from participating NRAs.
Completed procedures	225 (as of May 2020)	11 (as of May 2020)	1 (as of May 2020)	11 (as of Dec 2019)	1 (as of May 2020)
Strengths and Limitations	Comprehensive access program, but limited to one indication	Targeted review[a], but no MA granted in EU	Lengthy, bureaucratic process, validity of license only 2 years before renewal	Incentive for new developments for NTDs, but no targeted review[a]	Targeted review[a] with the objective of capacity building, pilot procedure needs to build trust

Note. **CAMR** = Canada's Access to Medicines Regime, **MAGHP** = Marketing Authorization for Global Health Products, **PEPFAR** = The U.S. President's Emergency Plan for AIDS Relief, **TD PRV** = Tropical Disease Priority Review Voucher

[a] targeted review refers to an assessment taking into account the population in the LMICs, not (exclusively) in the SRA's country

PEPFAR

The U.S. President's Emergency Plan for AIDS Relief (PEPFAR) is not only a regulatory pathway, but a comprehensive program to support the countries most affected by the HIV/AIDS pandemic. One pillar of the program is the procurement of antiretroviral medicines based on final or tentative approval (for products that cannot yet be marketed in the US due to patent protection).[137] Since its establishment in 2003, PEPFAR has been very successful with 225 application as of May 2020. PEPFAR even incentivizes the development of new antiretroviral combination products by waiving the fees for certain new drug applications. Additionally, the review is prioritized for recommended antiretroviral combinations to improve and ensure access in PEPFAR-supported countries.[146] A downside of PEPFAR is the restriction to antiretroviral medicines only, which strictly limits the scope of potential products.

CAMR

Canada's Access to Medicines Regime (CAMR) is not a marketing authorization, but works via a compulsory license issued by the Canadian IP office (please refer also to section 4.1.3 for more information on licenses for patented drugs) and tenders put out by the receiving countries. Due to the complex and cumbersome process, there is only a single case where the procedure has been used. In the current configuration, it can therefore not be considered relevant.[139]

TD PRV

Applications for tropical diseases (TD) are awarded a priority review voucher (PRV) by the US FDA upon approval if they meet the program criteria. The application must be eligible for priority review itself, must be indicated for one of the tropical diseases defined by the FDA, and contain an active substance not yet registered in the US. Since September 2017, applications must additionally involve new clinical data (other than bioavailability studies) that are crucial for the application and were sponsored by the applicant to be eligible for the TD PRV. This clinical data may not yet have been used for applications to NRAs in defined countries.[140] This change of eligibility criteria was introduced to hamper the use of drugs that are new to the US but are already in use worldwide and thus not constitute a real innovation, which has been frequently critized.[141] On the other hand the TD PRV eligibility criteria exclude cases of known molecules repurposed for new indications, an approach that has been observed for EU-M4all in some cases.

The priority review voucher can either be redeemed by the receiving sponsor or sold to another company. Upon redemption for another application, priority review will be granted, which leads to a shortened review time by FDA (i.e. six instead of ten months standard review time).[141] The redemption is related to an extra voucher user fee, however. The mechanism provides an incentive to develop products for tropical diseases since the voucher can be used for products where the expedited approval represents significant commercial benefit. So far, vouchers have sold from 67.5 million to 350 million USD (~60 million to 315 million EUR), for recent cases prices have narrowed to a range from 80 to 130 million USD (~72 million to 117 million EUR). The future value of PRVs has been doubted since there are two additional programs to win PRVs for rare pediatric diseases and medical countermeasures that might lead to a price decay for the vouchers. In contrast to the tropical disease programs, the two other programs will, however, expire by 2022 and 2023 if not renewed.[141]

If the TD PRV really acts as an incentive for developments for tropical diseases is not entirely clear. While a study in 2017 could not conclude an increase in the number of developments, drug sponsors and stakeholders reported the PRV positively impacted on their development decisions.[141]

A major point of criticism is that the TD PRV does not guarantee actual access to the drug at an affordable price in LMICs as the procedure primarily leads to a marketing authorization for the US market. Users of the pathway are not obliged to any measures or pricing requirements for developing markets although being rewarded the PRV.[141]

As of December 2019, eleven priority review vouchers have been granted for tropical diseases since the start of the program in 2007. The overall number of applications is the same as for EU-M4all, which has been established three years earlier, although six of the TD PRV have been awarded only in the period between June 2018 and December 2019.[141,142]

Compared to EU-M4all, the TD PRV offers a remarkable financial incentive for the development of medicines for tropical diseases by offering a (partial) reimbursement of the development costs by selling or using the PRV. On the other hand, there are no specific benefits with regard to LMICs, which are neither involved nor considered during the review for TD PRV. Additionally, the TD PRV is only open to a specific range of products.

MAGHP

The Marketing Authorization for Global Health Products (MAGHP) is a recent procedure resulting from a cooperation between Swissmedic and the Bill & Melinda Gates Foundation, which has been extended for another three years in March 2020.[147] The procedure is still a pilot with focus on sub-Saharan African and on diseases that disproportionally affect this region. Swissmedic plans to implement MAGHP as a regular procedure following closure of the pilot and taking into account feedback of the involved parties for potential adaptations.[148]

The particular focus and strength of the MAGHP is capacity building and acceleration of access in the participating LMICs by a strong involvement in the procedure and thus both increasing knowledge and trust in the process at the NRAs' side.[143] The procedure leads to authorization either for the Swiss market or for export only. It is not restricted by the type of product or indication apart from the fact that the product or indication should be new to the Swiss market.[144] During the pilot phase, applicants can indicate their preferred markets from the East African Community (EAC), which may participate actively or passively (observer status), and from other markets outside the EAC (only observer status possible, not more than five countries). Actively participating NRAs receive the full documentation, are involved in meetings and provide their comments for the LoQ. Observers receive access to Swissmedic's evaluation reports and internal correspondence, but do not receive the applicant's documentation. Also the WHO PQT can be involved as active or passive participant if prequalification status is intended.[144]

Since the start in 2017, three procedures have been completed for MAGHP: a scientific advice procedure and two applications for marketing authorization. However, the first application for a new indication was withdrawn after the preliminary decision in November 2018.[148]

As the first MAGHP product, Carbetocin Ferring injectable solution has received approval for the Swiss market in May 2020. Carbetocin Ferring is a heat-stable formulation of the known molecule carbetocin for the new indication prevention of uterine hemorrhage due to postpartum uterine atony. Experts from the NRAs of seven African countries (Uganda, Kenya, Tanzania (mainland and Zanzibar), South Sudan, Nigeria, Democratic Republic of Congo and Ethiopia) were involved in the assessment. These countries are supposed to issue their local registration within 90 days after receiving the application in the next step.[145] The manufacturer plans to start with applications in India, Kenya and Nigeria.[149]

The development is the result of a collaboration between Ferring Pharmaceuticals, WHO and MSD for Mothers.[149]

Compared to EU-M4all, MAGHP offers some advantages: Where EU-M4all does not grant access to the European market, MAGHP grants authorization for the Swiss market if requested by the applicant. This enables launch of the product in Switzerland so that CPPs can be issued with the status "marketed", which is required for registration in many LMICs. If a Swiss MA is not requested, Swissmedic will issue an export registration. The review by Swissmedic follows national rules and considers the Swiss population, but at the same time takes into account concerns and comments of the actively participating NRAs and WHO PQT for the review and risk benefit evaluation.[144]

Moreover, if involved in the procedure upon the applicant's wish, the participating NRAs commit to issue the local authorization and WHO to list the product for prequalification within 90 days. For both MAGHP and EU-M4all, co-listing on the WHO prequalification list is possible without further assessment because WHO is participating in the assessment (exception: additional requirements for vaccines). Accelerated registration in the LMICs for EU-M4all products is only possible via the WHO CRP for SRA-approved products by an independent, subsequent submission, where the issue of national authorizations by the participating NRAs within 90 days is already part of the MAGHP procedure.[144] This may compensate for the prolonged timeline of 330 days for decision making by Swissmedic vs. 210 days by EMA.[150]

A benefit that might lead to an increased usage of MAGHP over EU-M4all are the lower fees. Leaving aside fees for variations and inspections, the currently applicable fees to Swissmedic for the registration of a medicinal product containing a new active substance are 80,000 CHF (corresponding to about 75,000 EUR), compared to the fees to EMA starting from 296,500 Euro for the initial scientific opinion and annual fees of 106,300 EUR.[151,152] This is of great relevance for products for which pricing is crucial for distribution in LMICs.

Summary

CAMR has not turned out as a relevant pathway for LMICs products and no further usage is expected if no significant changes are made to the procedure. PEPFAR and TD PRV are open to a narrow range of defined indications only, but both pathways offer specific incentives that render them more attractive than EU-M4all for the products in scope. MAGHP is a comparatively new procedure with merely one successful example. It is

similar to EU-M4all in several aspects: both pathways focus on indications that disproportionally affect LMICs, involve WHO and NRAs in the procedure, conduct an assessment that takes into account the situation in the LMICs, and enable direct WHO prequalification listing. At the same time MAGHP has further advantages through lower fees and the option to obtain a registration for the Swiss market at the same time. The future will show how these advantages are perceived by potential candidates for EU-M4all and MAGHP.

7.6. Evaluation and improvements of the EU-M4all procedure

7.6.1. EMA review of EU-M4all

EMA has conducted a comprehensive review of EU-M4all and is continuously working on the improvement of the procedure, despite some drawbacks and delay caused by Brexit and the COVID-19 pandemic.[5,153]

In 2015, ten years after the introduction of Article 58 of Regulation (EC) No 726/2004, EMA evaluated the role of the EU-M4all procedure and potential steps for improvement in a joint study with the European Commission and the Bill & Melinda Gates Foundation. The analysis was performed via case studies and various stakeholder interviews. Back in 2015, the conclusion was that the impact of EU-M4all was low, with seven positive opinions at that time. This was attributed to the limitation of the scientific opinion to be used for non-EU markets only and the fact that is more fitting for innovative than generic products. Also, the market success in the LMIC was considered moderate, the recognition of the EU-M4all opinion by the NRAs was limited, and competitiveness of the products was low. Challenges the manufacturers faced were low awareness about EU-M4all by the NRAs, missing acceleration to obtain national approvals post-opinion, and the lack of successful role models.[54]

Furthermore, the fees for EU-M4all from initial procedure throughout maintenance are as high as for the centralized procedure without the grant of any market access. Apart from the support for SME, no fee waivers/reductions or other incentives are available to increase the attractiveness of EU-M4all.

Alternative pathways proved more interesting than EU-M4all due to specific benefits or incentives, like the WHO prequalification for generic products, EMA's centralized

procedure or other dedicated pathways for LMIC products. Please refer to section 7.5 for a detailed discussion.

The study in 2015 identified the following categories, where EU-M4all provides specific benefits compared to other pathways:

1. Innovative products only targeted at LMIC but not qualifying for TD PRV
2. Innovative products only targeted at LMIC with significant differences in the benefit-risk evaluation between high income and low- and middle-income countries
3. Innovative products targeted only at LMIC manufactured in Europe and requiring a CPP by EMA
4. Modifications of products already registered in the European Union for prevention of reimportation
5. For the support of pre-qualification of vaccines from manufacturers in countries where NRAs don't yet fulfill WHO prerequisites for PQ[54]

7.6.2. Barriers and measures for improvement

To overcome the obstacles, EMA has taken several steps to improve the procedure and increase recognition by LMIC regulators. For example, EMA conducted a workshop with African regulators in Malta in 2017 to get a better understanding of both sides and discuss potential improvements of the EU-M4all procedure. Main points of the discussions were improved ways of communication between EMA, WHO and concerned countries, better tailoring of CHMP's benefit-risk assessments and risk management plans, and earlier and deeper incorporation of national experts into the procedure, also with regard to capacity building.[154]

A stronger involvement of experts and observers from NRAs in the EU-M4all procedure has been desired for capacity building as well as increased recognition of EU-M4all and thus faster national approval. Additionally, experts from NRAs bring insights to the local situation and requirements into the CHMP's assessment.[55] EMA has also engaged closely with WHO, donors, procurers and further stakeholders to increase awareness and improve communication on EU-M4all.[5]

Supporting these activities, the Article 58 procedure was renamed to "EU-Medicines4all" (EU-M4all) in 2019 to provide the mechanism with a more approachable name.[5] The 2015 study discovered that "Article 58" has been associated with a negative image and a

rebranding was seen beneficial to support an enhanced Article 58 procedure even if resulting in additional costs for finding and promoting the new name.[55]

The EU-M4all opinion has often been perceived as of inferior standard by many LMICs since no marketing authorization is granted for the European Union.[55,155] Starting from March 2020, the centralized procedure has been opened for parallel assessment with EU-M4all leading to a harmonized assessment for EU and non-EU markets by the same assessors. The future will show if this change leads to an increased usage of EU-M4all.[9]

The hurdle that long national registrations procedures in the LMICs were still needed after the EU-M4all opinion has been improved by access to the WHO collaborative procedure for accelerated registration of finished pharmaceutical products approved by SRAs. This procedure offers the opportunity for accelerated decision making (within 90 days after acceptance of the submission) by the NRAs of the participating countries. To facilitate the decision, full assessment and inspection reports from the SRA are submitted with the application, where necessary supplemented by bridging reports for innovative medicines. So far, 24 countries have joined this pilot, almost all of them African, but also from the Caribbean Community (CARICOM) or Georgia. More countries can join the procedure upon invitation.[77] Additionally, automatic listing on the WHO's prequalification list has been established, which further increases the reputation of EU-M4all.[155] Nevertheless, the abbreviated WHO PQ process for vaccines remains and requires an additional application, which requires up to 3 months after a positive EU-M4all opinion.[55]

A major drawback to the use of EU-M4all have been the costs. They are as high as for a regular centralized procedure without leading to an actual marketing authorization. The high expenses related to inspections, application, post-approval activities and annual fees to EMA are an obstacle to many companies. In the current set-up, waivers or reductions only apply to SME or upon request. Although a simultaneous review for EU-M4all and the centralized procedure have finally been implemented in 2020, it does not come with any fee reduction, even if large parts of the reviewed documentation will be identical.[10]

Although the implementation of incentives as priority review vouchers, fee reductions, market exclusivity provisions or similar concepts was observed as a potential way to increase attractiveness and popularity of EU-M4all in the 2015 study by EMA, no steps have been taken in that direction as of today.[54]

7.6.3. Strengths of EU-M4all

Despite all benefits and incentives offered, many of the alternative pathways often only comprise a review for the respective population, i.e. US or European. The assessors do have great expertise in the evaluation of innovative medicines, but are not familiar with conditions that occur disproportionately in developing countries like tropical diseases. Also, the prerequisites for safe use and the benefit-risk balance may differ significantly between highly developed and developing markets.[155]

Therefore, a central strength of EU-M4all is that the resulting opinion is according to the standards of a highly regulated health authority, but at the same time takes into account the intended population and the setting in the developing countries for the benefit-risk balance.[11] Resources and capabilities are often limited at NRAs in LMICs. Typically, medicines are evaluated according to the standards and situation in the SRA's country and later on registered in developing countries on basis of a CPP issued by the SRA. This requires the expertise at the receiving NRA to assess the benefit-risk balance for their country by themselves. Often, their focus is on generic rather than innovative medicines.[155] During EU-M4all, WHO experts and experts from the target countries are already directly involved as scientific experts to contribute to the CHMP rapporteurs' assessment with their knowledge about the disease and the respective medical context.[11] Thus, the scientific know-how of the EMA is combined with local needs and knowledge of the epidemiology in the LMICs. This approach serves both the building of capacities and facilitation of decision making at the NRAs.

This approach is also an advantage in the WHO collaborative procedure for SRA approved products, where it is acknowledged that the EU-M4all opinion already extensively discusses relevant factors for registration in the targeted countries.[132]

Likewise, the option to seek scientific advice and thus develop an appropriate clinical development program has been praised by applicants of EU-M4all.[155]

8. Conclusion and Outlook

To date, the story of the Article 58 procedure has not been an overwhelming success with only a couple of cases over the 16-year period of its existence. Nevertheless, a review by EMA in 2020 concluded that the existing EU-M4all products have had a meaningful impact on global public health, even if further detailed analysis is needed.[15]

The cases investigated for this thesis demonstrated that EU-M4all has led to marketing authorizations of medicines for the treatment and prevention of diseases with high unmet medical need in developing countries. At the same time, it was noted that affordable pricing and implementation programs are important to ensure availability and safe use. Despite being open to generics, the pathway is mainly of interest for innovative medicines. EU-M4all is of particular relevance for medicines that are targeted at LMIC countries only. Typically, such products arise from product development partnerships.

The major strength of the EU-M4all procedure is the tailor-made review for the intended non-EU populations. This is a significant advantage over other pathways offered by SRAs, where the review is conducted for the respective country's population, which might significantly differ from populations in developing countries. Also, the involvement of NRAs in the EU-M4all procedure is a prominent feature, which can tremendously accelerate local registration as seen in the DRC for Fexinidazole Winthrop. These two benefits might be the key factors leading to usage of the procedure despite its high costs. Other potential situations in which EU-M4all might be of value are either niche or not commercially viable (combat of reimportation, basis for CPP of products manufactured in Europe for LMICs, basis for prequalification of vaccines manufactured in non-WHO recognized countries), or there are alternative pathways that are more attractive for specific kinds of products (PEPFAR, TD PRV).

The recently established MAGHP procedure by Swissmedic is very similar to EU-M4all and might become a huge "competitor" to EU-M4all after acquiring a certain recognition, since it strongly emphasizes involvement of NRAs and WHO in the procedure and is less costly.

Several improvements have been made to the procedure over the years by elaborating the collaboration between EMA and WHO, providing automatic prequalification status to medicines with positive EU-M4all opinion and access to the collaborative registration

procedure. Especially the use of the WHO collaborative procedure combined with intensified involvement of experts from NRAs in the EU-M4all procedure may lead to noticeable acceleration of approvals in LMICs. In addition, EMA has worked with stakeholders and NRAs in developing countries to identify hurdles and promote awareness.

EMA has not yet established any incentives awarded to users of the pathways or fee reductions to increase EU-M4all's attractiveness and fuel the development of products for developing countries. The fees are of high relevance for such procedures since clinical trials are costly, while revenue in the LMICs is low and the price must be affordable for LMICs. The recent innovation to allow simultaneous review in EU-M4all and the centralized procedure might be beneficial for certain products, but future will show if it really leads to increased usage of the pathway.

In the final programming document 2020-2022, EMA forecasts two scientific opinions according to Article 58 for 2020.[156] One of them is not yet disclosed, the other is the Dapivirine vaginal ring, for which the opinion is expected by Q2/2020.[38]

It remains to be seen how the strengths and incentives of the different pathways will impact development decisions and regulatory strategies, and if EU-M4all will continue to be an option for a specific set of products or if EMA will succeed in enlarging its attractivity to a broader range.

In a distant future, WHO capacity building measures, regional regulatory initiatives or the centralized African Medicines Agency may increase capacities at a national or regional level in a way that no or only little support from today's highly regulated authorities will be required anymore.[2]

9. Summary

Due to limited resources and capacities, regulatory authorities of many countries with low and middle incomes rely on previous review and approval of medicines by stringent regulatory authorities to safeguard the quality, efficacy and safety of the products.

To stimulate the development of medicines and vaccines for low- and middle-income countries (LMIC), Article 58 of Regulation (EC) No 726/2004 was implemented into the European legislation in 2004, providing EMA with a mechanism to give tailor-made scientific assessments of medicines to developing countries, following the same high standards as for products intended for the European market. From 2019, the procedure has been renamed to "EU-Medicines4all" (short: "EU-M4all").

To date, the story of the Article 58 procedure has not been an overwhelming success with only twelve applications over the 16-year period of its existence and just six active scientific opinions as of May 2020. Nevertheless, the existing EU-M4all products have had a meaningful impact on global public health. EU-M4all has led to marketing authorizations of medicines for the treatment and prevention of diseases with high unmet medical need in developing countries. At the same time, affordable pricing and implementation programs are important to ensure availability and safe use of the medicines. Despite being open to generic medicines, the pathway is mainly of interest for innovative medicines. EU-M4all is of particular relevance for medicines that are targeted at LMIC countries only. Typically, such products arise from product development partnerships.

Major strengths of the EU-M4all procedure are the tailor-made review for the intended non-EU populations and the involvement of national regulatory authorities from target countries in the EU-M4all procedure, which has the potential to tremendously accelerate local registration.

This thesis analyzes the use of the Article 58 procedure until the present day and examines three case studies in detail. It further investigates trends within the procedure and adaptations made to the mechanism to improve it, and discusses major strengths and weaknesses in relation to further potential pathways for LMIC products offered by other highly regulated authorities.

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Miesbach,

Anja Krug