Université de Lille 2
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Faculté des Sciences Pharmaceutiques
et Biologiques de Lille

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POUR LE DIPLOME D'ETAT
DE DOCTEUR EN PHARMACIE

Soutenue publiquement le 24 Mars 2017
Par M. Dirson Lucas

Axes de développement à l'enregistrement des médicaments dans les pays d'Afrique sub-saharienne

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Glossary

AFRO: African Region

AMRH: African Medicines Regulatory Harmonization

AMRO: Region of the Americas

API: Active Pharmaceutical Ingredient

CHMP: Committee for Medicinal Products for Human Use

CRO: Contract Research Organization

CTD: Common Technical Document

DALY: Disability Adjusted Life Years

EEA: European Economic Area

EFTA: European Free Trade Association

EMA: European Medicines Agency

EMRO: Eastern Mediterranean Region

EOI: Expression of Interest

EPAR: European Public Assessment Report

EU: European Union

EURO: European Region

FDA: Food and Drug Administration

FPP: Finished Pharmaceutical Product

GMP: Good Manufacturing Practices

GNI: Gross National Income

HIC: High-Income Countries

HIV/AIDS: Human immunodeficiency virus infection and acquired immune deficiency syndrome

HQ: Headquarters

ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

LMIC: Low- and Middle- Income Countries

LoQ: List of Questions

MAGHP: Marketing Authorisation for Global Health Product

MAH: Marketing Authorisation Holder

MoU: Memorandum of Understanding

NGO: Non-Governmental Organization

NMRA: National Medicine Regulatory Agency

PIL: Patient Information Leaflet

PQ: Prequalification

QCL: Quality Control Laboratory

Q&A: Questions and Answers

SEARO: South-East Asia Region

SmPC: Summary of Product Characteristics

SRA: Stringent Regulatory Authority

TPA: Therapeutic Products Act

UN: United Nations

USD: United States Dollar

WHO: World Health Organization

WHOPAR: World Health Organization Public Assessment Report

WHOPIR: World Health Organization Public Inspection Reports

WHO PQP: WHO Prequalification of Medicines Programme

WHO/PQT: WHO Prequalification Team

WPRO: Western Pacific Region

Introduction

In Africa, the role of health authority is carried out at the local level by each National Medicine Regulatory Agency (NMRA) for each country (1). Those NMRAs are responsible for ensuring that the population is only taking efficient and safe drugs of good quality; indeed, a drug has to be approved by the NMRA of the country where it wants to be commercialized (1,2).

However, the regulatory environment in Africa is challenging due to the lack of harmonization between the countries but also because of the lack of regulatory knowledge and expertise at the NMRA level (1). Therefore, a drug can be approved in a country and not in another and some counterfeit drugs can arrive on the market and be taken by the patients (3). Some drugs are not even available for patients that are in need of them (4).

In this context, the World Health Organization took the opportunity to improve the access of medicines within the low- and middle- income countries by being one of the major contributors who is enhancing the regulatory framework globally (5). Hence, the WHO took a first step in 2001 by elaborating the WHO Prequalification of Medicines Programme (also known by WHO PQP) to ensure the safety, efficacy and safety of the drugs (6). However, the prequalification is not resulting in a national marketing authorization. Thus, several years later, the WHO went one step further by setting up a collaborative registration procedure of WHO-Prequalified Medicines which is accelerating the registration of those prequalified medicines in developing countries and thus facilitating early access of the drugs to the local population (7,8). However, this procedure is limited to the products that are prequalified by the WHO, therefore, most recently, in 2015, the WHO launched another collaborative registration procedure to allow more products to be registered in those countries, e.g. the products that are approved by Stringent Health Authorities; this procedure is currently undergoing a pilot phase (7,9).

Besides this first initiative, to address the disease burden in developing countries, the European Medicines Agency created, in 2004, the Article 58 of the Regulation (EC) No 726/2004 to allow the Committee for Medicinal Products for Human Use (CHMP), in collaboration with the WHO, to give scientific opinions for medicinal products intended

exclusively for markets outside the European Union (EU) (10). However, as the prequalification, this procedure doesn't result in a marketing authorization.

Most recently, in 2014, Swissmedic have launched the Marketing Authorisation for Global Health Product (MAGHP), currently under pilot phase and waiting for its first candidate. This procedure will enable Swissmedic to improve the access of high quality medicines in low-income countries by granting a Swissmedic approval which can be recognized directly by the countries as the NMRAs can be involved in the procedure.

The purpose of this thesis is to make an assessment of those different procedures, to see if they fulfilled their objectives and see if there are some gaps that are arising from them.

In order to do that, we will describe, in a first part, the WHO Prequalification of Medicines Programme (WHO PQP) initiated by the World Health Organization in 2001 as well as the two Collaborative Procedures for Accelerated Registration. In the second part we will focus on the Article 58 of the Regulation (EC) No 726/2004 and finally, in a third part we will dwell on the procedure created by Swissmedic, the Marketing Authorisation for Global Health Product (MAGHP).

Part One:

The World Health Organization Prequalification Programme of Medicines & the Collaborative Registration initiatives

Résumé de la partie 1: Le programme de Préqualification des médicaments et les procédures d'enregistrement collaboratives de l'OMS

L'Organisation Mondiale de la Santé (OMS) est une agence qui fût créée en 1948 au sein de l'Organisation des Nations Unies (ONU) et est spécialisée dans le domaine de la santé publique.

Chaque pays du monde n'a pas le même accès aux médicaments. En effet, dans beaucoup de pays en développement, la population y a un accès limité. Certains de ces pays ne peuvent même pas se permettre d'avoir accès aux médicaments qui sont inclus dans la liste des médicaments essentiels établie par l'OMS.

L'un des principaux objectifs de l'OMS est de veiller à ce que tout patient dans le monde puisse avoir accès à la même qualité de médicaments. Dans ce but, l'OMS participe à divers programmes visant à remédier aux inégalités entre les différents pays.

L'un de ces programmes est le Programme de Préqualification des médicaments de l'OMS.

Ce programme a été créé en 2001 et constitue une sorte de procédure règlementaire dont le but est de préqualifier les médicaments destinés à traiter les maladies qualifiées de prioritaire (principalement le sida, la tuberculose et le paludisme).

Un médicament préqualifié est un médicament recommandé par l'OMS qui répond aux normes internationales concernant la qualité, la sécurité et l'efficacité.

Deux possibilités existent pour préqualifier un médicament :

La première est destinée aux produits déjà évalués et autorisés par des Autorités règlementaires strictes (SRA). Dans ce cas, l'OMS reconnaît l'évaluation scientifique effectuée par les SRA sur le médicament.

La seconde, quant à elle, est destinée aux génériques qui n'ont ni été évalués ni enregistrés par aucune autorité de santé et dont l'OMS devra effectuer l'évaluation. Cette seconde possibilité est destinée aux génériques car l'OMS effectue une analyse de la partie qualité et des études de bioéquivalence du dossier du produit.

Ce programme a eu un impact majeur sur la disponibilité de médicaments sûrs, efficaces et à un prix abordable dans les pays en développement. En effet, il a permis de rendre disponible, aux patients dans le besoin, des médicaments de haute qualité traitant des pathologies qualifiées de prioritaires.

Avant la mise en place du programme de Préqualification par l'OMS, les agences des Nations Unies achetaient les médicaments approuvés par les Autorités Réglementaires « rigoureuses » parce que la qualité, la sécurité et l'efficacité étaient jugées prouvées. Cependant, ces médicaments étaient coûteux. Ce programme de Préqualification a permis de donner aux agences des Nations Unies le choix d'un large éventail de médicaments de qualité pour les achats en gros.

Au fur et à mesure des années, l'inclusion des médicaments sur la liste des médicaments préqualifiés est devenue une condition préalable pour les agences des Nations Unies avant de procéder à l'achat de médicaments sûrs et de haute qualité. Ces organisations non gouvernementales sont fortement impliquées dans la distribution des médicaments à prix abordables dans les pays en développement. Ainsi, la préqualification par l'OMS donne accès au marché public via les Agences des Nations Unies.

Cependant, le marché privé ne peut être atteint par ces médicaments car ils ont besoin d'être au préalable approuvés par les Autorités Nationales de Réglementation des Médicaments. En effet, la préqualification ne correspond pas à une approbation du médicament sur le marché.

Par conséquent, deux initiatives ont été développées pour accélérer les procédures d'enregistrement des médicaments. Deux types de médicaments sont visés par ces procédures : les médicaments préqualifiés et les médicaments approuvés par des autorités réglementaires « rigoureuses ».

L'enregistrement accéléré des médicaments préqualifiés est une procédure visant à accélérer l'enregistrement des médicaments préqualifiés dans les pays en développement et donc à en

faciliter l'accès par la population locale. La collaboration est établie entre le Programme de Préqualification des Médicaments et les NMRAs qui sont intéressés par la procédure. Cette procédure collaborative vise à obtenir une autorisation du médicament préqualifié dans les pays et a été conçue pour contrer le retard accumulé, au sein des NMRAs des pays à faible ou moyen revenu, dans le nombre d'applications en attente d'évaluation. Ceci dans le but de rendre disponible plus rapidement ces médicaments de haute qualité à la population locale. Le concept de la procédure repose sur le partage d'informations confidentielles entre le Programme de Préqualification des Médicaments par l'OMS et les NMRA participants afin d'obtenir un enregistrement national des médicaments préqualifiés.
Cette procédure est maintenant bien acceptée par les fabricants et les NMRAs. Cependant, elle ne concerne que les médicaments préqualifiés, c'est à dire les médicaments traitant les maladies considérées prioritaires par l'OMS comme le SIDA, la tuberculose et le paludisme. Ainsi les pathologies comme le diabète, l'hypertension ou les cancers ne sont pas éligibles à cette procédure.

La procédure d'enregistrement accéléré des médicaments approuvés par des autorités réglementaires strictes, actuellement en phase pilote, va quant à elle, permettre à ces médicaments déjà approuvés par une SRA de pouvoir bénéficier d'une procédure permettant d'accélérer leur enregistrement dans des pays en voie de développement.
Les objectifs de cette phase pilote sont de tester la faisabilité de la procédure et de développer la collaboration entre les pays, les autorités sanitaires et les entreprises pharmaceutiques. Ceci dans le but de faciliter l'enregistrement des médicaments dans ces pays à faible et moyen revenu. Cette procédure est similaire à la précédente cependant les informations partagées viennent non pas de l'OMS mais de la SRA.

1 The World Health Organization Prequalification Programme of Medicines and the Collaborative Registration initiatives

1.1 The WHO Prequalification of Medicines Programme

1.1.1 The World Health Organization

In 1945, the United Nations (UN) were founded by 51 countries which are *"committed to maintaining international peace and security, developing friendly relations among nations and promoting social progress, better living standards and human rights"*(11). Starting the creation of the UN, it was discussed to set up a global health organization (12).

The World Health Organization (WHO) is an agency built in 1948 within the United Nations (UN) and specialized in Public Health. It represents the directing and coordinating authority for International Public Health Policy (13).

Contrary to the EMA or the FDA, the WHO is not a health authority per se; however, it is involved in the global health and is focused on addressing the global disease burden. The countries all over the world don't have the same access to medicines; indeed, in many of developing countries, people have limited access to medicines (14). Some of them cannot even afford the drugs that are listed in the list of Essential Medicines adopted the first time in 1977 (4,14,15). At that time the list included 208 essential medicines, nowadays, the list includes 340 drugs that satisfy the priority health needs of the people (15).

These drugs are not available to all people who need them, indeed, 60% of essential medicines are not accessible to people in Africa, South-East Asia and the Western Pacific where a lot of LMICs countries are located (14).

LMIC refers to Low- and Middle-Income Countries. According to the definition of the World Bank, a low-income country is defined by a gross national income (GNI) per capita of 1.025 US Dollars or less in 2015 (16). The calculation of the GNI is based on the World Bank Method (17). Dated July 2016, the following countries are classified as low income countries: Afghanistan, Benin, Burkina Faso, Burundi, Central African Republic, Chad, Comoros, Congo, The Democratic Republic of the Congo, Eritrea, Ethiopia, Gambia, The Guinea, Guinea-Bissau,

Haiti, the Democratic People's Republic of Korea, Liberia, Madagascar, Malawi, Mali, Mozambique, Nepal, Niger, Rwanda, Senegal, Sierra Leone, Somalia, South Sudan, Tanzania, Togo, Uganda, Zimbabwe (18). Therefore, we can observe that the majority of the low income countries are African countries.

The middle-income economies are sub-divided into lower-middle-income economies and upper-middle-income economies (16). While the lower-middle-income countries are defined with a GNI per capita between 1,026 USD and 4,035 USD, the upper-middle-income are those with a GNI per capita between 4,036 USD and 12,475 USD (16). This represents in total countries 107 countries (18).

One of the main goals of the WHO is to make sure that every person, any patient in the world can have access to the same quality of medicines, thus, the WHO is involved in various program aimed to address those inequalities between the different countries. One of these programmes is the WHO Prequalification of Medicines Programme that I will explain in the next paragraphs.

1.1.2 Scope of the WHO Prequalification of Medicines Programme

The WHO PQP is a United Nations program managed by the WHO created in 2001 (6). It is basically a regulatory procedure aimed to "prequalify" medicines intended to treat diseases with high public health needs (6). As described in their website, the mission of the WHO PQP is the following: *"In close cooperation with national regulatory agencies and partner organizations, the Prequalification Programme aims to make quality priority medicines available for the benefit of those in need. This is achieved through its evaluation and inspection activities, and by building national capacity for sustainable manufacturing and monitoring of quality medicines"* (6). In other words, the WHO set up the Prequalification of Medicines Programme to ensure the safety, efficacy and quality of the drugs. Thus, a medicine prequalified by the WHO is a drug recommended by the WHO that meets the international standards regarding the quality, safety and efficacy (6).

When it was launched in 2001, the WHO PQP was focus on drugs for treating HIV/AIDS, tuberculosis and malaria. In 2006, it was extended to cover drugs and products for reproductive health and again in 2008, to cover prequalification of zinc, for managing acute diarrhea in children (19). Finally as of February 2017, the WHO List of Prequalified Medicinal Products contained 533 medicinal products (20).

1.1.3 Process of the WHO Prequalification of Medicines Programme

The prequalification process consists of five components starting with the invitation (a) of the manufacturer for applying to the WHO PQP; this invitation is followed by the submission of the dossier (b), its assessment (c), inspection (d) and decision (e) (19).

We will now give details of each of the stages:

a. Invitation

Any manufacturer wishing to include its drugs in the prequalified products list is invited to apply, provided the medicines are on the invitation for expression of interest (EOI). This invitation is issued by the WHO Prequalification of Medicines Programme, other UN agencies (UNAIDS and UNICEF) and UNITAID. Only the products which are included in an EOI are eligible for prequalification (19).

To be included in an EOI, the medicines need to meet at least one of the three following criteria (19):

- the medicine is listed on the WHO Model List of Essential Medicines;

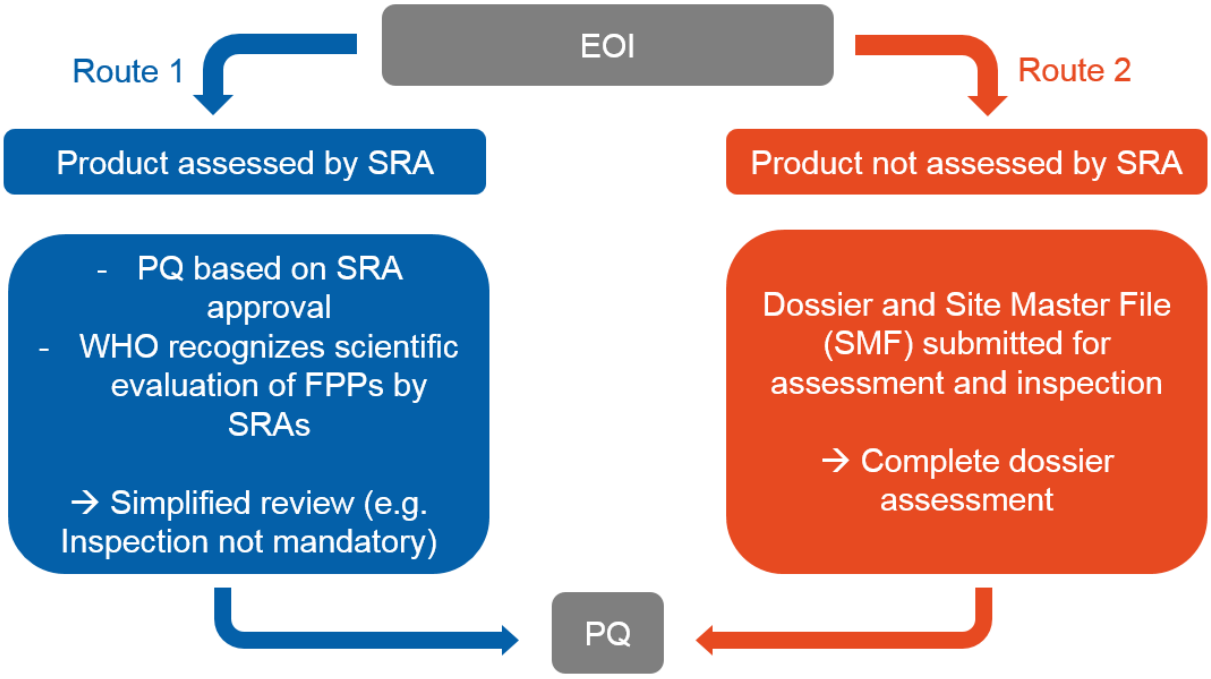
- an application for its addition to the Model List has been submitted to the relevant WHO Expert Committee for assessment, and is likely to meet the criteria for inclusion (based on public health need, comparative effectiveness, safety and cost-effectiveness);

- it is recommended for use by a current WHO treatment guideline.

This procedure is aimed for both innovators and generic finished pharmaceutical products (FPPs). An innovator is the originator of a medicinal product and has the first authorization for marketing.

As we can see on the **Figure 1-1**, two routes can be pointed out.

Figure 1-1 Simplified diagram of the two possible routes of the WHO PQP



i. Route 1: SRA-approved Generic or Innovator FPPs

This route is commonly named the Innovator route as the generic companies will prefer to use the route 2.

The route 1 is aimed for innovator or generic Finished Pharmaceutical Products approved by Stringent Regulatory Authorities (SRAs).

SRA is the acronym for Stringent Regulatory Authority; as per the WHO definition, a SRA represents a regulatory authority which is (21):

- a member of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH); or

- an ICH observer, being the European Free Trade Association (EFTA), as represented by Swissmedic and Health Canada (as may be updated from time to time);

- or a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

This is the case where the drug needs to be approved beforehand by a SRA, such as the EMA, the FDA or Swissmedic (21). The prequalification of the WHO is based on the SRA approval, indeed, the WHO recognizes the scientific evaluation of FPPs by SRAs (21). Thus, the manufacturer can use an abbreviated submission procedure that relies on the opinion of the SRA (21). In such case, the inspection of the manufacturing sites will, normally, not be conducted by the WHO which rely on SRA. Therefore, no or a few additional documents is required to receive the prequalification status.

ii. Route 2: Full Assessment – Generic FPPs

This route is aimed for generic Finished Pharmaceutical Products to be assessed by the World Health Organization.

This route is commonly named the Generic route as the assessment of the dossier focuses on the quality part and bioequivalence studies (22). It concerns the generics or fixed combinations of patented and approved therapies. Manufacturing sites as well as the Contract Research Organizations that led the clinical trials are inspected by the WHO (22). In other words, when a company goes via the generic FPP route, the WHO performs a complete assessment of the quality part.

b. Dossier submission

A comprehensive set of data about the quality of the product submitted for evaluation needs to be provided by the manufacturer. This includes data on the purity of all ingredients used in the manufacture as well as data on the finished pharmaceutical product (19). Moreover, results of in vivo bioequivalence tests need to be sent unless a waiver was granted (19).

The data are submitting in the WHO Common Technical Document format (2). The CTD is a set of specifications for a dossier for the registration of medicines developed by the International Conference for Harmonization. It combines all quality, safety and efficacy information of a drug and is organized in different modules and sections. It is an internationally agreed format for the preparation of applications regarding new drugs intended to be submitted to each of the European Union, Japan and the United States regions.

c. Assessment

The assessment is made by assessors who evaluate all the data presented. Assessment teams consist of WHO staff as well as experts from national regulatory authorities worldwide (19). The assessors are appointed by the WHO and are mostly coming from NMRAs and operate as consultants to the WHO, however, it is not possible to find the exact composition of the assessors as the members of the PQT are bound by confidentiality agreements (23,24). During the assessment of the dossier, inspections are conducted at manufacturing sites and at CROs (19). Moreover, if needed, samples are tested (19). This is strengthening the reliability of the assessment.

In order to get the prequalification of a product, the norms and standards as per the WHO recommendation have to be met by the applicant (21,22).

d. Inspection

The manufacturer must open its manufacturing sites for the finished pharmaceutical product and its active pharmaceutical ingredient(s) to an inspection team who assess working procedures for compliance with WHO Good Manufacturing Practices (GMP) (19). However, the inspections carried out by stringent regulatory bodies are often recognized and their work is generally not duplicated by the WHO (19).

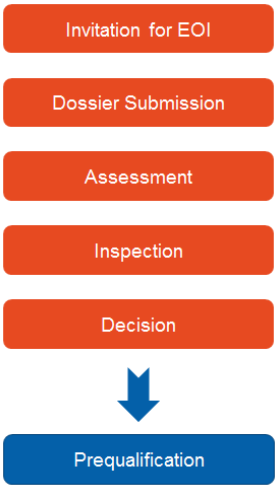
e. Decision

If the product is found to meet the specified requirements, and the associated manufacturing site(s) are compliant with the WHO standards, the product is added to the WHO list of prequalified medicinal products which is published on the WHO website, including product information (SmPC, PIL), assessment report (WHOPAR) and inspection report (WHOPIR) (19).

This process can take approximately three months provided that the data presented are complete and can demonstrate that the product meets all required standards. However, if the data are insufficient, the process can take more time as the manufacturer will have to re-submit the necessary data for a second assessment (19).

The **Figure 1-2** is giving a summary of the different step.

Figure 1-2 Summary of the WHO PQP process



Furthermore, after a positive decision, there is the maintenance of the prequalification status; indeed, the prequalification status for a product is not unlimited in time: all medicines are requalified by the WHO after five years, or when requested to do so (23). This is similar to the renewal process of marketing authorization in Europe.

In addition, similarly to nationally authorized medicines, prequalified medicines are also followed up throughout their lifecycle. Therefore, applicants are required to communicate to the WHO any changes in manufacture and control that may have a consequence on the quality, safety and efficacy of the product. This is done by submitting variations to the WHO Prequalification Team (WHO/PQT). Indeed, any administrative or substantive changes to the details of the product are referred to as variations and may be subject to acceptance by the WHO Prequalification of Medicines Programme prior to its implementation (23). Information on the types of variations, their conditions, data and documentation requirements are outlined in the Guidance (25) on Variations to a Prequalified Product. The variations are organized according to the structure of the Common Technical Document (CTD).

From its creation, in 2001, to September 2013, the WHO PQP was free; indeed the WHO did not charge the companies at that time. The WHO PQP depended only on funds and donation, mostly provided by the Bill & Melinda Gates Foundations and UNITAID (26,27).

However, it is risky to base a program only on funds and donations, therefore, the application fees were introduced to develop the program in a long-term perspective (27).

Before the 1st of January 2017, when a company was submitting its first application, it was exempt from application fees (27). Then, the second application cost 3000 USD and the third application 6000 USD (27). Afterwards, all other application to prequalify a medicine cost 8000 USD (27).

However, the financial system has been reviewed with higher fees. As described in their website (28), this new fee structure is taking several variables into account for medicines:

- "product nature: active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP);
- type of assessment: full or abridged assessment of new application, or assessment of major variation;
- an annual maintenance fee tailored to whether the initial assessment was full or abridged."

The **Table 1-1** below gives the new fee structure of the WHO PQP.

Table 1-1 Fee structure of the WHO PQP (28)

	Single Registration Fee		Annual Fee Per Product			
	New application Full assessment	New application Abridged assessment	Annual fee Full assessment	Annual fee Abridged assessment	Major variation	Minor variation or variation in an abridged assessment product
FPP (Rx)	$25,000	$6,000	$20,000	$5,000	$3,000	
API	$20,000		$8,000		$3,000	

We can see that the fees are much higher than the previous ones and that there is no longer an exemption for the first application anymore. This increase is expected to secure the financial sustainability of the Programme by covering the half of the annual operating costs of the WHO PQP (28).

1.1.4 Outcomes of the WHO Prequalification of Medicines Programme

a. Benefits of the Programme

Before the prequalification, the UN agencies were purchasing the medicines approved by stringent regulatory authorities because the quality, safety and efficacy were deemed proved. However those products were expensive. Thus, the WHO PQP was originally created to give the choice, to the UN agencies, of a wide range of quality medicines for bulk purchases (26). Indeed, many companies (which are not always following the Good Manufacturing Practices) are commercializing medicines at low cost with a non-guaranteed quality (26). Over the years, the prequalification of a medicine by the WHO has become a "standard" for most Non-Governmental Organizations (NGOs) and other organizations that subsidize the purchase and importation of the essential medicines (26). Those NGOs are highly involved in the distribution of the medicines at affordable prices in developing countries; for example, those organizations buy directly the medicines from the manufacturers in large quantities at a cost price and then, these stocks are distributed to endemic countries states or directly alongside the populations (26). Therefore those NGOs are involved in the accessibility of medicines in LMICs countries and nowadays, the majority of these organizations consider the inclusion of the medicines on the list of the prequalified medicines as a mandatory prerequisite before buying the drugs that they subsidize. The prequalification procedure has also an outstanding reputation among sub-Saharan NMRA and many of them rely on the list of prequalified drugs before giving their approval for the registration of a drug in their countries.

Thus, the WHO PQP enables the accessibility of drugs to these large markets with high medical needs via the NGOs, which partly explains the commitment of manufacturers as it has become a surrogate for the NGOs to purchase and distribute high quality medicines (26).

Furthermore, the WHO PQP helps to build capacity at the NMRAs level as the PQT involve people from NMRAs (23). The WHO also helps the manufacturers that don't have any experience in this field by providing them technical support and guidance throughout the procedure (23). Those people from NMRAs can, after the procedure, shared their experiences

with their colleagues and further develop the knowledge of the entire NMRA, notably in the regulatory processes and inspection fields.

Nonetheless, the major outcome of the PQP is the facilitation and acceleration of access to high quality medicines in the poorest population in a cost effective way. Indeed, even if the WHO is not granting an approval as performed by the Health Authorities, it acts like a surrogate on which the developing countries can rely on. Hence, as some authorities accept pre-qualification approval or data for registration purposes, the prequalification can lead to faster regulatory approval compare to the product that don't have the prequalification status (29).

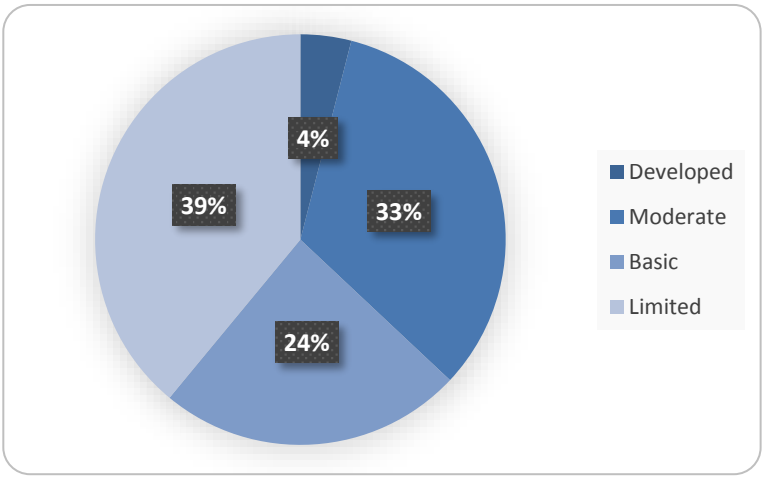
Thus, the WHO Prequalification of Medicines Programme has raised the standard for quality assurance of medicines (2). Its standards are recognized and promoted by others, helping to expand quality medicines production (2). Moreover, since the Prequalification of Medicines Programme proved to be a successful one, it had been extended to the Quality Control Laboratories (QCLs), in 2004, and Active Pharmaceutical Ingredients (APIs), in 2011, in order to ensure qualified control of procured medicines (30,31).

b. Limits of the Programme

However, the lack of human and financial resources dedicated to the health resulted in a slowdown of the prequalification process and in a whole limits the capacity of drug regulatory agencies (32). Therefore, the prequalification procedure, which theoretically may only take a few months, can actually be extended to several years (2,26).

Indeed, in LMICs countries and specially in the African countries there are insufficient of regulatory capacities and lack of harmonized technical requirements for marketing authorization (5). As we can see in the **Figure 1-3**, from 46 countries (out of 54 in total in Africa), only 4% of all National Medicine Regulatory Agencies (NMRAs) have developed capacity when 63% don't have the full limited or basic capacity to perform most core regulatory functions due to chronic shortages of resources (human, technical, financial…) (5).

Figure 1-3 Medicines Regulatory capacity in 46 WHO AFRO Member States (5)



As said previously, the prequalification is a "standard" for the UN agencies and other medicine suppliers to purchase safe and efficacious medicines of good quality at reasonable prices; however it does not give an approval to the drug in that country or those countries. Thus, the WHO Prequalification is giving an access to the public market via the UN agencies but the private market cannot be reached by those products as they need an approval by the NMRAs. In order to obtain an approval of their drugs, the manufacturers have to submit a dossier to the NMRAs of the countries where they want to market the concerned medicinal product. This is requiring an assessment by those NMRAs and as said before, they are facing limited resources (e.g. human resources, budget, and experience), hence, the time for granting an approval is long.

c. A difference between the innovators and generic companies:

The WHO set up the WHO Prequalification of Medicines Programme to make access of quality medicines to the patient at a reasonable price. This is their point of view and, obviously, it is a Programme that is more relevant for the generics as it enables the generic companies to certify the quality of their medicines without going through a full evaluation process by a Stringent Regulatory Authority which is lengthier and more expensive. This Programme has improved the population state of health through quality assurance of generic medicines and

has enabled more medicines to be brought to the patients by vitalising price competition. About 70% of WHO prequalified medicines are generic (33).

Therefore, the goal of the WHO fulfills the objectives of a generic company. On the contrary, an innovative company will focus on how to introduce new medicines to the patients with unmet medical needs in order to treat their diseases or conditions and is most likely searching to be the first one in the market. Thus, we cannot really compare the point of view of the innovator with the one of the WHO PQP as their objectives are not identical. However, the innovators are eligible to the Prequalification Programme as it can be a pathway they could use to gain access to potential new patients. In that case, there is no scientific assessment made and the prequalification is more an administrative step since the proof of the quality, safety and efficacy have already been completed by the SRA.

In order to address some limits, the WHO/PQT has developed two Collaborative Procedures for Accelerated Registration.

The first one is the Accelerated registration of prequalified FPPs procedure *(full name is the Collaborative Procedure between the World Health Organization Prequalification of Medicines Programme and National Medicines Regulatory Authorities in the Assessment and Accelerated National Registration of WHO-prequalified Pharmaceutical Products)* and is aimed to facilitate and accelerate national registration of medicines that have been prequalified by the World Health Organization (7,34). This procedure was piloted in July 2012 and officially approved in May 2013 (34–36).

The second one is a procedure that was created by the WHO/PQT for the medicines that have been assessed and authorized by SRAs (9). This procedure is the Accelerated registration of FPPs approved by SRAs procedure *(full name is the Collaborative Procedure in the Assessment and Accelerated National Registration of Pharmaceutical Products Approved by Stringent Regulatory Authorities)* (9). Contrary to the first one, both prequalified products (by the WHO SRA-prequalification route) and non-prequalified drugs are eligible (9).

We will now give more details on the Accelerated registration of prequalified FPPs, and information on the Accelerated registration of prequalified FPPs which is in the pilot phase.

1.2 The Accelerated registration of prequalified Finished Pharmaceutical Products procedure

1.2.1 Objectives of the procedure

The Accelerated registration of prequalified Finished Pharmaceutical Products procedure is a procedure aimed to accelerate the registration of prequalified medicines in developing countries and facilitate the access of the drugs to the local population (8). The collaboration is made between the WHO Prequalification of Medicines Programme and the NMRAs who are interested in the procedure (37).

The difference between the WHO PQP and this procedure lies in the fact that this collaborative procedure is a procedure which aims to get an approval of the prequalified drug in the countries, what the WHO PQP doesn't do (37). With an approval in the country, the drug can be marketed and is available to the population. Thus, it will give to the LMICs countries that are not supplied by the UN agencies, an access to the product.

This procedure was designed to countered the backlog of NMRAs, in LMICs countries, in the number of marketing applications assessment pending as well as give high quality medicines available faster to the patients in needs (35,37). This backlog is the result of the huge number of applications and the lack of resources at the NMRA level. Another objective of this procedure is to further building the capacities in NMRAs of LMICs countries by the share of documents during the process that we will explain later on.

This collaborative procedure was piloted in July 2012 by the first NMRAs that have joined the experimental phase (35,36). Eleven NMRAs of different African countries participated in this pilot phase: Botswana, Ghana, Ethiopia, Kenya, Namibia, Nigeria, Tanzania, Uganda, Zambia, Zanzibar and Zimbabwe (36). Taking into account the lessons learned during the pilot phase, the procedure was officially approved in May 2013 by the 66th World Health Assembly (35,38). Currently, the following countries are participating to the procedure: Armenia, Botswana, Burkina Faso, Burundi, Caribbean Community (CARICOM), Cameroon, Côte d'Ivoire, Democratic Republic of the Congo, Ethiopia, Georgia, Ghana, Kenya, Kyrgyzstan, Lao People's Democratic Republic, Madagascar, Malawi, Mali, Mozambique, Namibia, Nigeria, Philippines,

Senegal, Sierra Leone, South Africa, Tanzania, Uganda, Ukraine, Zambia, Zanzibar, Zimbabwe (8).

The Accelerated registration of prequalified Finished Pharmaceutical Products procedure is only limited for medicines listed on the list of prequalified medicinal products, meaning that they were assessed and inspected by the WHO (37). The medicines that are prequalified based on the approval of a SRA are out of scope of this procedure (37). Indeed, in these cases, as the WHO has not performed the assessment and the inspections, the respective reports does not exist and cannot be shared by the WHO/PQT with the NMRAs, and as the procedure rely on the confidential sharing of those documents, the procedure is not applicable (37).

1.2.2 Process of the procedure

The concept of the procedure is to share confidential information between the WHO/PQP and the participating NMRAs in order to have a national registration of the prequalified medicines (8). The information is shared, via a secure internet-based platform, to a designated person in each NMRA who can access to the password-protected information (8). Obviously, the application submitted for national registration must refers to the same pharmaceutical product prequalified by WHO; only minor administrative differences are acceptable to reflect some local regulatory requirements (8). Indeed, as per *the Collaborative procedure between the World Health Organization Prequalification of Medicines Programme and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products* guideline (37), "the same pharmaceutical product is characterized by:

- the same product dossier;[1]

[1] Only the technical data included in the dossier must be the same. There may be country-specific differences in administrative data, or if required by NMRAs under exceptional circumstances, additional technical data can be provided (e.g. bioequivalence with a country-specific comparator).

- the same manufacturing chain, processes and controls of materials;
- the same active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP) specifications;
- the same essential elements of product information."

In principle, the prequalification dossier is used, but it might happened that individual NMRAs agreed to submission of simplified dossier (8).

The process' steps are the following:

a. Submission of the application

Firstly, the applicant has to express its interest to have a prequalified product registered in a participating country using this collaborative procedure (8,37,38). For this purpose, the applicant has to complete and sign a consent form, which will enable the WHO/PQT to share assessment information, as well as an expression of interest (EOI) to apply for the procedure for a specific prequalified product (8,37,38). In the EOI, the applicant confirms that the product is, from the technical aspects, identical to the product prequalified and that the submitted data are the same as the data approved during the prequalification (38).

b. Assessment of the application

The NMRA either accepts or refuses (with providing justification) to use the procedure for the product (8). Then, the NMRA informs the WHO/PQT of the decision made (38). In the case where the NMRA accepts the procedure, the WHO/PQT shares the prequalification information (product-related assessment and inspection reports as well as other relevant documents providing details on which the WHO/PQT based their decisions to prequalify the product) to the participate NMRA who should issue a decision within 90 days (8,38).

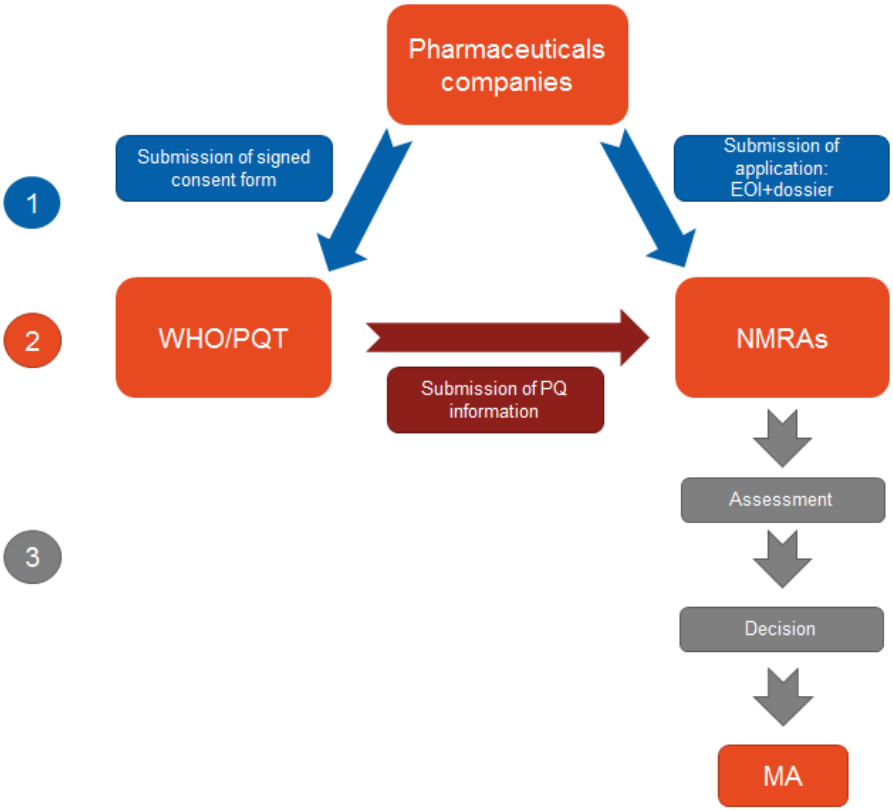
c. Decision

The NMRA communicates its decision to the WHO and the applicant within 30 days (8,38). The decision made by the NMRA can be different from the one issued by the WHO for the prequalification, indeed, the NMRA is free to deviate from the WHO/PQT opinion (38). However, in that case, the decision needs to be detailed and communicated to the WHO/PQT (38).

When the NMRA issues a positive decision, the new registered product is added to a list on WHO website (8,38).

The **Figure 1-4** gives a summary of the different steps of the procedure.

Figure 1-4 **Summary of the Accelerated registration of prequalified Finished Pharmaceutical Products procedure**



d. Post-registration phase

After the registration phase, all the stakeholders should collaborate to minimize post-approval differences between the nationally-registered and the WHO-prequalified product by submitting the same variations to WHO/PQT and to participating NMRAs (8,38). Furthermore, if a major decision is made for the product, the parties should communicate together regarding the decision made (8,38).

1.2.3 Outcomes of the Procedure

As we can see on the **Figure 1-5** below, the performance and statistics as per the 7th of November 2016, retrieved from the WHO website, shows that there were a growing acceptance of this collaborative procedure by manufacturers and NMRAs from 2013 to 2015, indeed from 15 registrations in 6 different countries in 2013 we reached 61 registrations in 15 different countries in 2015 (39). Moreover, from 2015 to 2016, we observed an established acceptance by manufacturers and NMRAs with 68 registrations in 13 different countries in 2016 (39).

As we can easily calculate on the **Figure 1-5** and see on **Figure 1-6**, from its creation in 2013 to November 2016, the Accelerated registration of prequalified Finished Pharmaceutical Products procedure enabled 180 registrations in NMRAs with approximately 100 registrations approved within 90 days (39).

The **Figure 1-7** shows also that the median time to registration is 78 days (39). Those numbers are very interesting for the companies when we know that they are facing registration timelines between one and three years perhaps more (40).

Figure 1-5 **Number of registrations and of countries that approved drugs via the Accelerated registration of Prequalified FPPs procedure per year (39)**

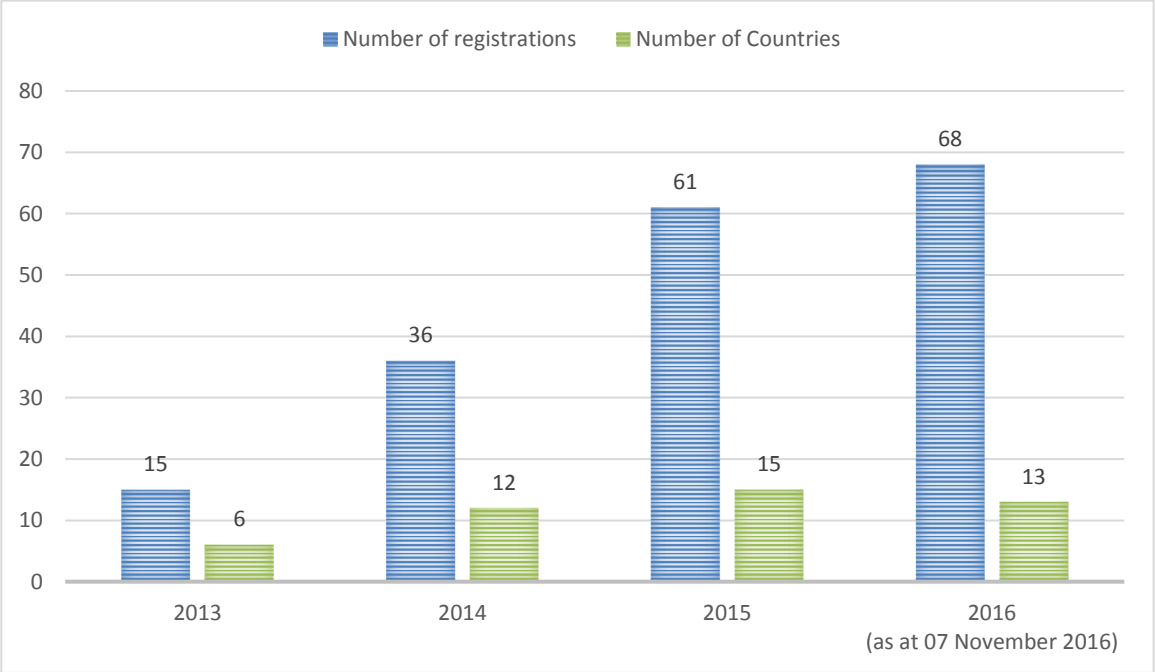


Figure 1-6 **Analysis of the registration time via the Accelerated registration of Prequalified FPPs procedure (Including regulatory time and applicant time) (data from 2013 to 2016, n = 180) (39)**

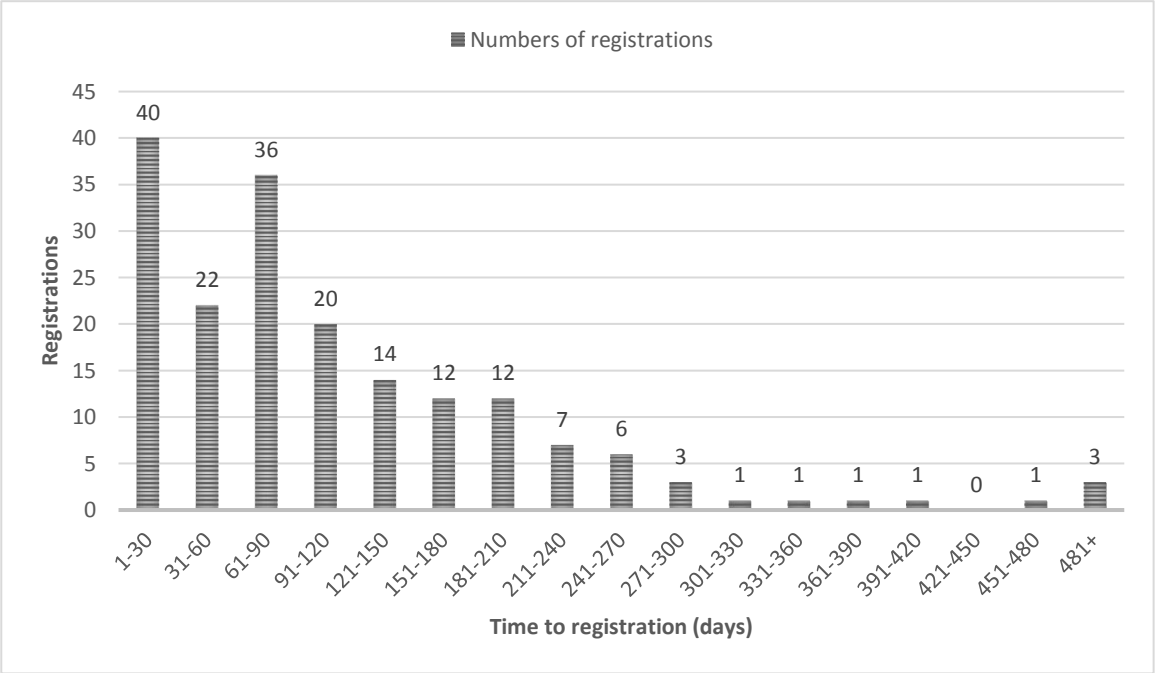
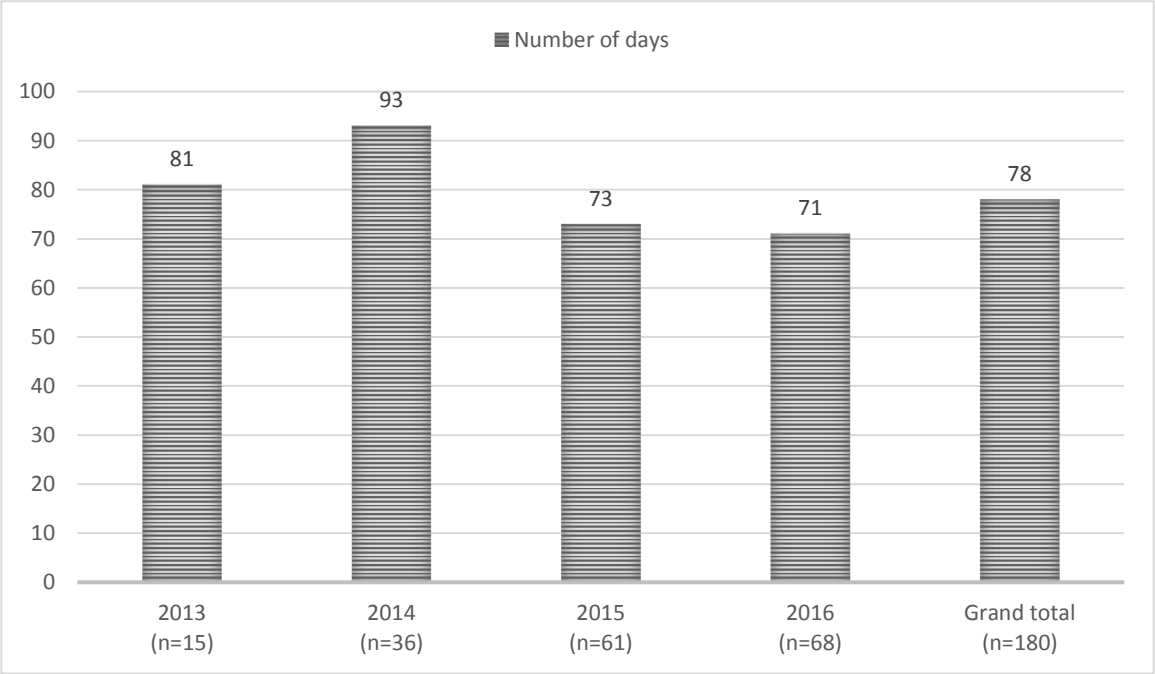


Figure 1-7 **Median time to registration via the Accelerated registration of Prequalified FPPs procedure (Including regulatory time and applicant time) (data from 2013 to 2016, n = 180) (39)**

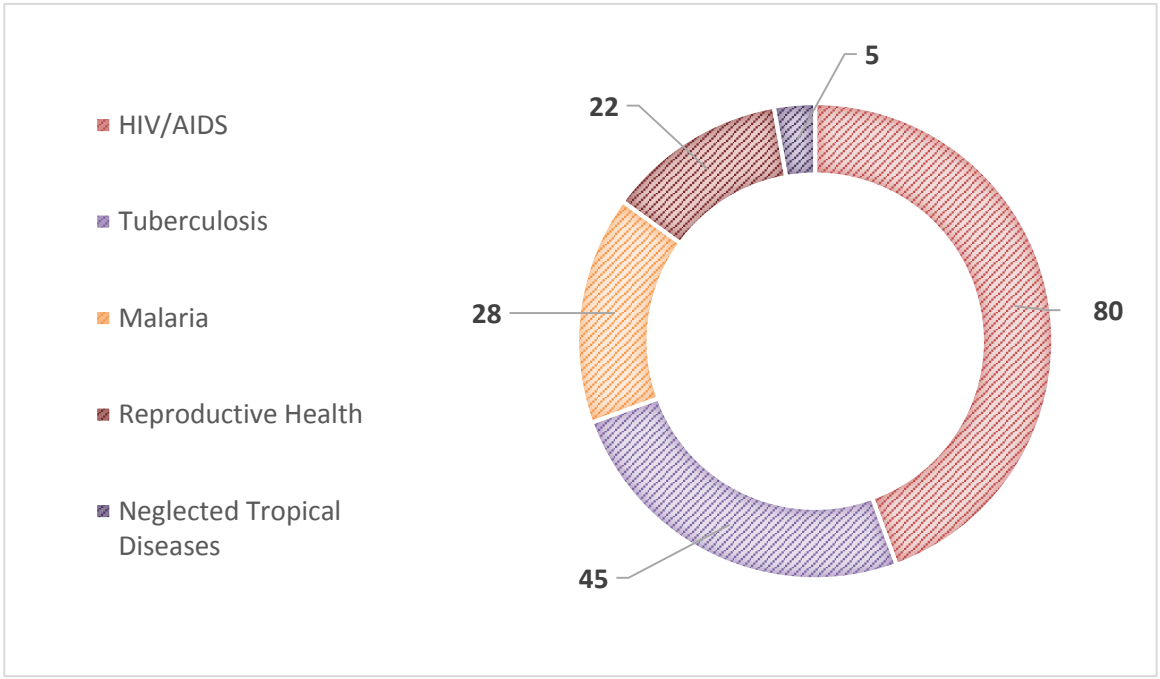


It is important to noticed that the procedure was, first, designed for new registration applications but during the pilot phase it happened that the applicant, who had an application pending in a NMRA, wanted to switch for the Accelerated registration of Prequalified FPPs procedure (37). In that case the Accelerated registration of Prequalified FPPs procedure enabled to save time for all parties (37).

In the **Figure 1-8**, we can see that 80 out of the 180 registrations are for products aimed to treat HIV/AIDS (39). The other therapeutic areas are tuberculosis, malaria, reproduction health and neglected tropical diseases (39), these are the same for the WHO PQP as this collaborative procedure is only allowed for prequalified products which is focused on a priority disease. These are very good numbers to treat those priority diseases. However, it can also be seen as a negative point for this collaborative procedure as it is only restricted to those therapeutic areas; therefore, diseases such as hypertension, diabetes, cancer are not eligible

to this procedure. Thus, we might see those diseases be in the scope of both, the WHO PQP and the collaborative procedure.

Figure 1-8 **Therapeutic categories of medicines registered via the Accelerated registration of Prequalified FPPs procedure (n = 180) (39)**



Another interesting outcome of the Accelerated registration of Prequalified FPPs procedure is that it enables the NMRAs to build regulatory capacity as well as saving regulatory resources (35,37). Indeed, through the sharing of the WHO assessments and inspections report of the prequalified-product the regulators and inspectors of the NMRAs have the opportunity to understand the regulatory basis of the decision made by the WHO/PQT. Thus, it is bringing knowledge to enable the NMRAs to build regulatory capacities and experiences. However, if the NMRA choose to directly adopt the decision of the WHO/PQT without verification, the NMRA will not acquire knowledge or experience. At least, the NMRA have the choice and are responsible at the end of approving the product on the market. Finally, the WHO organizes training as well as workshops regularly (41). All of these measures promote capacity building at the NMRAs level.

During the post-registration phase, the different parties are invited to work together in order to minimize the differences between the nationally registered and the WHO-prequalified product (35). This post-registration phase is based on the WHO guidelines on variations to a prequalified product (25). Thus, in order to keep fewer differences between the nationally registered and the WHO-prequalified product, variations have to be submitted simultaneously to the WHO/PQT and NMRAs where the product is registered via this collaborative procedure (37). This will save resources at local NMRAs through the sharing of the variation assessment reports and post-prequalification inspection reports from WHO/PQT with the relevant participating authorities (37). However, it is not mandatory for the NMRAs to adopt the decision made by the WHO/PQT ; in that case, NMRAs will have to explain the reasons why they are not following the decision made by the WHO/PQT (37). This will lead to the fact that the prequalified product and the national product won't be identical anymore. In that case, the medicine will be removed from the list of the products registered via the WHO Collaborative Registration procedure as its post-registration phase won't follow the one of the prequalified product anymore (37). However, the status of the national marketing authorization will still remain but the NMRA will become the only organization responsible for all post-approval changes of the product.

The Accelerated registration of Prequalified FPPs procedure is going one step further compare to the WHO PQ as it enables to have a registration at the country level. However, as we said before, only the products that are prequalified via the generic route can be part of this procedure, therefore, it would be interesting to have a procedure which enables the products that are prequalified by a SRA to be able to benefit for a procedure like this collaborative procedure. Furthermore, it could be also interesting to have a procedure for non-prequalified products assessed by a SRA.

Therefore, in this context, the WHO is currently having a pilot phase of the Accelerated registration of prequalified FPPs *(full name is the Collaborative Procedure in the Assessment and Accelerated National Registration of Pharmaceutical Products Approved by Stringent Regulatory Authorities)* (42) to which we will give an overview in the next part.

1.3 The Accelerated registration of Finished Pharmaceutical Products approved by Stringent Regulatory Authorities procedure

The WHO cannot assess and prequalified all essential and needed medicines, however, those medicines might have been already assessed and authorized by a globally recognized regulatory body (EMA, FDA or another SRA), thus, the WHO is currently piloting a complementary procedure named the Accelerated registration of prequalified FPPs *(full name is the Collaborative Procedure in the Assessment and Accelerated National Registration of Pharmaceutical Products Approved by Stringent Regulatory Authorities)* since 2015 (9).

The purpose of this procedure is to benefit the assessment already made by a SRA by sharing the outcome of the SRA assessments and inspections with the NMRA in order to reduce the delay in the access of medicines in the LMICs countries due to limited regulatory resources. The data that documents the decision made by the SRA will be provided to facilitate and get a faster registration by the NMRAs.

The procedure is open to any interested NMRA and pharmaceutical company and can be applied to any SRA-approved medicine for public health needs. Both innovative and generic medicinal products are eligible whether they are prequalified or not (42).

The objectives of this pilot phase are to test the procedure as well as develop the collaboration between the countries, the health authorities and the pharmaceutical companies in order to facilitate the registration of medicines in those LMICs countries (9).

The procedure is similar to the Accelerated registration of prequalified FPPs procedure regarding the information sharing, management of confidentiality and timeframe (42). While in the Accelerated registration of prequalified FPPs procedure it was the WHO prequalification team that was assessing the dossier, here it is the SRAs that are providing the regulatory expertise (42).

As we saw in this first part, the WHO PQP has taken the first step to bring high quality medicines to the patient in LMICs countries by elaborating diverse procedures and is still continuing to find solutions to bring more medicines to the patients that are in need of them.

It is now interesting to see what the European Medicines Agency has established to address the disease burden in developing countries, indeed, 12 years ago, the EMA created the Article 58 of the Regulation (EC) No 726/2004 which enables the CHMP to give scientific opinions for medicinal products intended exclusively for markets outside of the European Union (EU) and this, in collaboration with the WHO and regulators from NMRAs (10). This procedure is aimed to market products outside of the EU market only, by having first an opinion by the CHMP which can be used by the manufacturers in order to get an approval by the countries they wish to use their medicines in.

We will now give more details on this procedure in the next part.

Part Two

The Article 58 of the Regulation (EC) No 726/2004

Résumé de la partie 2: L'article 58 de la Réglementation CE No 726/2004

L'Agence Européenne du Médicament (EMA) a été fondée en 1995 et est chargée de coordonner les ressources scientifiques existantes mises à sa disposition par les États membres pour l'évaluation, la surveillance et la pharmacovigilance des médicaments.

L'EMA compte sept comités à son actif. L'un d'entre eux est le comité des médicaments à usage humain (CHMP), chargé notamment de la préparation des avis de l'Agence sur les questions relatives aux médicaments à usage humain. Le CHMP joue un rôle essentiel dans la procédure de commercialisation des médicaments dans l'Union européenne en évaluant les dossiers des médicaments sur des critères purement scientifiques.

En plus de ce rôle majeur, le CHMP intervient notamment dans l'évaluation des demandes d'application d'article 58 du règlement européen (CE) n° 726/2004 pour les médicaments à usage humain destinés exclusivement aux marchés situés en dehors de l'Union européenne. Cet article permet au CHMP de préparer, en collaboration avec l'OMS, des opinions scientifiques sur les médicaments destinés exclusivement aux marchés extérieurs à l'Union Européenne.

Les médicaments éligibles au titre de l'Article 58 doivent être destinés à prévenir ou à traiter les maladies présentant un enjeu majeur pour la santé publique dans les pays tiers (SIDA, tuberculose, paludisme etc.)

Bien que suivant le même schéma qu'une évaluation en procédure centralisée et donc d'une grande qualité, cette procédure présente de nombreuses limites qui lui coûte une sous-utilisation par les entreprises. Une de ces limites consiste en le fait que cette procédure ne se finalise pas par une autorisation de mise sur le marché mais par une opinion scientifique sur laquelle les Autorités Nationales de Réglementation des Médicaments (NMRA) pourront se référer lors de leur propre évaluation. En outre, le fait que cette opinion ne se traduit pas par un enregistrement plus rapide au niveau des pays en développement ainsi qu'un manque de clarté sur les bénéfices octroyés aux demandeurs lors de son utilisation freine considérablement son utilisation.

Dès lors, cette procédure est utilisée de façon secondaire comparé à d'autres procédures offrant plus d'avantages et donc plus attractives pour le demandeur.

Cependant, après dix ans de mise en place, une révision de cette procédure a été effectuée afin de mettre en évidence les principaux obstacles à l'utilisation de cette procédure. Suite à cela, des améliorations sont proposées pour permettre de redonner un nouvel élan à cet Article 58, notamment très apprécié d'un point de vue qualité d'évaluation du dossier, par les demandeurs ayant participés à cette procédure.

2 The Article 58 of the Regulation (EC) No 726/2004

2.1.1 The European Medicines Agency

The European Medicines Agency was founded on the 1st of January 1995 and is currently located in London (43). The EMA is responsible for coordinating the existing scientific resources put at its disposal by the Member States for the evaluation, supervision and pharmacovigilance of medicinal products.

This European Regulatory Authority has seven committees, supported by Working parties and other groups, that are carrying out its scientific assessment (44). Among others, there is the Committee for Medicinal Products for Human Use (CHMP) that is responsible for preparing the Agency's opinions on questions regarding medicines for human use, in accordance with Regulation (EC) No 726/2004 (10,45).

The CHMP is composed of different members (45):

- a chair, elected by serving CHMP members;

- one member and an alternate nominated by each of the 28 Member States;

- one member and an alternate nominated by Iceland and by Norway;

- up to five co-opted members, chosen among experts nominated by member States or the Agency and recruited, when necessary, to provide additional expertise in a particular scientific area.

The CHMP plays a vital role in the marketing procedure for medicines in the European Union by assessing on purely scientific criteria, whether or not the medicines concerned meet the necessary quality, safety and efficacy requirements (in accordance with EU legislation, particularly Directive 2001/83/EC) (46,47).

In addition to this major role, the CHMP is particularly involved in the assessment of Article 58 applications of Regulation (EC) No 726/2004 for medicinal products for human use that are intended exclusively for markets outside of the European Union (48).

2.1.2 Legal Basis and Scope

"Article 58

1. The Agency may give a scientific opinion, in the context of cooperation with the World Health Organisation, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. 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 Organisation, 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."(10)

In 2004, the European Parliament enacted Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (10).

Article 58 of this Regulation enables the EMA's Committee for Medicinal Products for Human Use (CHMP), in collaboration with the WHO, to give scientific opinions for medicinal products intended exclusively for markets outside the European Union (EU)(10). However, the application for this procedure does not exclude a future application for a MA in the Community (49).

Medicines eligible for Article 58 process must be intended to prevent or treat diseases of major public health interest in third countries (48,50). This includes, among others, medicines for WHO target diseases such as HIV/AIDS, malaria, tuberculosis and other neglected diseases (48,50). Medicines eligible for this procedure also include vaccines aimed to be used in the WHO Expanded Programme on Immunization or for protection against a public health priority disease (48,50).

Furthermore, Article 58(2) offers the possibility, for applicants, to ask for scientific advice on medicines intended to be marketed exclusively outside the Community (10,51). The purpose is to provide to applicants advice regarding different aspects, such as the clinical trial design, that may influence the development of the product. Those scientific advisories can be provided during the whole development process of the product (50,51).

The aim of Article 58 is to help increase access to medicines by LMIC and improve public health (48).

In addition, it is important to notice that the Applicant, or its contact point, must be based in the European Economic Area (EEA) i.e. a Member State of the European Union, Norway, Iceland or Liechtenstein (51). Evidence to support this must be provided for the request of an eligibility and for the submission of the application (49,51).

2.1.3 Process for submission of the application for a CHMP scientific opinion

a. Eligibility

The eligibility of a product for evaluation under Article 58 is assessed on a case-by-case basis by the EMA, in consultation with the WHO (51). Once accepted, the applications are subject to a stringent scientific assessment during a "standard EMA Centralized Procedure" (48,50).

b. Submission

Applicants should notify the EMA of their intention to submit an application for a CHMP scientific opinion at least six months prior to the submission by sending a letter of intention to EMA (49).

Then, an EMA Product Team Leader will be officially appointed as well as rapporteur/co-rapporteur that are named at the CHMP meeting following the receipt of the letter of intention to submit (49). Following their appointment, the rapporteur/co-rapporteur are informing the CHMP of the names of the experts they have chosen for the evaluation of the application.

Under Article 58 procedure, full complete, full/mixed, well-established use, new fixed combination, informed consent, generic, hybrid and similar biologicals applications can be submitted (51).

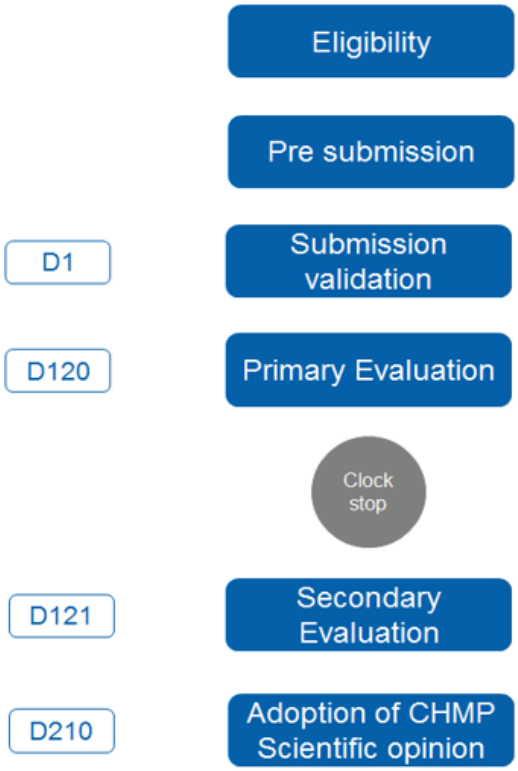
c. Assessment

As soon as the application has been validated and the rapporteur/co-rapporteur have confirmed that they have received the dossier, the procedure can start (51). The CHMP has 210 days to issue a scientific opinion, including a clock stop at day 120 if questions to applicant have been raised (51).

During the assessment, the WHO, as needed, can provide experts or appoint representatives from NMRA who may be invited to participate in plenary sessions as well as inspections of the manufacturing facilities (49).

The **Figure 2-1** below gives an overview of the procedure's timelines.

Figure 2-1 Simplified timetable of Article 58 Assessment (49).



However, even if the assessment follows the same steps and timelines as the assessment of a Marketing Authorization Application under the centralized procedure, medicines reviewed under Article 58 do not receive an approval from the European Commission (50,51).

Instead, the CHMP, after consultation with the WHO, adopts a scientific opinion and establishes an assessment report which includes the conclusions on the Quality, Safety and Efficacy of the medicinal product and which also defines the benefit/risk balance of the product based on the situation in developing countries where the product is aimed to be used (48–50). This assessment report, named European Public Assessment Report (EPAR), is published on the website of the Agency.

After the assessment, and in case of a positive opinion, the company has two options to register its product on the market, indeed the company can either go through the WHO PQP

in order to obtain the prequalification status and then submit a marketing authorization application to NMRAs or to apply directly to NMRAs (52).

2.1.4 Outcomes of Article 58

First of all, Article 58 is a procedure that is opened for both innovative drugs as well as established drugs (generics, new formulations of existing FPPs and new fixed dose combinations of existing APIs) (52); however the interest is not the same for those both types of medicines.

Article 58 of the Regulation (EC) No 726/2004 is aimed for targeting LMICs countries only; indeed a company that wants to target both LMIC and HIC at the same time cannot use this procedure to reach its goal as Article 58 is intended exclusively for markets outside the Community. However, an exception exists: if a company wants to target both LMICs and HICs countries, but not at the same time, it will be able to use this procedure to target LMICs countries first, and later on, register its product in HIC countries (most of the case Europe) via one of the numerous procedures described in the different legislation (52).

Moreover, there are reasons why the companies targeting both HICs and LMICs countries are not willing to use Article 58 which are coming from Article 58 on its own. Indeed, as Article 58 is not granting an approval there is no special interest to use it and the companies will prefer to go through other EMA or FDA pathways to register their products in HIC countries. Moreover, those products might qualify for an orphan designation and, therefore, receiving additional benefits such as fees reductions, market exclusivity. For generic companies it is even less interested to use Article 58 as they don't need the specialized expertise of the CHMP, hence they will choose to go directly via the WHO PQP or to a NMRAs using their home country CPP and MA.

The **Table 2-1** described the different reasons for innovative or established medicines to use Article 58 to target the LMICs countries only.

Table 2-1 **Main reasons for innovative and established medicines in the use of Article 58 to target LMIC market (52).**

	Reasons for targeting LMIC market
Innovative drugs	• The drug do not qualify for the FDA Tropical Disease Priority Review Vouchers (FDA TD PRV)[2] • The drug has not the same perspective (regarding the benefit-risk of the drug) according to the difference in the prevalence and epidemiology of a disease between LMICs and HICs countries • The drug, without any MA in any European country, is manufactured by an EU manufacturer and need a CPP prior to LMIC registration *(pre-requirement for EU-based manufacturer to register their product in LMIC countries)*
Established drugs	• A manufacturer that wants to develop a chemically and clinically identical product but with a physical distinction to fight re-importation risks

As we can see in the **Table 2-1**, the main reasons for using Article 58 are more secondary reasons, indeed, for example one of the reasons is when the company cannot use the FDA TD PRV because the drug does not qualify for this system. Another reason, which can be seen as a regulatory strategy, is to use the fact that the sunset clause is not applicable to Article 58.

[2] System allowing the FDA to award priority review vouchers to sponsors of a human drug application for a tropical disease drug product that can be used to obtain a priority review for another drug application (53)

The sunset clause is defined by the EMA as "a provision leading to the cessation of the validity of the marketing authorization if:

- the medicinal product is not placed on the market within three years of the authorization being granted or,
- where a medicinal product previously placed on the market is no longer actually present on the market for three consecutive years."

Moreover, exemptions on public health grounds and in exceptional circumstances (if duly justified) might be granted for the sunset clause by the European Commission.

In our case, as Article 58 is made for products intended exclusively for markets outside the Community, the exemption, mentioned above, is considered applicable. Therefore, some EU-manufacturers of products targeting LMICs countries are using Article 58 to obtain a CPP that would not end due to the sunset clause.

Roughly speaking, nowadays, the manufacturers only use Article 58 if the other pathways are not applicable. This can be seen through the few products that have received a positive opinion for this procedure: 9 (54). Furthermore, 2 out of the 9 products have been withdrawn from the manufacturer for commercial reasons (55,56).

For those 9 products it is important to study what happened to them in the post-opinion phase regarding the registration. The report assessing the first 10 years after the implementation of Article 58 says that "These *seven*[3] products have experienced mixed commercial success in the LMICs post-opinion (57). While over 60% of these products have been hampered by poor NMRA recognition of Article 58 opinions, most of the products with positive opinion from Article 58 have suffered from poor commercial viability, unrelated to the regulatory pathway."

[3] The 8'th product, Mosquirix and the 9'th Umbipro, received scientific opinion after the review of the report

In addition to this, the products that have received a positive opinion have faced limited registration success in LMICs (52), indeed, the consecutive approvals have differed greatly between the different products due to the regulatory requirements as well as the previous versions of the drugs already on the market. Thus, Article 58 has not been transferred into faster LMIC registration. The **Table 2-2** below, extracted from the strategic vision for the EMA Article 58 process, describes the reasons for each product to have used Article 58 as well as the status regarding any approval obtained after the positive opinion (52).

Table 2-2 Overview of the products that went under Article 58 procedure (52)

Medicinal product	Reasons for using Article 58	Post-opinion status
Lamivudine ViiV, Lamivudine/ Zidovudine ViiV (ViiV)	• Having LMIC-only versions of EMA approved drugs to fight the re-importation	• Positive opinion in 2005 • Most LMICs approved the drugs without additional review
Aluvia (Abbvie)	• Having LMIC-only versions of EMA approved drugs to fight the re-importation	• Positive opinion in 2006 • Approved in many important LMICs after the positive opinion
Pyramax (Shin Poong)	• Having an automatic Prequalification of the drug	• Positive opinion in February 2012, listed on May 2012 on the WHO PQL
Hemoprostol (Linepharma)	• Given the current standard of care, Linepharma was unable to market the drug in EU since the oral medication is not appropriate for EU context (IV oxytocin). However, using the benefit-risk assessment to support marketing of the product in LMICs due to the limitation of LMIC healthcare setting (syringes, refrigeration)	• Struggled with Article 58 awareness with LMIC regulators • Not launched in any LMIC
Hexaxim (Sanofi)	• Gain a CPP that would not end due to the sunset clause	• Approved in South Africa after Article 58 positive opinion Centralized Procedure approval in 2013

Tritanrix HB (GSK)	•Gain a CPP that would not end due to the sunset clause	•LMIC approval before Article 58 positive opinion as Article 58 was sought to maintain the CPP in EU to allow further selling in LMICs

In addition to this, regarding the benefits in terms of prequalification, the contribution of the WHO does not guarantee an automatic inclusion of the drug in the list of prequalified medicinal products, indeed the time between the opinion and the prequalification can vary considerably between different products. For example, Pyramax was prequalified only 3 months after receiving its positive opinion from WHO, however it took 2 years for Hexaxim to receive its (1,52). Furthermore, the drugs that have received a positive opinion are not part of the Accelerated Registration of Prequalified FPPs procedure (52,58).

One of the main causes for the lack of usage of Article 58 is due to the lack of incentives being offered towards the manufacturers, notably, it does not set up clearly the fee waivers/reductions that the manufacturers could benefit (1,52). Indeed, in its Q&A the EMA informs that "in exceptional cases and when an opinion is required for imperative reasons of public health, total or partial fee exemptions may be granted by the EMEA's Executive Director on the recommendation of the CHMP. Fee waivers or fee reductions are granted after consultation of the CHMP". Therefore, the manufacturers venture into a procedure with no clear criteria regarding the fee waivers they could benefit from, and this is obviously linked to the underuse of Article 58 by the companies. Moreover, the fees for an application under Article 58 are the same as the ones for an application under the centralized procedure (51). This is explained by the EMA by the fact that the same resources are needed for both Article 58 and CHMP; only the eligibility request is free (51). For information, the basic fee of an application for a single strength associated with one pharmaceutical form and one presentation is 278.800 EURO (59).

Moreover, even if a company asks for scientific advice, it will have to pay the same fee as for an application for scientific advice for a product evaluated under the centralized procedure (51). On top of this, even the fee for an inspection is applicable from 18.900EURO for each distinct inspection of an individual site (51). Additional fees could be added to the 18.900EURO if activities on the site need a specific inspection; or for each contract in a manufacturing site or testing laboratory that requires an inspection linked to an application and also if the

inspection has to be done outside the Community (the applicant will have to pay the travel and accommodation expenses for the inspectors) (51).

At the end, all of these costs increase the final invoice and this can be seen expensive as it is the same assessment as a centralized procedure but without any MA granted in Europe at the end. This is linked to another point, which is why no EU MA is granted with this procedure. This can be misinterpreted, especially from the point of view of the African countries that can basically ask themselves: why a product that has been assessed by the EMA/CHMP is not ending in a MA in the European Union? Why is the product not marketed within the EU but can be marketed within the African Countries?

This can be shown by the example of Hemoprostol. The company Linepharma was not able to market the product in EU due to the standard practice existing in EU: "the oral medication is not appropriate for EU context"(52). However, regarding the limits of LMICs healthcare facilities (e.g. syringes, refrigeration) the benefit-risk assessment of the drug is supporting a registration in LMICs countries (52). This example shows that the benefit-risk assessment can lead to different outcomes between the countries, when the different standard practice are taken into account.

In addition to this, Article 58 is not linked to the Orphan Drug and the incentives that come with it: protocol assistance, a type of scientific advice specific for designated orphan medicines, and market exclusivity once the medicine is on the market (1,52,60).

To summarize, five barriers have limited the use and the full exploitation of Article 58 (52,57):

- The fact that Article 58 has not been transferred into a faster LMIC registration is an important barrier as the medicines cannot be used to treat the patient before being approved by the NMRAs.
- The high costs and the lack of transparency regarding the possible waivers/reductions of the fees that the manufacturer could benefit

- The uncertainty for the manufacturers regarding the benefits of Article 58 notably on the post-opinion phase for the registration of the product by the NMRAs and the lack of successful precedents that is strongly restricted the use of Article 58 by the companies.

The two following points show that the manufacturers are sometimes reticent in the use of this procedure due to some unawareness as well as uncertainty of the benefits.

- The unawareness of the NMRAs regarding Article 58 and the possible feeling of a lower grade assessment as it does not give an EU MA is also one barrier that needs to be addressed.

- The poor coordination between the WHO and the EMA in the process, notably in term of logistic and the lack of integration of the drug into the collaborative registration procedure developed by the WHO.

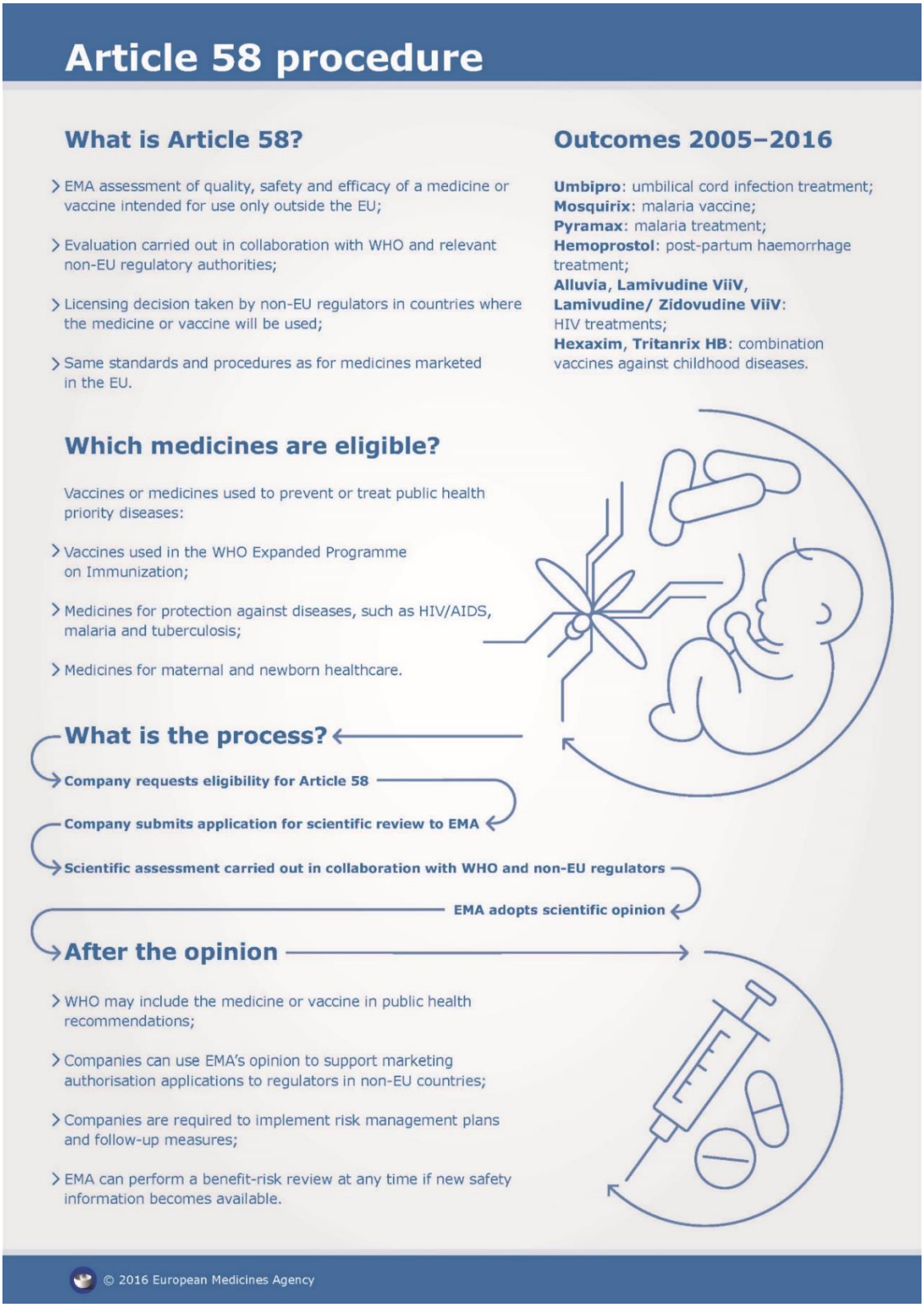
Those 5 core barriers need to be addressed and a new vision of Article 58 wants to be given by the EMA. In this way, some recommendations from the study made by the EMA, the European Commission and the Bill & Melinda Gates Foundation have arisen.

To address the five core barriers, five improvements will be made to Article 58. First, it is important to remind the applicant about the aim, the benefits and the use of Article 58. We will then explain the possible incentives that could be created for Article 58 as well as how we could ensure a faster WHO Prequalification of Article 58-relevant products and access to the Collaborative Procedures for Accelerated Registration. Then, we will focus on the increase of LMIC country review through capacity building and end with the creation of partnerships with core stakeholders (52,57).

- **Clearly communicate the aim, use and benefits of the Article 58**

It is important to explain what is feasible with Article 58 and what is not. This can be done via new communication materials and communication plan. As we can see on the **Figure 2-2** below, the EMA has started to implement this by creating an infographic on Article 58 procedure as well as its purpose.

Figure 2-2 EMA communication on Article 58 procedure (61)



It will also be important to clearly express the current incentives and fee waivers/reductions as well as remind to the manufacturers that the use of Article 58 does not exclude the use of the Centralized Procedure at a later stage. This last point can be presented through the example of Hexaxim (Sanofi) that have initially targeted LMICs countries and that have received an approval from the EMA through the centralized procedure one year after having received a positive opinion for Article 58.

In addition to this, Article 58 review process needs to be enhanced by defining clear procedures for the review of variations, renewals, label updates. Currently, the EMA has no clear view to know if the products that received a positive opinion are subsequently approved nationally and is not involved in any post-approval communication with NMRA. Therefore, the idea would be to give to manufacturers, new requirements on post-opinion country approval that need to be reported to the EMA, including variations, renewals, label updates (52,57).

It is also important to communicate on the scientific advice which is of "high quality, pragmatic and valuable in shaping clinical development plans" according to the manufacturers (52,57).

Moreover, the NMRAs that have been involved as experts/observers have acquired knowledge and found the process to be valuable for them (52,57).

- **Create further incentives**

It is apparent that the current incentives are not enough for the manufacturers to use Article 58, thus, more incentives need to be created in order to attract companies.

The main point concerns the fees, indeed, as said earlier the costs of the procedure are very expensive, and it might be interested to have reductions of the cost of the procedure or at least to have an EU MA granted at the same time. This is something that the EMA could consider for the future. Moreover, having a combined pathway for Article 58 and Centralized Procedure might increase the interest of the manufacturers because most of them want to get an EU MA even if the main market is in the LMICs countries. The idea that came up from

the study made by the EMA, the European Commission and the Bill & Melinda Gates Foundation would be to either indicate during scientific advice if the manufacturer wants to target both LMIC and EU markets or having a combined pathway which could involve a single rapporteur team, LMIC disease experts, NMRA observers, the WHO PQT with a timeline of 210 days, as currently, and a single fee structure (52). However, it will be necessary to explore the feasibility of having two different benefit/risk analyses for an identical drug: one for EU market and the other for the LMIC market.

- **Ensure faster WHO Prequalification of Article 58 products and access to the Accelerated registration of prequalified FPPs procedure**

The creation of a working group, between the EMA and the WHO, which could meet every month in person in Geneva (WHO HQ) or London (EMA HQ) would be the starting point to improve collaboration between EMA and WHO and improve the coordination on variations, renewals, and label changes (52,57).

The main point would be to accelerate the Prequalification of medicines that received a positive opinion from the CHMP and why not starting this review during Article 58 process, as the WHO is already involved. In addition to this, granting the access to the Accelerated registration of prequalified FPPs procedure is also important for those products (52,57).

The nomination of a coordinator on WHO side to make the connection with the EMA during the procedure and would represent the unique contact point for Article 58, Prequalification Programme and NMRAs would further enhance the collaboration. This could be done by also creating a pool of NMRA contacts: experts and observers (52). This will build NMRA trust in Article 58 opinions.

- **Increase LMIC country review through capacity building**

With the involvement of NMRA contacts in the review process, the capacity building as well as the trust in Article 58 will be improved. Again, this could only be successful if the communication between the EMA and the WHO is efficient.

- **Creation of partnerships with core stakeholders**

As per the number of products that have received a positive opinion for Article 58 (i.e. 9) the global health environment seems to be unaware of this procedure or even worse that nobody thinks that there is any value in the procedure. Therefore, as it is the companies who can start the procedure, it is important to develop collaboration with core stakeholders such as Global Fund, UNITAID (52,57).

All of these changes can further improve the use of Article 58 by the companies. The study made by the EMA, the European Commission and the Bill & Melinda Gates Foundation has identified approximately 30 products, that are currently split between the phase 1, 2 and 3 of the clinical phases, to be good candidates for Article 58 (52).

As already mentioned, Article 58 is a procedure that has been underused since it has been launched, however, the assessment made by the CHMP are highly appreciated by the manufacturers. Article 58 procedure is an interesting process and the EMA is trying to communicate further on it. However, this procedure doesn't give an approval in Europe and this can be wrongly interpreted from the African countries.

Therefore, in the last part of this thesis, we will focus on a new pathway created by Swissmedic which is the Swissmedic procedure for Marketing Authorization for Global Health Products, also called MAGHP. This procedure is under its pilot phase and has an interesting benefit as it gives an approval by both, NMRAs and Swissmedic.

Part Three:

The Swissmedic Procedure for Marketing Authorisation for Global Health Products (MAGHP Procedure)

Résumé de la partie 3: La procédure d'autorisation de mise sur le marché de produits pharmaceutiques mondiaux de Swissmedic.

Swissmedic est l'Autorité de santé suisse qui s'occupe, entre autres, de l'autorisation et de la surveillance des produits pharmaceutiques.

Swissmedic est en collaboration avec des acteurs externes nationaux et internationaux. En janvier 2014, la Fondation Bill et Melinda Gates, le Département fédéral des affaires étrangères de la Suisse ainsi que le Département fédéral de l'intérieur ont signé un mémorandum de compréhension dont le but fondamental est d'accélérer et d'accroître l'accès à des médicaments de haute qualité en Afrique subsaharienne.

La procédure d'autorisation de mise sur le marché de produits pharmaceutiques mondiaux, nommée MAGHP est l'un des projets développés pour atteindre cet objectif.
Ce projet a pour but d'accélérer et d'améliorer l'accès aux médicaments de haute qualité dans les pays à faible revenu en mettant en place une procédure d'autorisation qui permettra l'implication des NMRAs de l'Afrique et de l'OMS.

Cette procédure présente un réel intérêt. En effet, la version de la Guideline utilisée pour la phase pilote est très précise et bien expliquée. Cependant il est encore tôt pour dire si elle sera vraiment efficace, car, à ce jour, elle est toujours en attente d'un premier candidat.

3 The Swissmedic Procedure for Marketing Authorization for Global Health Products (MAGHP Procedure)

3.1 Swissmedic

Swissmedic is the Swiss Agency who is taking care of the authorization and supervision of therapeutic products. It is a public institution of the Swiss government and is affiliated to the Federal Department of Home Affairs. The Agency was born from the merger of the Intercantonal Office for the Control of Medicines and the Therapeutic Products Section of the Swiss Federal Office of Public Health. The headquarters is based in Bern, Switzerland. The Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act – TPA) is the legal basis of Swissmedic, hence Swissmedic started to operate when the Federal Act on Medicinal Products and Medical Devices came into force, on 1st of January 2002. (61)

The competencies of Swissmedic include:

- "the authorization of medicinal products
- licences for manufacturing and wholesale, and inspections
- market monitoring of medicinal products and medical devices
- establishing standards
- clinical trials and laboratory testing regarding the quality of medicines
- information
- national and international co-operation." (61)

Swissmedic is also in collaboration with external national and international stakeholders and in January 2014, the Bill & Melinda Gates Foundation, the Swiss Federal Department of Foreign Affairs as well as the Federal Department of Home Affairs signed a Memorandum of Understanding (MoU) whose basic purpose is to accelerate and increase access to high quality essential medicines with a focus to sub-Saharan Africa / East African Community (62).

Two projects have been developed:

- Project Component I: Support the implementation of the African Medicines Regulatory Harmonization (AMRH) Programme

- Project Component II: Swissmedic procedure for scientific advice and for Marketing Authorization for Global Health Product (MAGHP)

In the rest of this thesis we are going to focus on the second project, called MAGHP.

The aim of this project is to accelerate and improve the access of high quality medicinal products in low-income countries, by granting, to representatives of regulatory authorities in resource-constrained countries and the WHO, a Swissmedic authorisation procedure and a procedure for scientific advice. Those procedures will allow the involvement of East African Community NMRAs and the WHO and are intended to apply, first, to medicinal products designated for the African market (62). In addition to this, if the drug could be added to the WHO Prequalification list of prequalified medicines, the WHO PQT will be involved as well (63). Within the MAGHP procedure, Swissmedic will have the role of the SRA.

The MAGHP procedure is currently under a two-year pilot phase but there is not candidate under the assessment of the procedure yet.

3.2 Process of the Procedure for Marketing Authorisation for Global Health Product

3.2.1 Prerequisite to the MAGHP procedure

First of all, any MAH or working-representative (regulatory office) based in Switzerland can apply for this procedure (63).

There are two conditions that need to be fulfilled in order to allow an applicant to be assessed under the MAGHP procedure (63):

- "The authorisation application must concern a medicinal product with a new active pharmaceutical ingredient (new API), a new indication for a medicinal product or for a known active pharmaceutical ingredient (known API)

And,

- The clinical and preclinical trials must be completed at the time of application submission. Any results from foreign assessments available to the applicant, particularly assessment reports from the European Medicines Agency (EMA) or the U.S. Food and Drug Administration (FDA), must be included with the submission"

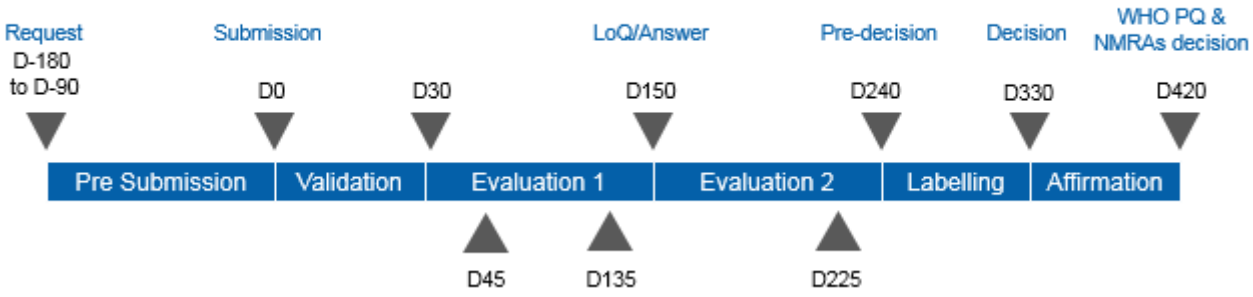
A "prior-notification" (request) needs to be sent by the applicant to Swissmedic six to three months prior the scheduled submission date (63). This will enable the planning of the different resources including the EAC NMRAs and the WHO PQT (63). Then Swissmedic has six weeks to validate or invalidate the use of the MAGHP procedure (63). Within those 6 weeks, the Swissmedic Networking will, notably, contact the NMRAs and the WHO PQT in order to know if they will either be participating actively to the procedure or being only observer (63).

3.2.2 Procedure of the MAGHP

The procedure of the MAGHP is built on the current regulatory authorisation process at Swissmedic (63).

The **Figure 3-1** gives an overview of the timelines and steps of the procedure.

Figure 3-1 Overview of the timelines and steps of the MAGHP (64)



The procedure consists of 12 phases from the submission to the decision of concerned NMRAs (63):

a. Submission of the application

Once the applicant is submitting its application, including a full documentation for quality, preclinical and clinical aspects, to Swissmedic, the procedure is starting at day 0.

b. Validation of the application

Swissmedic has 30 days to validate or invalidate the dossier and communicated the decision to the applicant:

- If the application is accepted, Swissmedic will inform the WHO PQT as well as the concerned NMRAs and communicate the timelines of the assessment with them.

- If the application is not accepted due to the fact that the formal requirements are not fulfilled, Swissmedic will inform the applicant about the gaps in the documentation. The

concerned NMRAs and the WHO PQT will be informed as well. The applicant has then 120 days to rectify its dossier and complete the gaps; after this deadline, the dossier will be rejected by Swissmedic. However, if the applicant submit its updated dossier within the timeline but some deficiencies still remain, it will be allowed to 120 days more to rectify the dossier.

c. Assessment Phase 1

If the dossier is accepted, the product will enter into the first assessment phase which will last 120 days (from day 30 to day 150).

During this phase, the dossier will be assessed, first, by Swissmedic reviewers who will prepare a preliminary assessment report that they will share with the concerned NMRAs and the WHO PQT within 63 days (9 weeks) after the start of the assessment and at day 125 the latest. They will also prepare a list of questions for day 135. The concerned NMRAs and the WHO PQT are also invited to send their comments and feedbacks to the list of question by day 135.

During the 120 days of the assessment phase, the reviewers will have 2 meetings named “case team meeting” mostly at day 45 and around day 135 to, in the first case, discuss coordination and potential challenges in the review of the dossier, and in the second case, to consolidate the list of question. The concerned NMRAs and the WHO PQT will have the opportunity to attend those case team meetings to provide their comments/feedback.

d. Submission of the List of Questions

At day 150 the List of Questions (LoQ) is submitted to the applicant who will have 90 days to respond to those questions. The time to answer to the question can be extended to 90 days more.

Those 90 days, (or 180 days), are in a clock stop phase, meaning that once the applicant will answer, the procedure will restart at day 151.

Moreover, after receiving the LoQ, the applicant has to communicate its response planned date.

e. Submission of the answers to the LoQ

During the clock stop the applicant will send its answer to the LoQ and the reviewers from Swissmedic will check the completion of the formal requirements:

- If everything is correct from a quality point of view, the second phase of the assessment will take place

- If the quality of the documents is not acceptable, the applicant will be asked to change its answer within 30 days

It is important to notice that if the applicant submits additional information that were not required by the LoQ, Swissmedic might proceed to a second assessment phase 1 which will follow the same process and timeline as the first assessment phase 1, thus 120 days.

f. Assessment phase 2

At the beginning of the second phase of the assessment, which also lasted 120 days, the answers to the LoQ provided by the applicant will be reviewed by Swissmedic and will result in a preliminary decision and if required a second LoQ will be prepared.

An assessment report will be prepared by Swissmedic and will be shared with the concerned NMRAs within 63 days (9 weeks) after the start of the assessment and at day 215 the latest. The concerned NMRAs will have 10 days to send their comments and feedback on the preliminary decision. At day 225 will take place the third case team meeting in which the concerned NMRAs and the WHO PQT can attend those case team meetings to provide their comments/feedback.

At this stage the SmPC, PIL and packaging will also be reviewed by Swissmedic.

g. Submission of the Preliminary Decision

The preliminary decision will be shared by Swissmedic to the applicant together with any conditions that would need to be considered by the applicant for the final decision. The correction on the SmPC, PIL and packaging will also be shared with the applicant.

h. Submissions of the answers to Preliminary Decision

A clock stop of 90 days will give time to the applicant to answer to the preliminary decision.

i. Labelling Phase

From day 241 to day 330, the labelling phase will start, meaning that the SmPC, PIL and packaging will be completed:

- If the applicant agrees with Swissmedic on the changes made by the Swiss Health Authority, the final decision will be issued.

- if the applicant disagrees with Swissmedic, a period of 90 days will be given to the applicant, to work on the labelling documents, followed by another period of 90 days for the review by Swissmedic.

j. Decision

At day 330, the final decision is submitted to the applicant and is sent to NMRAs as well as WHO PQT. In the case of a positive opinion, a MA will be granted by Swissmedic for Switzerland.

k. Sample testing

A sample testing phase is then handled by Swissmedic in accordance with the instructions that apply to the authorisation procedure.

l. WHO PQT and concerned NMRAs decision

Regarding the approval at the country level (LMICs), the concerned NMRAs will be given 90 days, after the positive opinion granted by Swissmedic, to confirm their decisions on allowing the product in their countries. The SmPC will be adjusted according to the requirements by the concerned NMRAs. If the NMRA is giving a positive decision, a MA will be granted by the NMRA within 3 months. This step is named the affirmation phase.

Furthermore, the product will be listed on the list of prequalified medicines within 90 days after the positive opinion granted by Swissmedic if the product fall in the scope of the WHO PQ.

3.2.3 Outcome of the procedure

As the procedure is still under the pilot phase, it is difficult to visualize a perfect picture of this procedure, however, we can still offer some general outcomes on the MAGHP.

First of all, the MAGHP differs from the previous procedures described before in this thesis by the fact that it is ending by an approval at the SRA level (Swissmedic) and this is an important outcome on which the LMICs countries will refer to.

Another positive outcome lies is the fact that the procedure is well described with precise timelines and a lot of review steps. This is simultaneously a positive and a negative outcome: the positive side of this is that all of the steps are well described and the process is really easy to follow. Every organization (Swissmedic, Applicant, concerned NMRAs, WHO/PQT) knows exactly what they have to do and for when their input is needed. However, the timelines are not well-distributed to the different parties:

- On the one hand, the concerned NMRAs and the WHO/PQT might face stretched timelines; indeed, during the two assessment phases the assessment report could be shared at the latest 10 days before either the finalization of the list of question, or the finalization of the preliminary decision. And as we saw previously that some NMRAs are facing lack of resources, the NMRAs might have not the time to provide their comments.

- On the other hand, Swissmedic is making sure that the applicant has a perfect dossier during a “preloading” phase, indeed, the validation of the application can last 270 days maximum (30 + 120 + 120), if the applicant needs to rectify the dossier (which can happened twice). This represents approximately 9 months for the validation of the application only.

In addition to this, the clock stop when the applicant needs to prepare the answer to the questions can be extended to 180 days upon request of the applicant, which is the double of what the procedure allows first. Furthermore, during the submission of the answers to the LoQ, it is important from the manufacturers side to be careful with the documents that they are sending as it can lead to a longer process of 120 days more (63).

Finally, we can observe that this procedure is highly driven by Swissmedic, we can see that from the timeline according to the concerned NMRAs, WHO/PQT but also in the fact that it is not mandatory for the NMRAs or the WHO/PQT to participate actively in the procedure; indeed, they can participate as observer. In that case they will not provide any feedback or comments but they will still be able to decide on either adding the product on the list of prequalified medicines for WHO or authorized the product in the country for the NMRA (63). Another point is that at any time during the procedure, the applicant can switch to the standard process of Swissmedic without the involvement of the concerned NMRAs and WHO/PQT (63).

In my opinion this procedure has a lot of potential, however, there is no candidate under this assessment yet.

Conclusion

The regulatory environment in Africa is challenging and the patients might not have access to the medicines they need. The three procedures described in this thesis are trying to address the situations faced in the sub-Saharan African countries.

The WHO has started the initiative of the Prequalification of Medicines Programme in 2001, which has raised the standard to make priority medicines of quality available to the benefit of those in need. It has been shown that this initiative has a major impact on the availability of safe, efficient and affordable medicines to developing countries. The inclusion of the medicines in the prequalified medicines list has become over the years a prerequisite for the UN agencies in the purchase of safe and high-quality medicines.

However, with the WHO PQP, the WHO is not granting an approval, as performed by the Health Authorities. Therefore, Collaborative Procedures for Accelerated Registration have been developed, the Accelerated Registration of Prequalified Finished Pharmaceutical Products procedure in 2012, and the Accelerated Registration of Finished Pharmaceutical Products Approved by Stringent Regulatory Authorities procedure in 2015. Each of these two new procedures has broadened the scope of the products that can entered in the Collaborative Procedures for Accelerated Registration; indeed, at the beginning only the prequalified medicines could have benefited to this pathway but now also the products that are already approved by a SRA can be part of it.

There is a growing acceptance of the Accelerated Registration of Prequalified Finished Pharmaceutical Products procedure as it is improving the registration of medicines in those countries but are also helping the countries to further develop themselves and acquire knowledge in the field of regulatory affairs. It will also be interesting to look at the results of the pilot phase of the Accelerated Registration of Finished Pharmaceutical Products Approved by Stringent Regulatory Authorities procedure once the pilot phase has ended.

The EMA has established Article 58 of the Regulation (EC) No 726/2004 to also improve the situation in the sub-Saharan African countries by allowing the CHMP to give a scientific opinion on a medicinal product intended exclusively for markets outside of the European Union. This procedure, following the same timelines as the assessment of a submission under the centralised procedure, is recognized by the manufacturers as being of good quality and is highly appreciated by them. However, the lack of incentives as well as the high cost and the limitation in terms of registration success in the countries are limiting its attractiveness. An assessment of the first ten years in the use of the Article 58 has been performed and data has been analyzed in order to give a new vision on this procedure. One major issue of the procedure is the lack of approval at the end of the procedure as the assessment made by the CHMP is an opinion. Then, the applicants still have to go through the registration phase at the country level.

It is this main issue that the MAGHP procedure of Swissmedic is trying to address. While it brings the different stakeholders working together, it is ending with an approval, in both, Switzerland and the NMRAs with also the prequalification status given by the WHO. However as it is still in the pilot phase and waiting for its first product, it is still difficult to visualize a picture of this procedure in the "real life".

All of those procedures show that, even if the situation is challenging, there are pathways to support the registration of medicines in sub-Saharan African countries. There is an increasingly successful construction of different procedures that try to enhance the access of medicines to the patients that are in needs of them; indeed, each procedure tries to address different concerns and improves this situation, for example, by enabling different products to be in scope; or giving to the NMRAs the possibility to be part of the assessment phase in order to strengthen regulatory knowledge at the local level.

Obviously, there are still some limits that need to be addressed, but the situation is much better than ten or fifteen years ago.
To quote the famous John Heywood, "Rome wasn't built in a day, but they were laying bricks every hour".

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For purposes of index and clarification, some information was researched via the WHO Prequalification Programme URL link http://apps.who.int/prequal/ but has since been deleted from viewing.
For existing information, the WHO has been introduced a new website where I also obtained research & information for my thesis the URL being https://extranet.who.int/prequal/.

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Université de Lille 2 DROIT ET SANTÉ

DEMANDE D'AUTORISATION DE SOUTENANCE

Nom et Prénom de l'étudiant : Lucas Dixon

Date, heure et lieu de soutenance :

Le |2|4| |0|3| |2|0|1|7| (jour / mois / année) à 18 h.. Amphithéâtre ou salle : Amphi Allais

Avis du conseiller (directeur) de thèse

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Motif de l'avis défavorable : .....

.....

.....

Date : 10/02/2017

Signature:

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Motif de l'avis défavorable : .....

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DIPLOME D'ETAT DE DOCTEUR EN PHARMACIE
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Nom : Dirson
Prénom : Lucas

Titre de la thèse : Axes de développement à l'enregistrement des médicaments dans les pays d'Afrique sub-saharienne

Mots-clés : Médicaments ; Programme de Préqualifcation de l'OMS (WHO PQP) ; Procédures Collaboratives de l'OMS ; Article 58 du Règlement CE No 726/2004 ; Autorisation de mise sur le marché des produits de santé mondiaux (MAGHP) ; Afrique ; Autorité Nationale de Réglementation des Médicaments (NMRA) ; Autorité Réglementaire Rigoureuse (SRA) ; Pays à faible revenu et à revenu intermédiaire

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Résumé :

En Afrique le rôle d'autorité de santé est exercé au niveau local par chaque Autorité Nationale de Réglementation des Médicaments (NMRA). Ces NMRAs veillent à ce que la population ait accès uniquement à des médicaments sûrs et efficaces en approuvant le médicament au niveau local. Cependant l'environnement réglementaire est difficile en raison du manque d'harmonisation entre les pays mais également en raison d'un manque d'expertise et de connaissances réglementaire au niveau des NMRAs. Par conséquent, certains médicaments peuvent être approuvés dans certains pays et pas dans d'autres et des patients dans le besoin peuvent se retrouver sans accès à certains médicaments.

Dans ce contexte, L'OMS a élaboré, en 2001, le Programme de Préqualification des Médicaments afin d'assurer la qualité des médicaments. Cette initiative a été poursuivie par la création de deux procédures collaboratives par l'OMS afin d'accélérer l'enregistrement des médicaments dans les pays en développement. En 2004, c'est l'Agence Européenne du Médicament qui a créé l'article 58 du Règlement (CE) No 726/2004 pour les produits destinés à être commercialisé exclusivement hors de l'Union Européenne. Plus récemment, en 2014, l'Agence de Santé Suisse, Swissmedic, a lancé une procédure pour adresser la situation rencontrée dans ces pays.

Cette thèse décrit donc ces trois axes de développement qui tentent à améliorer l'accès à des médicaments sûrs et efficaces auprès des patients dans les pays en développement.

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