

The WHO Collaborative Registration Procedure for Medicines in Developing Countries

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II. List of Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
AMRH	African Medicines Regulatory Harmonization
API	active pharmaceutical ingredient
CHMP	Committee for Medicinal Products for Human Use
CMC	chemistry, manufacturing and control
CP	Centralised Procedure (at the EMA)
CRL	list of products registered via the WHO collaborative registration procedure
CRP	WHO Collaborative Registration Procedure
CTD	Common Technical Dossier
DPML	Direction de la pharmacie, du médicament et des laboratoires, Cameroon
DRC	The Democratic Republic of the Congo
EAC	East African Community
EFTA	European Free Trade Association
EMA	European Medicines Agency
EML	Essential Medicines List
Eoi	expression of interest
EU	European Union
EUR	Euro
FDA	United States Food and Drug Administration (also: USFDA)
FDC	fixed-dose combination
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GNI	gross national income

HIC	high income country
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
LMIC	low- and middle-income country
MA	marketing authorisation
MAH	marketing authorisation holder
MSF	Médecins Sans Frontières, Doctors Without Borders
NAFDAC	National Agency for Food and Drug Administration, Nigeria
NMRA	national medicines regulatory authority
NTD	neglected tropical disease
PEPFAR	US President's Emergency Plan for AIDS Relief
PQ	WHO Prequalification
PQL	List of WHO Prequalified Medicines
PQP	WHO Prequalification of Medicines Programme
PQT	WHO Prequalification Team
PV	pharmacovigilance
SRA	stringent regulatory authority
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USD	US Dollar
WHA	World Health Assembly
WHO	World Health Organization

1 Introduction

The protection and promotion of public health is an essential governmental task taken over partially by national medicines regulatory authorities (NMRAs). Based on drug legislation these authorities aim to ensure that only safe and efficient medicines of good quality are put on the market. Nonetheless, this regulatory oversight of pharmaceuticals is a challenging, sophisticated and resource-demanding task. However, NMRAs in developing countries have to cope with very limited funding, adequately trained staff and expertise. Hence, circulating substandard and counterfeit medicines are not detected and consequently commonly distributed and dispensed. Furthermore, some urgently needed drugs are not available on the local market for the patient population. Due to the fact that neither the government nor the people can afford high-priced medicines, innovative pharmaceutical companies are rarely interested in marketing their medicinal products in developing countries. Although in the past there were some generic versions available, their quality was doubted. Unfortunately, this could not be addressed and monitored adequately by the NMRAs because of their restricted resources.

To enable UN agencies to purchase high-quality, safe and efficient medicines at reasonable prices address, the WHO established the prequalification programme in 2001. This approach improved the situation in developing countries tremendously. Nevertheless, prequalification does not result in a national marketing authorisation and consequently required medicines are still not accessible for all patients via the regular distribution chain. That is why the WHO started a pilot project in 2012 to foster drug registration in developing countries. This collaborative registration procedure (CRP) not only aims to accelerate the authorisation process but also focuses on capacity building at the NMRA. Trainings, workshops and joint activities extend expertise as well as experience of local assessors and inspectors. Furthermore, the CRP programme promotes harmonisation and thereby the reduction of regulatory burden for the NMRAs as well as for the manufacturers.

This thesis describes the historical context that led to the establishment of the CRP. It further summarises experiences and achievements of the first 2.5 years and discusses advantages and drawbacks as well as the potential development of the programme in the future.

2 Registration of Medicines in Low- and Middle-Income Countries

2.1 Definition of 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 less than or equal to 1,045 US Dollars (USD) in 2013 (1). The calculation of this GNI is based on the World Bank Atlas method (2). In November 2014 the following countries were classified as low-income economies: Afghanistan, Bangladesh, Benin, Burkina Faso, Burundi, Cambodia, Central African Republic, Chad, Comoros, The Democratic Republic of the Congo, Eritrea, Ethiopia, The Gambia, Guinea, Guinea-Bissau, Haiti, Kenya, Democratic People's Republic of Korea, Liberia, Madagascar, Malawi, Mali, Mozambique, Myanmar, Nepal, Niger, Rwanda, Sierra Leone, Somalia, Tajikistan, Tanzania, Togo, Uganda and Zimbabwe (1). More than three quarters of these countries are situated in Africa (26 out of 34).

Countries with a GNI per capita between 1,045 USD and 12,746 USD in 2013 are defined as middle-income economies (1). These comprise 107 countries that are divided into lower-middle-income economies (1,046 USD to 4,125 USD) and upper-middle income countries (4,126 USD to 12,745 USD) (1).

2.2 Reasons for Medicines Registration

Medicines can have a major impact on the people's health, they can even make a difference between life and death, and thus are not regarded as ordinary consumer goods (3). Ideally, medicines prevent, treat or heal diseases and related symptoms. However, it must be kept in mind that taking medication is also associated with several risks. Firstly, drugs can cause adverse effects, especially if not administered properly (3) (4). Secondly, every individual patient might react differently to a certain drug due to his or her age, gender, different physiological situation or genetic background. Such issues are addressed during clinical trials aiming to find out about the proper dose, the target patient population or the duration of treatment. Furthermore, these studies try to elucidate the adverse event profile of a certain medicinal product. In summary, clinical trials investigate the safety and efficacy of a drug that must eventually be characterised by a clearly positive benefit-risk-ratio. It can be concluded that medicines have the potential to heal but, simultaneously, also to harm patients (4).

Moreover, it is obvious that a low quality of a medicinal product may shift the fragile balance towards its harmful potential. This effect might even be worse since medicines are primarily taken by sick people who are already affected and therefore particularly vulnerable.

There are several elements that define the quality of a medicinal product. Consequently, its quality can be impaired due to several reasons. For example, a deviation in the amount of an active pharmaceutical ingredient (API) or its complete absence may eliminate the drug's therapeutic potential partially or completely (3) (5) (6). In the case of antibiotics this could

even promote the development of microbial resistances which are increasingly becoming a global threat. Moreover, manufacturing non-compliant with Good Manufacturing Practice (GMP) may for instance cause batch to batch inconsistency and therefore unpredictable quality parameters. Additionally, inappropriate stability or suboptimal packaging of medicines may result in an accumulation of impurities, contaminations or degradation substances which in turn may have toxic effects (6).

It is also important to note is that people normally do not choose to take drugs but are obliged to do so due to an existing illness. Nonetheless, it is virtually impossible for the population to judge the quality, or the safety and efficacy of a medicinal product (3) (5). Even well-trained medical doctors, pharmacists or scientists are not able to evaluate every available medicine with regard to these properties (5). This is why governments have to take on this responsibility in order to protect their citizens and promote public health (3) (5). Therefore, national medicines regulatory authorities (NMRA) are established which aim to ensure, monitor and control the appropriate quality, safety and efficacy of medicines throughout their lifecycles (4) (7). This in turn must be based on a legal framework of medicines regulation.

Until the 20th century there was virtually no regulatory supervision of medicines at all. Pharmaceutical companies were allowed to put their products on the market without major restrictions by governments. The establishment of drug legislation and regulation was triggered only by medical scandals, for instance with Elixir Sulfanilamide in the USA in the late 1930s. This antibiotic included the toxic solvent diethylene glycol, which resulted in the deaths of more than 100 people (8) (9). Consequently, this event led to the adoption of the Food, Drug and Cosmetic Act in 1938 (8) (9). Another famous example is the Contergan case happening in in the late 1950s in Germany. Thalidomide, the API of Contergan, caused thousands of miscarriages, malformations of fetuses and deaths of children when taken by pregnant women (10). Unfortunately, at the time this effect was unknown. To make things worse, Contergan was specifically prescribed for pregnant women to soothe morning sickness. As a consequence of this tragedy, whose aftermath is still evident today, the German *Arzneimittelgesetz* (German Drug Law) was drawn up (11).

Drug legislation defines the legal framework of regulation of medicinal products by means of laws, regulations or directives. For and foremost, the NMRA needs to know which drugs are circulating in the market. This is achieved by drug registration. Additionally, medicines are evaluated scientifically by the authority (5). In principle it is prohibited to market medicines in a country without a respective marketing authorisation (MA). This follows the principle of preventive prohibition with the reservation of permission. A medicinal product is assessed according to certain standards, procedures and guidelines (5).

To achieve an MA a drug's quality, safety and efficacy in accordance with standards predefined by the NMRA must be demonstrated (3) (5). Optimally, this includes inspections of manufacturing sites to assure GMP compliance as well as inspections of testing laboratories and clinical trial sites to ensure compliance with Good Laboratory Practice (GLP) and Good

Clinical Practice (GCP) respectively (3) (5). Additionally, marketing, distribution and dispensation of medicinal products have to be overseen (3) (4) (5).

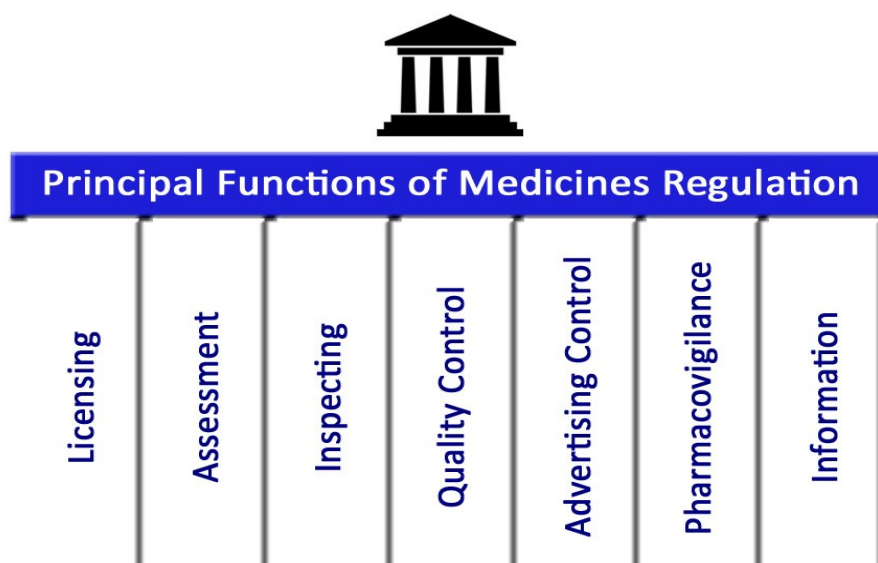


Fig. 1 Overview of the principal medicines regulatory functions according to WHO (4).

Because of the responsibilities outlined above, the WHO has defined some principal functions that NMRAs should fulfil (Fig. 1) (4). Firstly, an NMRA is responsible for licensing the manufacture, trade and advertising of medicines (4). Moreover, the authority grants and updates MAs based on a scientific evaluation of the drug's quality, safety and efficacy (4). As mentioned above, this also includes inspections of manufacturing sites, quality control testing laboratories and clinical trial sites as well as wholesalers and dispensers (4). Apart from that it is crucial to control and monitor a drug's safety throughout its lifecycle (pharmacovigilance) (4). An innovative medicine is normally authorised based on safety data from clinical trials with several hundreds to thousands of people only. Hence, rare adverse events are presumably not detected during these studies due to insufficient statistical power. That is why NMRAs continuously collect and evaluate safety data about medicines on the market. Based on these data a medicinal product is analysed regularly, also with respect to the current scientific and technical knowledge. If there is a shift towards a negative benefit-risk-ratio, also taking into account other drugs available on the market, the conditions of use are adjusted. This may refer to restriction of indications or additions of contraindications. As soon as the benefit-risk-ratio becomes principally negative, the MA is suspended or withdrawn. Thereby, the NMRA ensures therapies in accordance with acceptable standards and an acceptable benefit-risk-ratio for its population. Another less prominent but not negligible role of an NMRA is the control of medicine advertising which is sometimes taken over by specialised institutions (4). It has to be ensured that no misleading information is spread by pharmaceutical companies that may raise false hopes about the drug's effects. Finally, an NMRA is also an important contact point where scientifically gathered and independent information about medicines can be accessed by pharmaceutical companies, health care professionals as well as the population (4).

To be able to fulfil all these functions properly, NMRAs need appropriate organisational structures and facilities, adequately trained staff as well as appropriate and sustainable funding (4) (5). Today international cooperation, work-sharing and information-sharing are indispensable tools for NMRAs for accomplishing their tasks.

2.3 Situation in Low- and Middle-Income Countries

It is exactly these prerequisites mentioned above that pose a major challenge to NMRAs in LMICs. Developing countries have to cope with numerous problems outlined below that concern medicines and, even more generally, maintaining public health. Unfortunately, the respective NMRAs are often unable to address these issues properly and, consequently, to accomplish their actual tasks.

In less industrialised countries, compared to the developed ones, only very few medicines are produced locally (7). Hence, most of the drugs consumed have to be imported. These are often generics and manufactured mainly in India, China, Brazil or South Africa amongst others (12). Nonetheless, there has always been a general mistrust towards medicines produced by these countries which, at least partially, still prevails (12) (13). This doubt was reinforced in 1999 by a small undisclosed study in South Africa concluding that about 60 % of examined antimalarials were substandard and as a consequence clinically useless (12). More than ten years later, the WHO reported that sample testing of antimalarials in six African countries revealed that 30 % of these medicines were still not fully in compliance with international standards (14).

Interestingly, even products originating in high income countries (HICs) and fulfilling international quality standards on their domestic market are often of poorer quality when exported to less developed countries (4) (6). It seems that manufacturers do not feel obliged to ensure high quality per se but simply adapt to stringency of national requirements.

This clearly demonstrates that a legal framework and regulation are important to monitor medicines' quality. Although there are NMRAs almost in every country of the world, their actual conditions differ tremendously (4).

As mentioned above, medicine regulation is a complex as well as resource-demanding task which requires adequately qualified staff with a certain expertise. However, NMRAs in LMICs often have to deal with a general shortage of well-trained employees and lack of financial resources (7). Hence, they are unable to fulfil even the minimal functions of medicines regulation as stated by the WHO (15) (7) (12). Donatien Kabamb Kabey, Chief of Division of Direction de la Pharmacie et du Médicament of the Democratic Republic of the Congo (DRC) confirms: *"We have actually a problem of technical capacity for the assessment of all the technical parts of the dossier."* (16). A similar situation is described by the NMRAs of Malawi, Cameroon, Namibia or Georgia (17) (18) (19) (20). Dr Kouakap Solange, Sub-Director of Drugs at the Direction de la Pharmacie, du Médicament et des Laboratoires (DPML) in Cameroon explains: *"We do not have enough staff for all the work and we are also facing many financial*

problems." (18). In 2012 the NMRA of Zimbabwe received twice as many applications for MAs as they could handle within one year (15). Similarly, the NMRA of DRC reports the submission of approximately 1,000 dossiers a year, too many to be evaluated within an acceptable timeframe (16).

According to 2009 estimates by the WHO two thirds of all countries worldwide, comprising most LMICs, do not have a fully functioning drug regulatory system (21). Another WHO study revealed that in sub-Saharan Africa this was actually true for approximately 90 % of those NMRAs in 2010 (7).

The WHO declares that this situation is due to governments often being unaware of the potential benefits of a sophisticated medicines regulatory system and thus do not trigger its implementation or assure sustainable funding (21). Nonetheless, medicines registration is becoming more and more a prerequisite before a product can be marketed, also in developing countries (6). Although this development is appreciated, it is also recognised that MAs are often issued without a proper understanding of medicines quality parameters and benefit-risk-evaluation, irrespective if it is based on detailed dossier evaluation and inspections of manufacturing sites or evidence obtained elsewhere.

Although this development is appreciated, it is also recognised that marketing authorisations are often issued without a detailed dossier evaluation and without inspections of manufacturing sites have taken place (6). In consequence, the procedure is existent only pro forma and does not have a major impact on the quality of medicines circulating in the respective country. Due to this weak regulatory oversight it is almost impossible to eliminate substandard medicines from the very beginning or to detect them later on (6).

This situation is also promoted by the fact that health care professionals in LMICs are often less educated than those in industrialised countries (6). Most regulators and inspectors working at NMRAs in developing countries are trained on the job. *"There is no formal training for those working in regulatory affairs. Those with experience teach new employees whilst on job."* explains Edwin Chipala, Drug Registration Officer at the Pharmacy, Medicines and Poisons Board in Malawi (17). A similar situation is reported from NMRAs in Nigeria, Burkina Faso, Ethiopia, DRC and Côte d'Ivoire amongst others (16) (22) (23) (24) (25). Although most employees learn by doing as well as from experienced colleagues in house, many regulators also attend further courses externally (18) (22) (19) (26). NMRAs in Namibia and Burkina Faso further mentioned special training courses for their staff conducted by the WHO (23) (19). Only the authority in Zanzibar stated that there are special trainings for regulators (27).

Due to the lack of resources in terms of funding, staff and scientific expertise, and in order to be pragmatic in drug regulation, some NMRAs in developing countries refer to recognised stringent regulatory authorities (SRAs): Although there is no clear definition of an SRA, for the purpose of its prequalification process the WHO considers NMRAs in member states of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH observer states as well as in countries that signed

mutual recognition agreements with the ICH as SRAs (28) (29). Additionally, also NMRAs of the European Free Trade Association (EFTA) members Norway, Iceland, Liechtenstein and Switzerland are recognised as SRAs (29). Thus, SRAs encompass the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), the Pharmaceuticals and Medical Devices Agency, Japan (PDMA), the Swissmedic in Switzerland, the Therapeutic Goods Administration (TGA) in Australia as well as Health Canada amongst others (28) (29).

In compliance with this approach some NMRAs of developing countries only approve a medicinal product if it was granted an MA by an SRA before (5) (30). Thereby, it can be assumed that the product is in compliance with international quality standards. However, many drugs urgently needed in developing countries are not needed at all in HICs because some diseases are not even prevalent there. This holds especially true for neglected tropical diseases (NTDs) like filariasis (also known as elephantiasis), soil-transmitted helminthiasis or schistosomiasis. Additionally, regulators of an SRA are usually not familiar with such diseases and, therefore, are not able to assess the product's safety and efficacy properly in the correct context. This also applies to risk assessments that are normally based on local incidence and prevalence of a disease (30) (31). In consequence, a drug's benefit-risk-ratio would be evaluated totally differently if based on other reference data. However, SRAs are located in industrialised countries and, thus, do not take into account data from LMICs at all.

In reaction to this unsatisfactory situation, there have been different approaches from HICs to support resource-limited NMRAs in terms of drug registration. One of those is the Art. 58 procedure offered by the EMA that was implemented in 2004. Based on article 58 of Regulation (EC) No 726/2004 pharmaceutical companies may have medicines assessed by the EMA in cooperation with the WHO (32) (33). This Art. 58 procedure is applicable only for human medicines marketed outside of the EU and used for prevention or treatment of public health priority diseases such as HIV/AIDS, tuberculosis and malaria (32) (33). Nonetheless, these evaluations according to Art. 58 do not result in an MA but in a scientific opinion given by the Committee for Medicinal Products for Human Use (CHMP) in agreement with the WHO (32) (33). Another drawback of this procedure is that it does not directly involve regulators from all developing countries concerned and, therefore, there is no sufficient transfer of knowledge or expertise to the local NMRAs. In consequence, this will not support the development of an ideally autonomous working authority. However, the involvement of WHO experts that provide the required knowledge about the respective disease is a positive aspect.

Unfortunately, this Art. 58 procedure is used only rarely. During the ten years since Regulation (EC) No 726/2004 has come into force only seven applications have been evaluated successfully (34). Another one has been withdrawn by the manufacturer during the assessment (32). High costs of approximately 280,000 EUR, a relatively long assessment time of 210 days and a general lack of incentives for the pharmaceutical company such as tax deductions or market exclusivity may be reasons for this very low level of interest (30) (35).

Beside the European Art. 58 procedure the FDA offers a similar approach to promote medicines registration in resource-limited countries. Here, the review is linked to the US President's Emergency Plan for AIDS Relief (PEPFAR) that was initiated in 2004 and aims to assess generic antiretrovirals procured with PEPFAR funds (30) (36) (37). In contrast to the Art. 58 procedure this FDA approach is an expedited assessment and is meant to be finalised within six weeks (36). Nevertheless, FDA standards with regard to quality, safety and efficacy are applied (36). The FDA also involves NMRAs of developing countries to familiarise them with the science on which the drug assessment is based (36). This approach aims to accelerate subsequent medicines registration within the respective countries (36).

There are two possible positive review outcomes: a full approval that results in an MA or, in the case of an existing patent protection in the USA, a tentative approval (36). After patent expiration, the tentative approval is automatically transformed into a full approval (30). Nonetheless, also products only tentatively approved can be purchased within the PEPFAR programme (36). The most obvious shortcoming of this FDA approach is that it is restricted only to medicines against HIV/AIDS. Apart from that, there are also several advantages of the programme: The review is fast, no fees are charged and it involves NMRAs of developing countries to build capacity there (38). Compared with the European Art. 58 procedure the PEPFAR related approach is more widely used by pharmaceutical companies. To date 180 medicinal products have received approval by the FDA (36). Another approach to promote the availability of high-quality drugs in developing countries is the WHO Prequalification of Medicines Programme that will be outlined in detail in the following chapter.

3 The WHO Prequalification Programme of Medicines

3.1 The World Health Organization

In 1945, after the Second World War the United Nations (UN) were founded by 51 countries (39). Their objectives are *“international peace and security, developing friendly relations among nations and promoting social progress, better living standards and human rights.”* (39). The following year, in 1946, the World Health Organization (WHO) was established as a specialised agency of the UN. In its constitution, it enshrined the aim to achieve the best possible level of health for all people (40).

All member states of the UN may also become members of the WHO (41). Additionally, non-UN members may participate if this is supported by a majority of the World Health Assembly (WHA) (41). As of January 2015, there are 193 states in the UN (39). All these states but Liechtenstein are also members of the WHO (41). The organisation is further joined by the Cook Islands and Niue, small islands located in the South Pacific Ocean, and thus comprises a total of 194 member states (41).

The WHO headquarters is based in Geneva in Switzerland (42). There are additional regional offices, one in each of the six WHO regions: Africa, the Americas, Europe, South-East Asia, Western Pacific and Eastern Mediterranean (42). Affiliation of countries to individual regions does not always follow a geographical principle.

The WHO describes itself as *“the directing and coordinating authority within the UN system.”* (42). It addresses a wide range of health care related topics including research and health policies and aims to provide leadership and support for its member states in the respective areas (42). Furthermore, it establishes international norms and standards (42).

As enshrined in its constitution, the WHO pursues its objective to attain *“the highest possible level of health”* for all people which includes several tasks (40). In article 2 of this constitution the role and responsibilities of the WHO are laid down (40). Amongst others there are also several functions that concern drug policies and registration in a broader sense: The WHO establishes and recommends regulations concerning international health matters and offers administrative and technical services (40). Moreover, it develops international standards and promotes their global establishment (40). The WHO further supports governments to strengthen health systems and services in general and provides technical assistance if this is requested by the respective country (40).

3.2 The Concept of Essential Medicines

According to its constitution the WHO's responsibilities are *“to provide information, counsel and assistance in the field of health”*, to *“make recommendations with respect to international health matters”* and to *“to develop, establish and promote international standards with*

respect to [...] pharmaceutical and similar products” (40). In this context the WHA asked the WHO in 1975 to support its member states with the implementation of national medicines policies, since this very complex and demanding task is particularly difficult to achieve in resource-limited countries (3). In consequence, this led to the concept of essential medicines which are defined as *“those that satisfy the priority health care needs of the population”* (43). The WHO further states that these medicines should always be available in every health care system and must be affordable for the population (43). Moreover, essential medicines are required to be proved safe and efficient (43). Thus, in summary, essential medicines are those necessary to maintain public health but are, at the same time, cost-effective. Access to essential medicines is considered one of the basic human rights.

The first Model List of Essential Medicines (EML) was adopted by the WHO in 1977 and included more than 200 drugs for most communicable and non-communicable diseases (43) (44) (45). The EML is updated and published by the WHO every two years reflecting current needs in primary healthcare (43). Consequently, the HIV/AIDS epidemic led to the inclusion of the first antiretrovirals (ARVs) in 2002 (3) (12). Moreover, selection of medicines must be evidence-based and takes into account the current state-of-the-art in science and technology (46) (47). The 18th EML published in April 2013 comprised not only more than 350 essential drugs for the treatment of priority conditions as well as priority diseases including malaria, tuberculosis and HIV/AIDS but also products used in reproductive health (44). Since 2007 an additional EML particularly for children has been introduced (44).

The EML is not meant to be adopted completely by every country, but to be adapted according to the country's specific disease burden, i.e. incidence and prevalence of a disease (43). Thus, respective national lists of essential medicines should be established. Furthermore, the EML does not only list existing drugs but also those for which a medical need has been identified although these have not yet been developed (12). This in turn promotes research and development of new medicines.

The Alma-Ata Declaration of the International Conference on Primary Health Care in 1978 defined the provision of essential drugs as an essential component of primary health care (48). Since then, the concept of essential medicines has remarkably influenced the situation in developing countries remarkably, and still does today. Many governments as well as international non-profit organisations, such as the United Nations Children's Fund (UNICEF) or Médecins Sans Frontières (MSF, Doctors Without Borders), make decisions about purchasing and provision of medicines largely based upon the EML (12) (46).

3.3 The WHO Prequalification Programme

In March 2001, the Prequalification Programme (PQP) was established jointly by the WHO and UNICEF, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the United Nations Population Fund (UNFPA) in collaboration with the World Bank (13). It aims to guarantee

quality, safety and efficacy of medicines purchased by UN agencies for developing countries and is based on the concept of essential medicines (12) (13) (28). Only medicinal products listed as essential medicines or those that are recommended by WHO treatment guidelines can be prequalified (28) (49).

Before the establishment of the PQP, UN procurement agencies had to cope with several difficulties regarding the provision of high-quality medicines in developing countries together with an optimal investment of their financial resources (12). Medicinal products assessed and authorised by stringent NMRAs of highly developed countries were purchased by the UN agencies because their quality, safety and efficacy were considered to be proven (12). Nonetheless, these medicines were often patent protected and thus expensive. This was especially true for medicines used to treat HIV/AIDS at the turn of the millennium (3) (12). However, in many developing countries it was not yet mandatory to grant patents at the time (12). Consequently, these were not a major reason why people in developing countries had almost no access to necessary medicines. Nevertheless, as described above, the NMRAs of those countries had to cope with very limited resources in terms of staff, capacity and money and were therefore unable to ensure the quality of medicines with sophisticated dossier assessments and inspections of manufacturing and clinical trial sites. Additionally, innovative drug manufacturers were not very interested in having their products authorised in a poor country where most people could not afford their expensive medicines. For those companies, this also prevented the risk of parallel importation to high-income countries. Although there were manufacturers of generic versions of medicines that were patent protected in HICs, often the quality of these products was doubted (12) (13). Most of the manufacturers in question were located in India. However, the Indian NMRA's quality assurance system regarding medicinal products was not recognised as sophisticated and efficient enough to ensure quality of exported medicines in compliance with international standards (12). In addition to classic generic products, Indian companies also produced fixed-dose combinations (FDC) of medicines, first and foremost for ARVs (12). These are medicinal products that comprise different substances in a defined ratio combined in a single dose. For every single substance there is an originator product in a developed country, but there is no original finished pharmaceutical product (FPP) containing the different substances together in this specified ratio, although the combination is clinically proven and approved by SRAs. Such FDCs have been developed by manufacturers mainly upon request by the WHO due to the fact that it listed these products on the EML (12).

Besides the above mentioned concerns about medicines from India or other countries with relatively weak regulatory oversight, the quality assurance systems of the procurers themselves were often not yet sophisticated enough to assess the required quality of the products they purchased (12) (13). Thus, the procurers were not able to detect low-quality medicinal products and risked wasting their budgets on inefficient or even harmful drugs.

In 1999, an undisclosed pilot-study conducted by the WHO found that six out of ten examined medicines used for the treatment of tuberculosis did not have any therapeutic effect (12). This

result was very alarming since poor-quality or counterfeit medicines are not only clinically useless but may also harm patients in a variety of ways as described above (13). Thus, the WHO was asked by its member states to support the establishment of international standards of quality assurance of medicinal products (3) (12). UN agencies were especially interested in safe and efficient generics, since their cheaper prices could lower procurement costs and would further enable the provision of medicines to a higher number of patients (12). At the same time it had to be ensured that these medicines met global standards. Both aspects could in turn help to improve treatment of patients in developing countries and expose manufacturers to healthy competition that would affect costs positively.

The concept of prequalification was not invented in 2001, but it has been used successfully for vaccines over 30 years (3) (12). Since 1987, most vaccines purchased by UNICEF have been assessed by the WHO within the Expanded Programme on Immunization (3) (12). The PQP aimed to transfer this successful concept to other medicines. However, it was modified and was independent of the vaccine prequalification programme.

At the beginning, the PQP focused on medicines against HIV/AIDS (12). Around the year 2000 the pandemic spread on a global level and particularly fast in Africa where 25 million people were infected (50) (51). However, according to estimates only 1 % of them received ARV therapy (51). Later on, additional medicines were included, for instance against malaria and tuberculosis (2003/2004), pandemic influenza (2007), acute diarrhoea (2008) and the neglected tropical disease filariasis (2013) (12) (13) (52). All these are priority diseases by WHO standards. In 2006 the PQP further included medicinal products for reproductive health which are also defined as essential medicines (12).

The first list of prequalified medicines (PQL) was published in 2002 and included 41 medicines for the treatment of HIV/AIDS (12). As of January 2015, more than 400 medicines for different priority diseases are listed as prequalified (52). This also includes medicines that have not been evaluated by the WHO itself but by SRAs such as the FDA, the EMA or Health Canada (alternative listing procedures) (53).

Due to the success of the programme since its establishment, the PQP was extended. Today active pharmaceutical ingredients (APIs) and testing laboratories can be prequalified as well (13) (54).

For more than ten years, the WHO did not charge any fees for PQP. From the beginning in 2001, the PQP depended completely on donations and funding was mainly provided by UNITAID and the Bill & Melinda Gates Foundation (12) (55). Since depending merely on donations is quite risky, especially with regard to long-term perspectives, applications fees were introduced in September 2013 to contribute to a more stable financial base of the PQP (12) (55). Nevertheless, these fees do not equal the costs caused by dossier assessment and inspections. Furthermore, to date, fees are only charged for prequalification of medicinal products and APIs (55). Every first application submitted by a manufacturer is still free of charge, the following ones are charged in a staggered manner (55).

The prequalification of a medicinal product is not equivalent to an approval since no MA is granted and cannot be granted by the WHO either (28) (53). Still, only the NMRA has the right to issue MAs (28). First and foremost, the outcome of the prequalification procedure has implications for UN procurement. However, the prequalification of a product benefits manufacturers in several ways: The product can now be purchased by UN agencies that spend billions of USD every year on (prequalified) drugs (56). Other international suppliers of medicines such as non-governmental organisations (NGOs) refer to the list of prequalified medicinal products as well (12) (56). Additionally, PQ is recognised as a very stringent procedure and thus enables the manufacturer of a drug to fulfil requirements of SRAs too (3).

Another objective of the PQP is to build capacity in WHO member states with regard to regulatory processes and inspections. On the one hand, staff of NMRAs can take part in dossier assessments and inspections conducted by the WHO during the PQ procedure (28). On the other hand, WHO PQP offers inexperienced manufacturers support and technical guidance throughout the procedure if their medicines address an unmet medical need in public health care (3) (28). To further promote capacity building in resource-limited countries, the WHO established rotational fellowship positions at the WHO headquarters in Geneva (3) (13). For three months, regulators and inspectors of NMRAs from developing countries get the chance to work with the WHO Prequalification Team (PQT) (3) (13). In addition, the WHO recommends that manufacturers applying for PQ request their domestic NMRA to collaborate with the WHO (28).

3.3.1 The Prequalification Procedure

In principal the PQ procedure can be compared to a regular drug registration process at an SRA except for the fact that it does not result in an MA (5) (53). Corresponding to NMRAs, the PQP aims to ensure quality, efficacy and safety of medicines. Its vision is to achieve availability of *“Good quality medicines for everyone”*, especially for those in need in low-income countries (57). Nevertheless, the WHO emphasises that it is not a regulator per se (15). Its decisions are not legally binding and enforceable.

The WHO PQT assesses the dossier that comprises all relevant data about chemistry, manufacturing and control (CMC), preclinical and clinical data in detail. However, almost all prequalified products are generics. In this case no preclinical data are required and clinical data are mainly restricted to bioequivalence studies. The dossier has to be provided according to the Common Technical Document (CTD) format established by ICH (13) (58). Additionally, inspections of manufacturing sites, testing laboratories and clinical trial sites take place (59). Hereby, compliance with Good Manufacturing Practice (GMP), Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) has to be confirmed (28) (56).

The WHO collaborates closely with NMRAs and partner organisations (28). Although the general management and supervision of the PQ procedure is done by the PQT, the dossiers

are assessed in collaboration with regulators from WHO member states (38) (56). Moreover, inspections are carried out together with national inspectors, also with those from resource-limited WHO member states (12) (28). The reasons are twofold: Firstly, it would be too cost- and time-consuming to have the PQ carried out only by WHO staff. Secondly, this collaboration serves as training for regulators and inspectors from developing countries and thus helps to build capacity in these states.

The process of PQ consists of five main steps: Invitation for expression of interest (EoI), EoI and dossier submission by a manufacturer, assessment of the dossier by the WHO PQT, inspections conducted by the WHO PQT and finally the decision if the product is included in the WHO List of Prequalified Medicines (Fig. 2) (56).

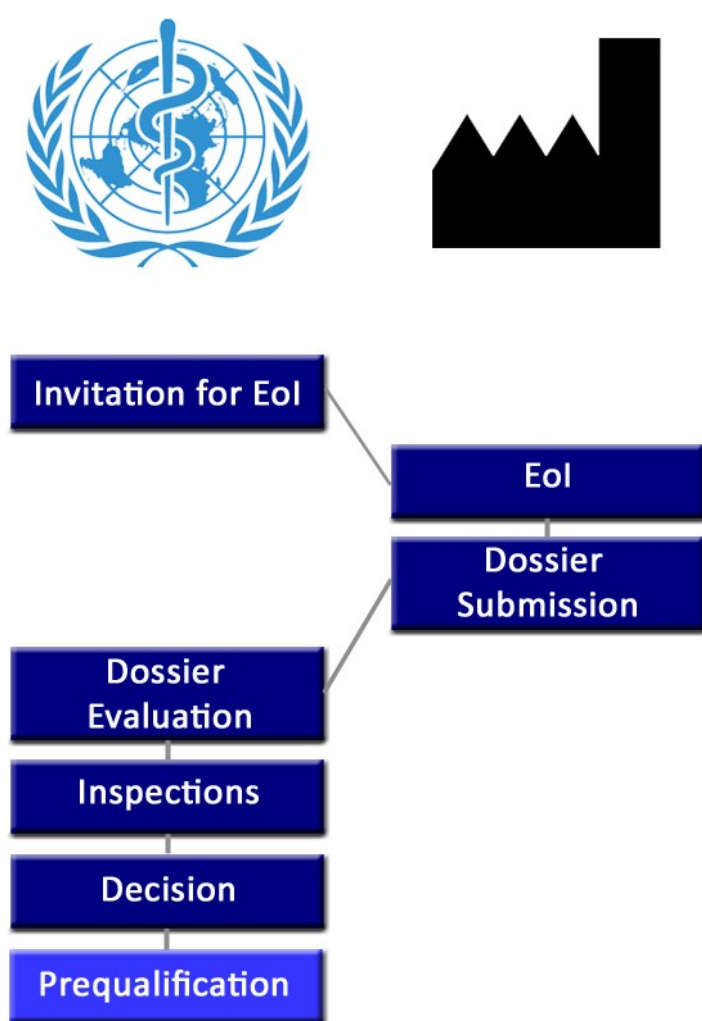


Fig. 2 Schematic process of prequalification for medicines. After the publication of an invitation to an expression of interest (EoI) by the WHO, a company submits an EoI together with a dossier to the WHO. The dossier is evaluated by a team of regulators from the WHO as well as from WHO member states. Inspections to confirm GMP-, GCP- and GLP compliance are carried out by WHO inspectors together with those from WHO member states. If the outcome of the dossier assessment as well as of the inspections is positive, the product is prequalified and included in the WHO List of Prequalified Medicines.

The PQP regularly publishes invitations for EoIs on its website (49). If there is an urgent need for specific medicines, an invitation for an EoI can also be triggered immediately (28). These invitations are worked out also in cooperation with UNICEF, UNAIDS and UNITAID (56). EoIs only concern medicines for WHO priority diseases such as HIV/AIDS, tuberculosis, malaria, influenza, diarrhoea and NTDs as well as those used for reproductive health (28). However, new categories of medicines can be added if needed.

Although it is also possible to have APIs and quality control laboratories prequalified, the following description focuses only on the process of PQ of FPPs (49).

As soon as an invitation for EoI is published a manufacturer may submit an EoI together with a dossier to the PQT (28). Participation in PQ is voluntary

and is thus initiated only by the manufacturer (13). The dossier has to be in CTD format and must be accompanied by a cover letter, samples of the product and the site master file of the manufacturing site of the finished product (49).

Dossier assessment is conducted by a team of regulators from the PQT, from NMRAs of HICs like Canada, Switzerland or some European NMRAs and also those from low- and middle income countries (13) (59). Furthermore, a group assessment takes place every two months in Copenhagen at the UNICEF offices (13). The dossier has to be in line with the requirements laid down in WHO guidelines (3).

Parallel to the dossier assessment the site inspections take place. These include the manufacturing site of the FPP as well as those of all APIs, quality control testing laboratories and clinical trial sites, which in turn comprise contract research organisations (CROs). All inspections are carried out by WHO inspectors in collaboration with national inspectors from WHO member states (56) (59). If a site was already inspected before by the WHO or another stringent institution, e.g. members of the Pharmaceutical Inspection Co-operation Scheme (PIC/S), the inspection of this site may be waived (3) (28).

Depending on the outcome of both dossier evaluation and inspections, the decision is made if the product fulfils all requirements and can be included in the WHO List of Prequalified Medicines (PQL) (56). Ideally, in case of a high-quality product as well as a high-quality application the whole prequalification takes approximately three months (59). Depending on the product and the application, this time span is extended.

Besides this regular listing, there are further alternative listing procedures. Medicines that were assessed by SRAs may be included in the PQL as well. In this case, the manufacturer files an application for prequalification to the PQT including amongst others a copy of the MA accompanied by a WHO Certificate of Pharmaceutical Product (CPP), the currently approved specifications as well as all product information texts in English and a declaration that the product submitted is identical to the one evaluated by the SRA (29). If there is a public assessment report, it has to be provided too (29). Preferably, for all those medicinal products, long-term stability studies for climatic zone IVb (30°C/75 % relative humidity) are included as well as accelerated studies at 40°C and 75 % relative humidity since these are the most stringent conditions and many developing countries are located within this climatic zone (29).

Furthermore, drugs that have received a positive opinion from the CHMP according to an Art. 58 procedure at the EMA, that were (tentatively) approved by the FDA under the provisions of a PEPFAR procedure or that were approved with regard to Canada's Access to Medicines Regime (CAMR) by Health Canada may also be listed on the PQL (53) (60). The decision about inclusion rests with the WHO and depends mainly upon the provision of relevant information from the respective SRA and manufacturers (28). Alternative listing procedures apply to generics as well as to innovative medicines (53). The drug is only listed as prequalified if the manufacturer and other concerned stakeholders apply for its inclusion on

the PQL (53). The respective products in the list are labelled with a reference to the respective authority (EMA, FDA, Health Canada) in the PQL (53).

Similar to nationally authorised medicines, prequalified drugs are also followed up throughout their lifecycle. Consequently, the WHO has to be informed about any changes to the product. This is done by submitting variations to the PQT. There is a special guideline for variations of prequalified products available (61). This guideline is based mainly on the European variation classification guideline and categorises possible changes as notifications, minor variations, major variations or those only concerning labelling information (61) (62). Furthermore, significant changes beyond the category “major variation” require a new application for prequalification or an application for a line extension. In case of prequalified products that were assessed by an SRA, variation and renewals are not within the WHO’s responsibility but within the SRA’s (29).

In addition to variations, the maintenance of a prequalified product also requires requalification every five years (59). However, the PQT may require an earlier requalification depending on the product (59).

3.3.2 Development and Current Situation

From 2001 to date, more than 500 medicines have been prequalified (12) (52). As of January 2015, 507 medicines can be found on the PQL that are used for the treatment of HIV/AIDS, diarrhoea, influenza, malaria, tuberculosis and the NTD filariasis as well as for contraception (52). The number of products prequalified in the respective therapeutic areas is shown in Fig. 3. More than two thirds of all prequalified products were ARVs (69 %) used in HIV/AIDS. 15 % of the products on the PQL are medicines against tuberculosis (76 products), followed by antimalarials which add up to 41 products (8 %). An additional 27 oral contraceptives used in the area of reproductive health were included (5 %), as well as ten antivirals used in influenza (2 %). Two zinc products to treat acute diarrhoea were added only recently (2012 and 2014). In 2013, the first medicine for the treatment of an NTD was prequalified (54). This drug is used in filariasis (elephantiasis), a parasitic disease 120 million people are currently infected with worldwide (63).

412 of the 507 drugs on the PQL were prequalified by the WHO itself (Fig. 4). An additional 90 medicines on the list were evaluated by the FDA (18 %). Due to the fact that these are PEPFAR linked, all of them are ARVs. Only four products were added to the list after a positive opinion of the CHMP according to an Art. 58 procedure at the EMA. These comprised two ARVs, one antimalarial and one oral contraceptive. To date, only one single medicine has been assessed by Health Canada within the CAMR programme.

WHO Prequalified Medicines - Therapeutic Area

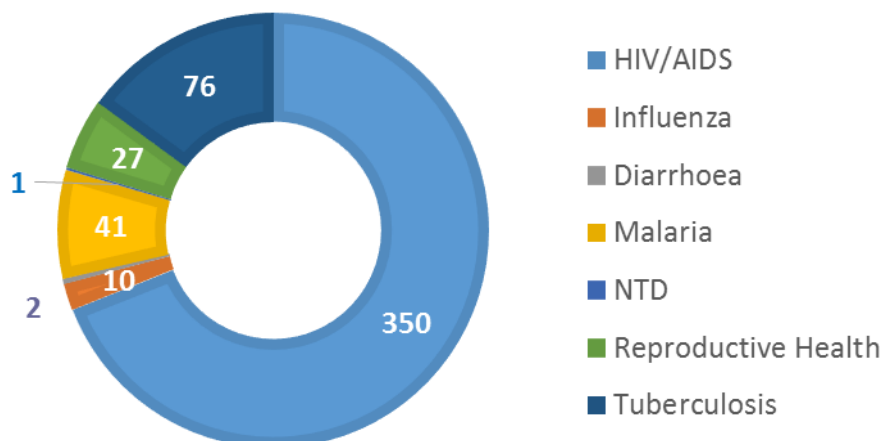


Fig. 3 As of January 2015, 507 medicinal products are listed as prequalified on the PQL (52). More than half of these products are used for the treatment of HIV/AIDS. The first medicine to treat the NTD filariasis (elephantiasis) was included in 2013.

Since the establishment of the PQP and the PQL, drugs also had to be delisted (12). In 2004 an ARV manufactured by the Indian company Cipla was deleted because major deficiencies of the bioequivalence studies concerning this medicine had been detected (12). Later on in the same year, several drugs produced by Ranbaxy, another Indian manufacturer, were delisted for the same reason (12) (64). In 2007, the MA of Viracept, an ARV by Roche, was suspended in Europe because potentially genotoxic impurities had been detected in several batches (65). In consequence, the drug was also delisted by the WHO from the PQL (65).

First it was feared that these delistings might undermine the trust in the PQP (12). However, it turned out the other way round: Since the WHO did not hesitate to exclude products from the PQL, it proved to be a stringent and thus trustworthy organisation (12) (64).

WHO Prequalified Medicines - Authority

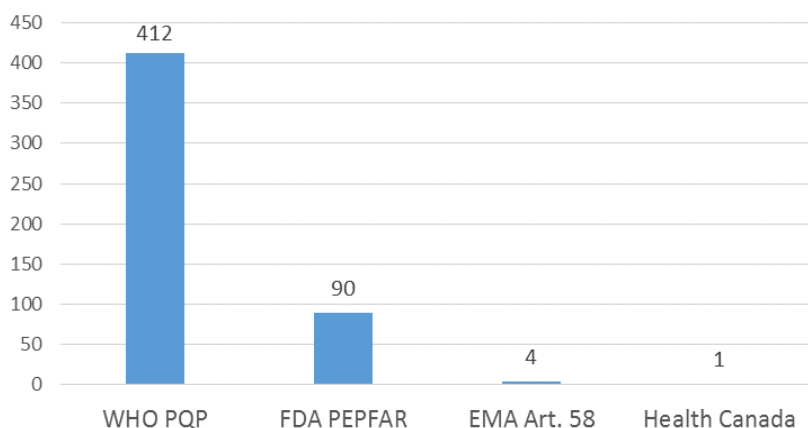


Fig. 4 As of January 2015, more than 80 % of all prequalified medicines on the PQL were assessed by the WHO PQT (412 products). Ninety antiretrovirals were included after a FDA approval according to PEPFAR. Four medicinal products were assessed by the EMA according to Art. 58 of Regulation (EC) 726/2004 and one product was evaluated by Health Canada.

Today almost all medicines for the treatment of HIV/AIDS, malaria and tuberculosis purchased by UN agencies were prequalified previously by the WHO (12). Hence, this adds up to 85 - 90 % of all ARVs, antimalarials and medicines against

tuberculosis procured by the Global Fund, UNICEF and UNITAID (12). This development had a major impact on the availability of safe, efficient and affordable ARVs in developing countries. According to statistics from UNAIDS as of December 2012, 9.7 million people in LMICs received ARV therapy, most of those in sub-Saharan Africa (66) (67). More than 80 % of these medicines are estimated to have been prequalified by the WHO (3) (12).

The increased availability and accessibility is particularly promoted by the tremendous cost decrease for ARV therapy. Within the first ten years of PQP, the price dropped by 99 % for some ARVs: from 10,000 - 15,000 USD per person per year (ppy) to approximately one hundredth of that (3) (12). Consequently, these medicines are now affordable for a much larger patient population.

Another important merit of the PQP was the stimulation of development of fixed-dose combinations (FDCs). These made it possible to reduce the number of tablets that had to be taken by patients and thus enhanced compliance and facilitated dosing (12) (13). Moreover, the defined ratio of the substances guarantees an optimal treatment.

The PQP not only enables UN procurement agencies to more usefully invest their budgets in high-quality products and to reach more people, it even saves money. In 2009 every USD that was invested into the PQP achieved a return of investment of 170 USD (12).

Nevertheless, the programme also has its drawbacks. The most obvious one is that it is more or less restricted to priority diseases defined by the WHO such as HIV/AIDS, tuberculosis, malaria and products used in reproductive health (28). Hence, many current unmet medical needs such as diabetes or cardiovascular diseases are still not being addressed because the respective medicines are not eligible for prequalification (12). However, the description of the procedure reads that prequalification is applicable also to "*other diseases*" (28). This in turn enables the WHO to adapt the indications covered by the PQP according to current needs. Another point of criticism of the PQT refers to limited resources of the PQT itself which slow down the prequalification process and result in extended timelines until the final decision is made (6) (30). In case of a high-quality application and good collaboration with the manufacturer, the PQ procedure may only take some months but also may extend to several years (3) (12).

One further objective of the PQP is capacity building which is particularly important for developing countries. Thus dossier assessments as well as inspections are conducted by teams consisting of WHO staff and members from HICs as well as from LMICs (12) (55). In addition, the WHO regularly organises training workshops. In 2012, more than 300 regulators participated in one of 27 of these workshops (50).

The fact that no or only very small fees are charged for an application for prequalification of a medicinal product is another great advantage for manufacturers (55). This also enables smaller companies to have their products prequalified. This is further promoted by the WHO by offering technical assistance throughout the procedure (28).

A survey of six African countries (Cameroon, Ethiopia, Ghana, Kenya, Nigeria and Tanzania) in 2011 revealed that approximately one third of antimalarial FPPs were of substandard quality (14). This was due to deviating quantities or the total absence of APIs, high amounts of degradation substances or poor dissolution of the FPP (14). Nevertheless, this survey also emphasised the effectiveness of WHO PQP, because fewer than 4 % of prequalified products were concerned (14). In summary, the PQP improved the quality of medicinal products enormously and further led to a tremendous drop in prices of essential medicines (3) (6) (12). Thereby, it became possible for millions of people in the developing world to receive treatment.

The PQP proved to be successful and was consequently extended to other categories. Due to the need to ensure qualified control of procured medicines, the prequalification of quality control laboratories started in 2004 and the PQP for APIs was added in 2010 (12) (13).

Although it is formally not an SRA, today the WHO is recognised as an equivalent to an SRA by many countries. The status of prequalification is thus accepted as some kind of MA to which some NMRAs refer to for granting a national MA (38) (68). This approach in turn is characterised by the same advantages and disadvantages as those of referencing to approvals given by SRAs: The national MA can only be issued after the prequalification is finalised. Furthermore, although the quality of the product is ensured, there is no gain of knowledge or expertise at the NMRA. Moreover, the narrow product range of the PQP is another drawback.

4 The WHO Collaborative Registration Procedure

As outlined above WHO PQP enables UN procurement agencies and other medicine suppliers to purchase safe and efficacious medicines of good quality at reasonable prices. The WHO Collaborative Registration Procedure (CRP) now goes one step further: It aims to accelerate drug registration of prequalified medicines in developing countries and thus to facilitate early access to those medicines for the whole local population (69).

A drug is only prequalified if its quality, safety and efficacy according to international standards are proven. Nevertheless, this product still lacks national MAs in most LMICs, also in those where it is dispensed by UN agencies, and thus cannot regularly be put on these local markets. Therefore, an MA is still a prerequisite in virtually all countries of the world. To obtain an MA, a manufacturer has to apply for registration at the NMRA of the country where it intends to market the respective medicinal product. The evaluation of eligibility for an MA usually comprises two distinct arms in most countries: assessment of a dossier including all product-relevant data and inspections (69). However, as described before, NMRAs have to cope with very limited resources in terms of staff, budget, knowledge and experience. This leads to longer registration times that may even extend to several years, which in turn restricts access to medicines in those countries. A second approach is to recognise decisions and inspections of other NMRAs without conducting the assessment and the inspections again (69). On the one hand, this strategy prevents duplication of work and thus saves resources. On the other hand, it has to be clarified upfront which NMRAs are trusted, a decision that is largely based on similar legislation and regulation. In this context harmonisation efforts may also be requested (69). It also has to be ascertained that the product submitted for registration is the same in all relevant parameters as the product approved by the trusted NMRA (69).

The WHO PQT aims to facilitate and accelerate such drug registration procedures in resource-limited countries, which is why it developed the CRP in 2012 (15) (69). It is intended to counteract the increasing backlog of pending applications for MAs in many NMRAs of LMICs and to make high-quality medicines available more quickly for more patients in need (15) (69). The second objective is building capacity in NMRAs of developing countries (15) (69). The third is to assure procurers that the product approved for use in the respective country is identical to the prequalified one (69).

The first NMRAs joined the pilot phase of the CRP in June 2012 (15) (70). In total, ten NMRAs of different African countries participated in this experimental phase: Botswana, Ghana, Kenya, Namibia, Nigeria, Tanzania, Uganda, Zambia, Zanzibar and Zimbabwe (70). Although Zanzibar is not recognised as a country, this semi-autonomous region of Tanzania has its own regulatory authority, the Zanzibar Food and Drugs Board, which also participated in the pilot phase. As the first months were quite successful, the procedure was officially approved in May 2013 by the 66th WHA taking place in Geneva, Switzerland (15) (71).

The CRP is eligible only for medicines listed on the PQL and those that were fully assessed by the WHO itself (69). Moreover, all inspections must have been conducted by the WHO too (69). Consequently, drugs on the PQL that were evaluated by the EMA, the FDA or Health Canada and other SRAs are excluded from the CRP (69). This is due to the fact that in these cases WHO assessment and inspections have not been organised, respective reports do not exist and thus cannot be shared by the PQT with NMRAs. As the procedure is based on the principle of confidential sharing of these reports with NMRAs, in this case the procedure is not applicable (69).

4.1 Participation in the CRP

The CRP is a completely voluntary procedure and open to all interested NMRAs (15) (71). NMRAs as well as manufacturers have to declare their interest by signing an agreement if they wish to participate (69) (72). With this agreement both parties declare that they recognise and respect the provisions of the CRP (69). For the NMRAs, these comprise amongst others confidential handling of shared proprietary information, accepting documents according to WHO formats and making a registration decision within 90 days after starting the procedure (69) (71). All participating NMRAs are published on the website of the CRP so that manufacturers are able to find out about where the CRP is applicable (72).

The information exchange at the CRP takes place between members of the WHO PQP and one or two designated contact persons (focal points) at the respective NMRA (69). These focal points are the only ones to receive data about the prequalification procedure, i.e. WHO reports about dossier assessments and inspection outcomes that are shared on a secure server (69).

As aforementioned, the CRP is only applicable for medicinal products that have been prequalified by the WHO itself (69). With regard to manufacturers this implies that only those with products already prequalified by the PQT may use the procedure. If a manufacturer is interested in a CRP for a medicine, the WHO PQT as well as the respective NMRA must be contacted and interests expressed (69). As a prerequisite for the CRP, the applicant has to agree that product-related proprietary information is shared between the PQT and the NMRA (69).

4.2 The Collaborative Registration Procedure

For every single product a specific CRP has to be initiated by the manufacturer of a prequalified product (71). Each CRP always refers to only one medicine and one NMRA participating in the programme. For every procedure an additional predefined declaration about the confidential handling of proprietary information must be signed by the respective focal points at the NMRA (69). Otherwise access to the information is denied by the PQT. If the focal points agree, they

are permitted to access the product-related data that were gathered during prequalification by the WHO if the NMRA has accepted a CRP for this product (69) (71).

Another prerequisite is a declaration by the manufacturer that its application refers to exactly the same drug as prequalified and that the identical technical data are submitted to the NMRA (15) (69). This is especially important since the dossier is submitted directly to the NMRA by the manufacturer (15) (69). The authority cannot access the dossier that was previously submitted to the WHO for prequalification (69). Finally, the applicant declares its commitment to follow the post-registration maintenance according to the CRP (69). In case the applicant and PQ holder are not identical, prior to the CRP the single contact point will have to be defined (71).

A schematic overview of the CRP is shown in Fig. 5. A CRP is activated by the interested company submitting an application to the NMRA in the country where it would like to market its prequalified product (69). Such an application consists of different documents: an EoI to initiate the process, a dossier and, if applicable, country-specific data (69). The EoI is a predefined WHO form that has to be filled in by the applicant (69) (72). Hereby, the manufacturer confirms that the product is identical to the WHO prequalified one (69). This refers to the approved dossier including all quality data such as specifications of APIs and the FPP, the description of the manufacturing process as well as analytical methods used for quality control of materials (69). Possible variations and certain parts of the product information are contained as well (69). By signing the EoI, the PQ-holder also agrees to the

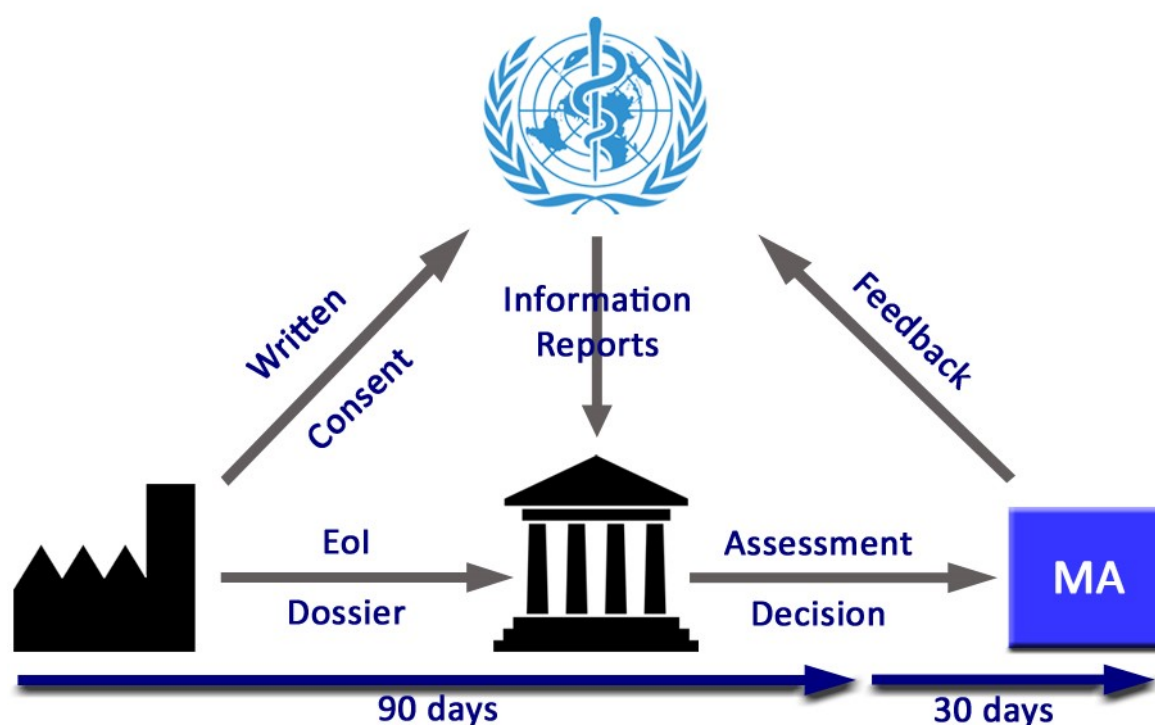


Fig. 5 Schematic overview of the WHO Collaborative Registration Procedure with a positive outcome resulting in a marketing authorisation (MA). The three different stakeholders involved are the WHO PQT, a prequalification holder (manufacturer) and a participating NMRA.

terms of the CRP and to the fact that the PQT may share and discuss proprietary information with the concerned NMRA and vice versa (69). Only data owned by the PQ holder or the WHO are shared by the PQT with the focal points (69). Therefore, in case of generic products clinical and preclinical data cannot be shared by the WHO with the NMRA. These originator data were not assessed by the PQT but by an SRA and, therefore, respective WHO reports are not available. This does not apply to data from bioequivalence studies since these studies are conducted by the manufacturer of the generic product. Furthermore, data from API manufacturers provided to the PQT in form of drug master files are not shared with the NMRA either (15). The dossier of the prequalified product itself is not shared with the NMRA by PQP since this is submitted separately and directly to the NMRA by the applicant (15) (69).

If the NMRA requests country-specific data to be submitted together with the application, the respective requirements have to be defined and published so that the applicant can address them (69). This may concern, for instance, administrative data and product information or labeling with regard to language and format (15). Furthermore, it is possible that additional data are required, such as bioequivalence data that compare the prequalified product to a specific local medicine in the country (15). Nevertheless, such deviations are only acceptable due to exceptional circumstances and within a restricted scope (15). In any case, country-specific requirements must not concern quality and clinical properties such as indications (15) (69). Although there may be specific local provisions regarding the format of some documents for regular drug registration, the NMRA agrees to accept WHO compliant formats for each CRP, e.g. the CTD format of application dossiers (58) (69). Other issues not determined by the WHO but by the local NMRA are fees and product samples (69).

Parallel to the submission of the EoI at the NMRA, a copy of it has to be sent to the PQT (69). Preferably, the EoI is submitted to both institutions before the actual application is filed since this enables both to plan resources for the upcoming CRP (69). The PQT additionally requires a written consent (predefined form) from the applicant that permits the confidential sharing of assessment and inspection reports with the concerned NMRA (69) (72).

In a second step the NMRA decides if it starts a CRP for this specific product and afterwards informs both PQT and the applicant about its decision (69). Again this is done by a predefined form (69) (72). If the NMRA rejects to apply the process for the specific application, no CRP is initiated. In case the NMRA accepts to activate a CRP, it requests the latest product-related information from the PQT (69). This includes assessment reports of the dossier as well as variations and inspection reports of the manufacturing sites (69). The reports are provided including annotations by the PQT and further include related questions from the PQT and the respective answers given by the manufacturer (71). These data can be accessed only by the focal points via a password-protected website hosted on a secure server (69).

Based on the provided information by the WHO and the dossier submitted by the applicant, the NMRA decides whether to authorise the medicinal product or not. This decision must be taken within 90 days after provision of all information by the PQT (69). The NMRA has several

options with regard to this decision: It can directly recognise the outcome of the prequalification or assess the documentation on its own, partially or in total (69). Nevertheless, the WHO recommends not to perform another full assessment since this would only be a duplication of work and does not correspond to the idea of collaborative registration (69). It recommends a “pragmatic approach” and to an evaluation only of data that may be of particular interest to the respective country in view of the local situation such as disease burden or typical comorbidities (69). In this context, the NMRA may also perform its own risk-evaluation. In addition to the regular reports, it is possible to request supplementary information from the PQT or discuss any ambiguities with it (69).

In the last step of the CRP the NMRAs informs both, the PQT as well as the applicant, about its decision within 30 calendar days by using another predefined form (69) (72). The NMRA may always decide sovereignly if an MA for the product in question is granted, independently from the outcome of the WHO prequalification (69). However, if the NMRA opinion differs from the WHO PQ assessment, this has to be justified to the PQT (69). In case of an adoption of the WHO opinion, the product is published on the list of products registered through the WHO collaborative registration procedure (CRL) on the CRP website (69) (72) (73).

During the CRP, the NMRA as well as the applicant may cancel the procedure at any time but have to inform the PQT and the applicant or the NMRA in written form respectively (69). From this point on, the NMRA no longer has access to the product-related information on the secure server.

The CRP also regulates post-registration activities such as the handling of variations. These have to be submitted in accordance with the WHO guidelines on variations to a prequalified product (61) (69). Following this, variations have to be submitted to the PQT as well as to all concerned NMRAs where the drug has been registered via the CRP or is still under assessment. This is aimed at having as few differences as possible between the particular national MAs and the prequalified product (69) (71). Variations are primarily assessed by the PQT and resulting reports are again shared directly with the concerned focal points via the access-restricted website (69). According to the previous pre-registration procedure all NMRAs may now evaluate the data and will inform the PQT about their opinion within 30 calendar days (69). Similar to the process of registration, the NMRA may agree with the WHO PQT in total or partially or even decline the application for variation (69). If the opinions of PQT and NMRA differ and the NMRA decides not to adopt the outcome of the PQT, the medicinal product is no longer identical to the prequalified one and is consequently deleted from the CRL (73) (69). From this moment on, the drug is independent of the lifecycle of the prequalified product and in consequence from the CRP. Thus, the NMRA alone is now responsible for the future regulatory handling of the product’s lifecycle within their country.

Two products are no longer considered identical if there are differences with respect to quality (e.g. specifications, manufacture) or clinical properties (e.g. indications, posology) (69). Deviations that do not result in a delisting include differences of the brand name or of some

aspects of the product information such as language or format that may be due to local requirements (69).

Another scenario during the lifecycle of a prequalified product is the suspension or withdrawal of its prequalification status or MA respectively. As soon as a product is delisted from the PQL it is subsequently also deleted from the CRL since a parallel lifecycle management of prequalified product and CRP-registered product in the respective countries is no longer possible (69). Consequently, collaboration may no longer take place between the PQT and the NMRAs. In this case, the PQT informs all concerned NMRAs about the deletion of the product from the PQL and CRL via the secure website. However, the delisting of the PQL does not necessarily lead to a suspension or withdrawal of the national MAs. If an MA of a CRP-registered product is suspended or withdrawn nationally by an NMRA, the authority also promptly informs the PQT outlining the underlying reasons as well (69). This information is then again forwarded by the PQT via its website to all other concerned NMRAs that received an application for this product or that already issued an MA for it (69). Depending on the reason for suspension or withdrawal of the MA, the NMRAs and the PQT decide about the consequences with regard to this product.

4.3 Development and Current Situation

The CRP approach offers the advantages of a fast market access for pharmaceutical companies as well as the possibility of capacity building at local regulatory authorities in developing countries. The NMRA decides case by case if it agrees totally with the PQP outcome or if it deviates from its opinion.

Collaboration during the CRP mainly takes place between the PQT and the NMRAs (69). Regulators and inspectors of participating NMRAs receive access to data gathered during prequalification and they may request additional information and explanations from the PQT (15). This in turn helps to expand the local regulators' knowledge. Based upon the provided data, the NMRA can take its decision sovereignly and independently of the WHO opinion and may even deviate from the WHO opinion (69).

Due to the promising pilot phase of the CRP in 2012, the procedure received its approval by the 66th WHA (15) (71). Since then the CRP has been open to all WHO member states and now operates routinely although there are still some difficulties that have to be addressed (15). As of January 2015, 23 NMRAs participated in the CRP of the WHO PQT, among them 18 African ones (72). In 2013, Georgia, Kyrgyzstan and Ukraine joined the programme as the first non-African countries. Madagascar and Mozambique were included in the CRP in the same year. Armenia, Burkina Faso, Cameroon, Côte d'Ivoire, the Democratic Republic of the Congo (DRC),

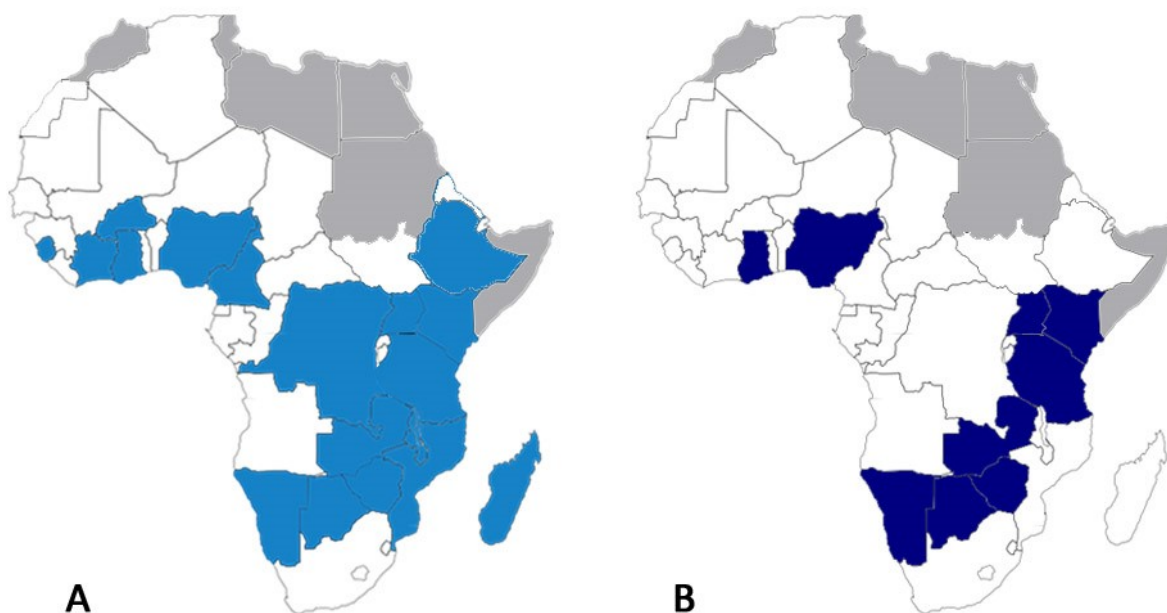


Fig. 6 Map of Africa with highlighted countries participating in the WHO Collaborative Registration Procedure (**A**, light-blue) and those countries where FPPs according to this CRP have already been authorised (**B**, dark-blue) (January 2015). The grey-coloured countries do not belong to the WHO African Region as defined by the WHO, but to the WHO Eastern Mediterranean Region.

Ethiopia, Malawi and Sierra Leone signed their participation agreements in 2014 (72). Therefore, roughly one third of all African countries are now participating in the CRP (Fig. 6A).

The four non-African countries currently involved in the programme are located in Eastern Europe (Ukraine), the South Caucasus (Armenia, Georgia) and Central Asia (Kyrgyzstan).

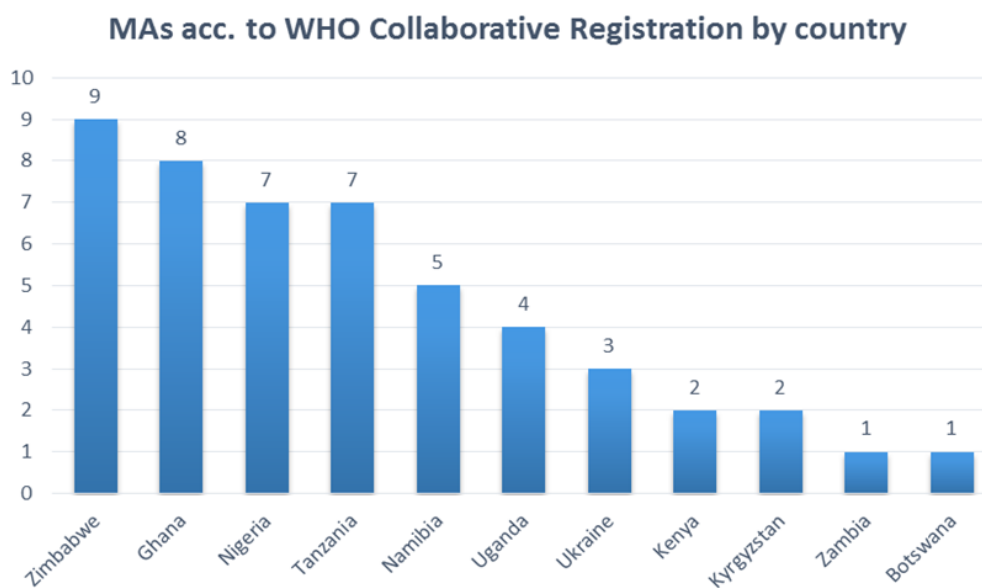


Fig. 7 Numbers of marketing authorisations issued by NMRAs as a result of a WHO Collaborative Registration Procedure by country (January 2015).

According to the World Bank's definition, all four countries are lower-middle-income economies with a GNI per capita between 1,046 USD and 4,125 USD (1).

As of January 2015, 49 national MAs were granted according to the WHO Collaborative Registration Procedure for 26 products in 11 countries (73). Forty-four of these MAs were issued in African countries. Hence, 9 out of 19 participating African NMRAs have already applied the WHO CRP successfully (Fig. 6B). To date, the greatest number of products has been authorised in Zimbabwe (9 medicines), followed by Ghana (8), Nigeria and Tanzania (7 respectively), Namibia (5), Uganda (4) and Ukraine (3). In Kenya and Kyrgyzstan 2 MAs were granted as well as one MA in Zambia and Botswana respectively (Fig. 7) (73).

To date, drugs for the therapeutic areas HIV/AIDS (13 different products), tuberculosis (8), malaria (3), the NTD filariasis (1) and reproductive health (4) have been registered (73). As of January 2015, no medicinal products for the treatment of influenza were authorised in any country according to CRP.

The first MA was granted for an oral contraceptive of Famy Care Ltd on January 31, 2013, in Kenya (73). Famy Care Ltd is an Indian company producing generic reproductive health care products for women.

By January 2015, ten different prequalification holders had registered products successfully using the CRP (Fig. 8). Most of these companies were Indian manufacturers of generic FPPs (70 %): Cipla Ltd, Famy Care Ltd, Cadila Pharmaceuticals Ltd, Hetero Labs Limited, Macleods Pharmaceuticals Ltd, Mylan Laboratories Ltd and Ranbaxy Laboratories Ltd (73).

These companies hold 92 % of all granted MAs resulting from a CRP (January 2015). Further MAs were obtained by DNDi (Switzerland), Dong-A Pharmaceutical Co Ltd (South Korea) and Eisai Co, Ltd – Japan (Japan) (73).

A retrospective analysis of the CRP project was done by the WHO in the first quarter of 2014 (15). At that time 46 EoIs had been submitted to participating NMRAs as well as to the WHO for 26 prequalified products (15). Out of these EoIs 12 had been rejected since an application for an MA of the respective products had already been under assessment (15). This seems to be the principal reason for rejection of applications for a CRP. The CRP is principally designed for new applications for an MA, however several EoIs had been received for pending products (15). In those cases the manufacturer had filed another application according to the CRP since the first regular application at the NMRA had not been finalised for a long time. The manufacturer thus hoped to speed up the process of registration of the respective product. Some of the dossiers submitted had not been processed for more than one year which illustrates the massive backlog in many NMRAs (15). Depending on the progress of the respective assessment, the CRP application was accepted or rejected by the NMRA.

Products authorised acc. to WHO CRP by Therapeutic Area

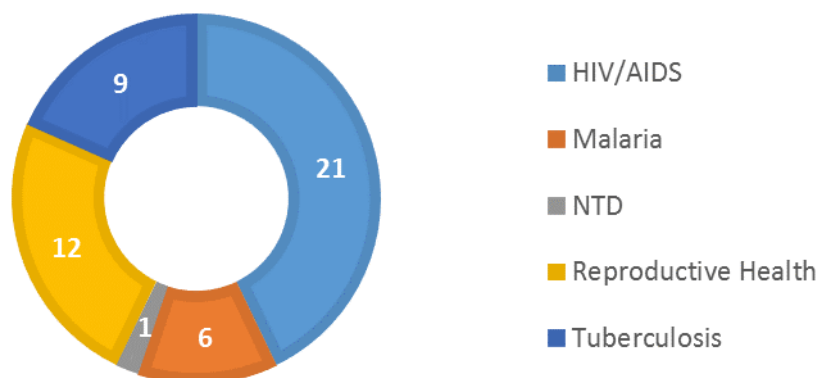


Fig. 9 Absolute numbers of granted national marketing authorisations according to the CRP by therapeutic area (January 2015).

The analysis conducted by the PQT regarding the first 21 months of CRP until March 2014 further concerned the duration of the procedures. The study revealed that a majority of 87 % of all assessments processed at the time was finalised within the foreseen timeframe of 90 days, half of them even within less than 60 days (15). Only 2 out of 16 procedures took longer: 111 and even 182 days (15). There were some delays with regard to CRPs in Uganda due to the fact that initially no approving board was established at the local National Drug Authority (74). Further delays were reported due to the fact that some NMRAs did not always promptly recognise the submission of an application via the secure website which postponed the initiation of a CRP. In consequence this should be addressed in more detail together with the NMRAs. Probably general problems, such as reported from one focal point in Sierra Leone, with respect to technology and internet connectivity in developing countries also play a major role (75). Moreover, the password-protected website as well as online forums or the process

MAs according to WHO CRP by Prequalification Holder

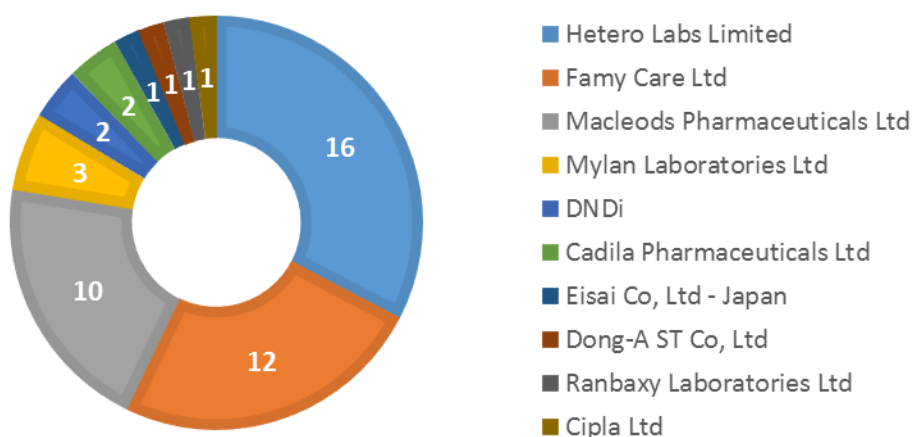


Fig. 8 Absolute numbers of granted national marketing authorisations according to the CRP by prequalification holder (January 2015).

of information sharing via the website was said not to be user-friendly enough which caused communication problems between the PQT and the NMRAs (15).

Not all NMRAs involved in the programme already had the chance to gain first experiences. Several authorities such as the ones in Armenia, Georgia, Côte d'Ivoire or Madagascar have not yet received any EoI for a CRP (20) (25) (26) (76). In some cases this may be merely due to the fact that the NMRA joined the programme only very recently like the one in Côte d'Ivoire. But there are also other reasons: According to Chipala from the Pharmacy, Medicines and Poisons Board, the regular drug registration in Malawi usually takes no longer than three to six months (17). In consequence there is no major advantage for pharmaceutical companies in using the CRP. Moreover, in this case the high quality standards that have to be fulfilled for WHO prequalification may even discourage manufacturers from using the CRP since these are considered even more stringent than those of the EMA or the FDA (13). *"The other reason could be that the Malawi market is so small with a population of about 16 million people. Hence, manufacturers may want to take advantage of the procedure of fast track registration in countries with both, large markets and long registration timelines."* Chipala assumes (17).

Zanzibar is in a special situation. This island is not an independent country but belongs to Tanzania. *"Tanzania is a Union of Tanganyika, nowadays called Tanzania Mainland, and Zanzibar. With regard to its market Zanzibar covers a smaller area with a little population. Thus, most of the manufacturers prefer registering their medicines in Tanzania since these may also be marketed in Zanzibar."* explains Mohammed Simba, Chief Drug Inspector at the Zanzibar Food and Drugs Board (27).

Nevertheless, the majority of participating NMRAs have received applications for CRPs although sometimes fewer than anticipated. Moreover, all interviewed contact persons at involved NMRAs were in principle very satisfied with the programme and appreciated being able to participate. Amongst others the NMRAs of Tanzania and Nigeria declared that their expectations were met (22) (77). *"Our expectations have been fulfilled."* says Michael Romeo Mutyaba, Head of Drug Assessment & Registration at the National Drug Authority (NDA) in Uganda (74). *"All products submitted to NDA under the collaborative procedure have been registered."* (74). Mutyaba further reports that applicants also welcomed the CRP since it shortened the timeline for drug registration in Uganda (74). Most of the applications received concerned ARV medicines which is also evident on the CRL (73). *"By now we have received seven submissions. Most products are medicines against HIV/AIDS and one is for reproductive health. Five assessments are completed, but the QC analysis of samples still needs to be done."* declares Abdulkadir Fato from the Food, Medicine and Healthcare Administration and Control Authority of Ethiopia (EFMHACA) (24). He further states, to date, no applications were rejected or procedures cancelled (24).

In principle the prospects of the NMRAs with regard to their participation in the programme are very similar and match the aims of the CRP: acceleration of drug registration despite resource limitations, thereby faster availability of high quality and essential medicines for

people in need and, in addition, expansion of knowledge and expertise of local regulators and inspectors (15). *"Malawi decided to join the procedure due to challenges in human resources."* explains Chipala (17). The CRP allows for a tremendously shorter assessment time of an application. Since the NMRAs can rely upon the dossier evaluation and inspections conducted by the WHO, which is considered an "SRA", the decision about an MA can be made relatively quickly. *"The collaborative procedures will help us to benefit of the expertise of the WHO prequalification group for decision making and save the time for the assessment."* confirms Kabey from DRC (16).

The local regulators benefit from the PQT expertise in several ways: They receive access to WHO assessment reports as well as to related additional information and may contact members of the PQT at any time when questions arise or ambiguities require discussions (15) (69). Thereby, the CRP promotes capacity building in participating NMRAs. This is already an important aspect of the PQP where local assessors and inspectors are involved in dossier evaluations and site inspections. For instance, the NMRAs of Zanzibar and DRC report that the local expertise has already grown since joining the CRP (16) (27). This is further promoted by trainings and workshops organised by the WHO (15) (16). *"The training exposed the responsible officers to the structure of CTD dossiers. They also acquire review skills through attendance of WHO training programmes in Copenhagen, Denmark."* explains Uchenna Moronu from the National Agency for Food and Drug Administration (NAFDAC) in Nigeria (22). *"We consider the knowledge we have gained as a big plus. However, we need more training for our officers regarding dossier review."* Moronu adds (22). Such regulatory workshops are organised regularly by the WHO. In addition, every two months a joint prequalification assessment session takes place in Copenhagen at the UNICEF offices that further builds and deepens regulatory knowledge and contributes to a common understanding and approach of dossier assessments of PQT and NMRAs (15) (71). As aforementioned, special rotational fellowships were also established at the WHO headquarter in Switzerland. As of March 2014, employees of seven NMRAs taking part in the CRP have already worked with the PQT on site in Geneva (15).

It is also important to note that the information provided by the WHO PQT is reliable. In consequence there is no need for detailed verification which avoids duplication of work and, in addition, familiarises NMRA staff with stringent international quality standards.

The respect of the NMRAs' sovereignty is another aspect of the CRP. Although the procedure is only applicable for prequalified products that were assessed by WHO PQT and thus proved to be compliant with very high international quality standards, it is still the prerogative of the NMRA to decide if the medicinal product is also granted a national MA (69).

Although most of the participating NMRAs consider the CRP a positive development and would not change anything, some also mention potential improvements of the programme. A major drawback is the restriction to medicinal products for only a few therapeutic areas. This is a consequence of the reference to prequalified products. Therefore, some NMRA suggest

the inclusion of more drug categories. Another issue are country-specific requirements with regard to the expected timelines. In Kenya for instance it is mandatory to perform an analysis of product samples before the drug can be registered (78). However, this may not always be possible within the given timeline of the CRP depending on the available resources (78). One NMRA regrets that currently not all pharmaceutical companies are yet aware of the CRP and are therefore not likely to use this approach. It is further criticised that there are no incentives for the focal points at the NMRAs. Although this role is associated with a lot of work, this seems not to be recognised adequately.

To date, only some experience with post-registration maintenance of prequalified products registered via the CRP could be collected. This is why one of the priorities of the PQT with regard to the CRP is to establish more detailed guidance in future.

5 Discussion

In almost every country of the world NMRAs require medicine registration. This enables them to control and monitor medicinal products circulating on the market. However, drug registration is generally a very resource-demanding process. The product's quality, safety and efficacy must be proven by a detailed dossier including all relevant scientific data about CMC, preclinical and clinical studies. Moreover, prospective risk monitoring and management are increasingly within the NMRAs' area of responsibilities. These complex and comprehensive data should be assessed thoroughly by adequately qualified staff at the NMRA, which often takes several months or even years. Ideally inspections of the manufacturing sites, laboratories and clinical trial sites take place simultaneously to guarantee compliance with predefined standards (e.g. GMP, GCP).

Accomplishing these tasks is already challenging for NMRAs in industrialised countries not to mention those in LMICs. The majority of NMRAs in LMICs does not manage to perform sophisticated data evaluation and to conduct all necessary inspections due to very limited resources in terms of staff, expertise and funding. In 2010 for instance, an assessment of the WHO revealed that 90 % of all NMRAs in sub-Saharan Africa were unable to carry out their essential regulatory functions (7). Globally an estimated two thirds of all countries lack any adequate and operational drug regulation (21). Due to weak or even absent regulatory oversight, the detection of circulating substandard or counterfeit drugs is hindered enormously or virtually impossible (30). This is why low-quality medicines can still be found in many countries worldwide, particularly in developing ones (5). To counteract this, NMRAs first of all need to know which drugs are present on the market. Therefore, drug registration and hence an MA is a prerequisite for distribution of medicines within a country. Usually, there are two aspects of drug registration that help identify low-quality drugs: Firstly, the assessment of the product's benefit-risk-ratio and quality before it may be put on the market. Secondly, the post-approval monitoring of both aspects throughout the medicine's lifecycle. All the time the quality must be appropriate and the benefits must outweigh the risks of the drug within the respective context (e.g. severity of disease). The regulation of distribution and dispensation further reduces the risk of counterfeit drugs within the distribution chain.

Commonly NMRAs use two distinct approaches to identify safe and efficient medicines of good quality. On the one hand, the NMRA itself assesses all data and conducts the necessary inspections. On the other hand, the NMRA may consider the outcome of an evaluation performed by another authority or organisation (69). As aforementioned, NMRAs often are not able to accomplish their regulatory functions appropriately due to existing resource constraints. The already very time-consuming process of drug registration is thereby extended even more. In addition, some NMRAs receive too many applications to address within an acceptable timeframe which in turn leads to massive backlogs as reported for instance from Uganda and DRC (16) (74). Trying to accelerate the review process, MAs are often issued without a sophisticated dossier assessment and without conducting any inspections (6). This

in turn counteracts the objective of drug registration and is discouraging for all stakeholders in the process: the manufacturer and the NMRA and the concerned patient population. Manufacturers have to cope with extended times-to-market and a lack of planning certainty, especially with regard to their return of investment. The NMRAs are not able to fulfil their designated tasks and consequently, patients do not have access to the medicines they need.



Fig. 10 The different stakeholders of the Collaborative Registration Procedure (CRP) of the WHO Prequalification Programme: WHO, manufacturers, NMRAs and patients.

Beyond these restrictions most resource-limited countries

simultaneously have to cope with a high disease burden (7). For instance, African countries struggle with large numbers of people affected by HIV/AIDS, tuberculosis or malaria (21). As of 2013, approximately 35 million people globally were infected with HIV, 70 % of them living in sub-Saharan Africa (79). Estimates show that only about 34 % of these HIV/AIDS patients received ARV therapy (79). However, at the turn of the millennium the situation was even worse: In 2000 only 1 out of 1000 HIV/AIDS patients had access to ARV therapy (51). Moreover, the medication was almost exclusively available in HICs and extremely expensive (10,000 to 15,000 USD per person per year) (80). As a consequence, ARVs were unaffordable and virtually inaccessible for patients in developing countries. In the following years different attempts were made to provide ARV therapy to a larger number of HIV-infected people and to reduce its high prices: e.g. the “3 by 5” campaign by the WHO (3 million ARV-treated patients by 2005) or the PEPFAR by the US government (3) (12). These objectives were also followed by the WHO PQP that was launched in 2001 (5). However, this programme focused not only on HIV/AIDS but also on other priority diseases such as malaria and tuberculosis.

5.1 Achievements

The PQP enabled UN procurement agencies to purchase high-quality medicines for patients in developing countries at reasonable prices. The unintended distribution of substandard and counterfeit drugs by UN procurers was avoided or at least reduced. Due to the fact that almost all prequalified medicines were generics, the price could also be lowered significantly.

The PQP also created new incentives for manufacturers of generic medicines. These usually realise less profit than innovative products and, additionally, some of the essential medicines like rifampicin for the treatment tuberculosis or artesunate used against malaria are quite complex to manufacture (6). Consequently, pharmaceutical companies are less interested in

their production (6). Nevertheless, the PQP raised interest in manufacturing generics since UN agencies purchase prequalified products that are mainly generics in large amounts for several billion USD a year (56). Thereby, prequalification of a generic medicinal product may lead to a significant return of investment for the manufacturer. Another major achievement of the cooperation between PQP and pharmaceutical companies was the development of FDCs that were only produced by generic manufacturers. Those FDCs enhanced patient compliance and simplified the supply chain (3) (12).

In addition to the PQP the PEPFAR-linked (tentative) approval of HIV/AIDS drugs in the USA also contributed tremendously to the accessibility of ARVs in developing countries and to their price drop (38). In combination with other measures the price of many essential drugs could be lowered essentially. For instance, today some HIV/AIDS medicines cost 99 % less than what they cost around the year 2000 (13).

The drug assessment at the EMA according to Art. 58 of Regulation (EC) 726/2004 had less influence compared to the PEPFAR since only very few medicines have been evaluated there to date. All three approaches by the WHO, the FDA and the EMA, have in common that they can verify appropriate quality, safety and efficacy of the medicine. However, none of them results in national MAs. Thus, the actual availability and accessibility of medicines for the local patient population in resource-restricted countries remain unchanged. The product is still not included in the regular distribution chain and hence outside the national health system. These approaches are mainly intended and used for procurement decisions by UN agencies and other international procurers.

5.2 Drug Registration in Developing Countries

To foster drug registration despite constrained resources, some NMRAs in poor countries rely on SRAs in industrialised countries. According to the decision of an SRA about a medicinal product, the NMRA grants or denies an MA in its country. The advantage of this approach is that the workload for regulators in resource-limited NMRAs is reduced enormously while the quality of the product meets high international standards. Nonetheless, this concept does not take into account that disease burden and consequently the medical need in HICs and LMICs often differ significantly. Therefore, medicines urgently needed in developing countries are not registered at all by SRA as there is no existent medical need in HICs (e.g. products for the treatment of NTDs), which eliminates the option of referencing to an SRA approval in such cases. Furthermore, it cannot be ensured that the dossier submitted at the SRA and the one at the NMRA are identical because the NMRA may not access the data submitted to the SRA and vice versa.

Since the process of prequalification is very similar to drug registration at SRAs, some NMRAs also consider prequalification of a medicine as a regulatory approval to which they reference before issuing an MA (81). The WHO PQP is even recognised as being more stringent than any

other SRA (13). In 2005 Ethiopia, Nigeria, Tanzania and Uganda rejected applications for MAs of a generic ARV because this drug had not been prequalified, although it had been approved by the FDA (68). Nevertheless, the PQT emphasises that the WHO is not a regulator and does not want to replace the NMRAs or their respective medicines registration procedures (15).

Although the aforementioned different approaches aim to facilitate access to medicines for patients in need, none of them results in national MAs which are the prerequisite for marketing, distribution and dispensing medicines in a country. This deficiency is now compensated by the CRP.

Based on the PQP, the CRP is an accelerated registration procedure eligible exclusively for prequalified drugs assessed by the PQT itself. The CRP entails several benefits for all its stakeholders. With regard to the manufacturers it offers the advantage of short times-to-market. In most cases this period is reduced significantly compared to the regular national timelines. The PQT reports 12 cases in which applications at NMRAs had been pending for more than one year (15). The applicants then decided to submit new applications for these products according to CRP to accelerate their registration (15). These examples demonstrate the sometimes massive backlogs at NMRAs as well as the potential of saving time by using the CRP. However, some NMRAs also report that regular medicines registration usually does not take longer than three to six months (e.g. in Malawi) (17). Thus, in comparison the CRP offers no real advantage for manufacturers with regard to registration times. It may even discourage applicants since the WHO time of prequalification is frequently about 18 months, requirements are higher than the local ones and initiation of a CRP after prequalification can be a loss of time. Because of that, some companies favour the strategy of parallel submissions to the PQP and NMRAs. In this situation national registration sometimes can be achieved before prequalification. However, if local drug registration is not achieved before the product is prequalified, these companies try to switch the national registration process to a CRP afterwards. This strategy can lead to shorter registration times, but total regulatory investment is higher. Moreover, the national MA is not synchronised with the prequalified product and additional MAs of the product in other countries. It also can be assumed that the national assessment of the NMRA within three months is largely administrative and thus cannot guarantee that only drugs of good quality are authorised. Since only prequalified medicines are eligible for CRP this uncertainty can be eliminated by applying this procedure.

The NMRAs also benefit from further aspects of the CRP. First of all, this accelerated registration procedure enables them to save resources and quickly grant MAs while the drug's quality, safety and efficacy are ensured. Moreover, the NMRA is reassured that it receives a dossier concerning the same product as was prequalified. This refers for instance to the manufacturing process, specifications of APIs and finished product, quality control and the key product information (e.g. indication, contraindications, safety information) (69). Even more, the NMRAs profit from a lifecycle synchronised with the prequalified drug. Since maintenance often ties significantly more resources than new applications, the positive effect of work-sharing is probably more experienced during post-approval lifecycle management. The time

saved for assessment of this medicine can be invested elsewhere, e.g. in the evaluation of regular applications for MA submitted to the NMRA, capacity building or the establishment of more stable and sustainable structures within the NMRA (15). The WHO clearly states that it does not intend to replace the NMRAs' drug registration but to complement it (15).

5.3 Capacity Building

Almost all NMRAs report that there is no specialised training for regulators and assessors within their country. Only Uganda and Ethiopia mentioned that, at the moment, there are university courses concerning drug registration exist or at least plans for such courses (24) (74). In consequence most regulators are trained on the job at the NMRA either by more experienced colleagues or by learning by doing. This can cause difficulties since these NMRAs principally lack qualified staff, structure and a solid legal framework.

Therefore, capacity building at the NMRAs is another main objective of the WHO which it follows within the PQP and the CRP programme even though in different ways. During prequalification, the staff of the NMRA is involved in inspections and dossier assessments. Both are completed in teams including experienced WHO- and SRA assessors as well as those from developing countries. On the one hand, this collaboration broadens the knowledge and experience of NMRA regulators. On the other hand, it recognises their local expertise, especially with regard to diseases mainly prevalent in developing countries. In addition, the WHO organises trainings and workshops regularly as well as joint dossier assessments. This is appreciated by the local regulators: *"We would like to continue with the collaborative procedure because we still have a lot to learn and the collaboration helps to improve the quality and speed of our assessment."* confirms Moronu from the NAFDAC in Nigeria (22).

All these measures mentioned above actively promote capacity building at NMRAs. In contrast, learning by applying the CRP is more optional and less proactive. Regulators and inspectors of NMRAs receive access to WHO assessment reports and thus have the opportunity to comprehend the decision making process of the PQT and its regulatory base. Moreover, it is possible to discuss unclear scientific matters with the WHO. Nevertheless, the NMRA may also choose not to refer to these options at all and merely adopt the PQP outcome without further verification. This could be considered a drawback of the CRP since in this case no gain of knowledge or experience takes place at all.

Capacity building is also promoted proactively by the FDA during PEPFAR-linked procedures. The FDA collaborates with NMRAs so that they get some insight into the decision making process of the authority and understand the underlying science and regulation (38). Indirectly this approach is followed by the EMA during Art. 58 procedures too, since these include the involvement of WHO teams with regulators from NMRAs in resource-restricted countries.

5.4 Collaboration and Work-Sharing

In addition to advantages for the single stakeholders, the CRP also offers benefits in a more global context. Due to the continuously growing complexity in drug regulation and the resulting requirements, NMRAs and manufacturers of industrialised countries also struggle with a shortage of resources. This holds especially true for pharmaceutical companies that intend to market their products worldwide. Due to the fact that every country regulates medicinal products on a national level, there is an extremely high number of varying regulatory requirements which in turn leads to a tremendous workload for companies that need to address those. Moreover, there is an ongoing development towards more and more detailed and sophisticated regulation due to constant progress in science and technology (82). Since the number of globally oriented companies is rising, the number of applications for drug registration at NMRAs is increasing too. This subsequently leads to a higher workload for regulators at the local authority. In summary the regulatory burden for both, manufacturers as well as NMRAs, is constantly increasing and tying up resources. Hence, the major challenge of the future will be the optimisation and prioritisation of regulatory activities to cope with available resources.

This reduction is one of the major objectives of the CRP. It is a perfect example for regulatory cooperation and work-sharing that decreases the duplication of work for manufacturers as well as for regulators and inspectors (13). This is achieved with the NMRAs' acceptance and recognition of the PQT's dossier assessments and inspections. In consequence, a repetition of work already accomplished is prevented which in turn benefits all stakeholders.

Consideration of assessments and inspections conducted by other authorities is common practice today although still in the early stage of development. Hereby, unilateral and mutual recognition procedures must be differentiated. The CRP as outlined above is a unilateral recognition procedure: The individual participating NMRAs may recognise the outcome of prequalification but not vice versa. The PQP does not consider inspections, dossier assessments or decisions of these NMRAs. Due to resource constraints and the absence of international standards these authorities are unable to accomplish their regulatory tasks. Some NMRAs in developing countries also reference to SRAs in the industrialised world, such as the EMA, the FDA or Health Canada. Hence, these NMRAs adopt the SRA's approval or rejection and authorise or decline the respective drug accordingly. Nevertheless, this approach is chosen only by few NMRAs (7) (83). In contrast to such one-sided considerations, mutual recognition procedures work bidirectionally: Participating NMRAs equally recognise each other's assessments and inspections. Such procedures exist for instance within the EU. Therefore, comparable standards are needed as a common base for successful bilateral mutual recognition. This in turn can be achieved by harmonisation.

5.5 Harmonisation

There are several harmonisation efforts on different regional levels worldwide: e.g. within the EU, the Arab region (Cooperation Council for the Arab States of the Gulf), Africa (African Medicines Regulatory Harmonization Programme, AMRH) or more globally the ICH that aims to harmonise regulation between the EU, the USA and Japan.

Drug regulation in the EU may serve as a good example for successful harmonisation. In all 28 member states of the EU national laws regulating medicines registration within the respective country are in existence. Additionally, there is a common legal framework for European medicine legislation issued in form of regulations (directly binding for every member state), directives (must be implemented into national law) and soft law (e.g. guidelines, best practice papers) which apply to European procedures. There are three different types: Centralised Procedures (CP), the Decentralised Procedures and Mutual-Recognition Procedures. The CP is mandatory for specific therapeutic areas (cancer, diabetes, neurodegenerative diseases, AIDS, further viral diseases, autoimmune diseases and other immune dysfunctions), advanced therapy medicines, biotechnologically manufactured medicines and orphan medicines (34). By applying the CP, an MA valid for all 28 EU member states can be received for a single medicinal product. In addition, MAs also for Norway, Iceland and Liechtenstein, all three belonging to the European Economic Area (EEA), are granted. The major advantage of the European procedures is that all lifecycle management of a medicine is synchronised and, consequently, the product is the same in all EU countries. Every variation concerning a centrally authorised drug is submitted at the EMA and concerns each national MA equally. Product information texts do not vary from country to country except for additional specific national requirements. This advantageous situation is also achieved by the CRP: The prequalified medicinal product and the national registered product are in principle identical, and so are all relevant parts of their product information texts.

Recently there have been similar harmonisation attempts in Africa: The AMRH was established in 2009 and aims to harmonise the regulatory environment across the continent with the objective to promote and protect public health of all African people (82) (84). Nevertheless, this programme is still at the beginning and far away from a common Pan-African legislation similar to the European one.

One of the associations participating in the AMRH is the East African Community (EAC). It was re-established in 1999/2000 by Kenya, Tanzania and Uganda and later joined by Burundi and Rwanda (85). The EAC was the first African economic community aiming to achieve regulatory harmonisation on a transnational level. Since 2010 several joint assessments of applications for prequalification have taken place with regulators from the EAC under WHO PQT leadership (83). Such joint assessments bring together the regulatory expertise of experienced WHO assessors and knowledge about the local situation necessary for an appropriate benefit-risk-evaluation of African regulators. The first product was assessed in a joint review by the WHO and the EAC in 2010 and was finally prequalified and subsequently registered relatively quickly

in all EAC member states (Kenya, Tanzania and Uganda at the time) (3). This example demonstrates that pooling expertise and resources also supports the establishment of a common understanding which can accelerate medicines registration. Furthermore, this may serve as a good basis for future harmonisation.

5.6 Post-Registration Maintenance

The CRP also includes provisions concerning the lifecycle management of the medicines registered applying this procedure. All post-registration maintenance is mainly based upon the “WHO guidelines on variations to a prequalified product” which is very much in accordance with the European variation classification guideline (61).

The WHO aims to keep the prequalified product as well as the related national medicinal products synchronised. Variations have to simultaneously be submitted to the PQP as well as all concerned NMRAs where the product was registered according to a CRP. The PQT then evaluates the data and provides assessment reports to the NMRAs involved. The NMRAs now each have 30 days to fully adopt the outcome of the PQT or to fully or partially assess the data themselves (86). However, “*participating authorities are encouraged to follow the outcome of the WHO variation procedures*” (86). If the NMRA does not object to the decision of the PQT within the given timeframe, its agreement is assumed (86).

The WHO’s objective is managing variations as efficiently as possible and thereby saving resources at the local NMRAs (15). The more national MAs are concerned about a variation, the more duplication of efforts is avoided and thus, the more resources are saved since most of the workforce is invested by the PQT. Nonetheless, it is not mandatory for the NMRAs to adopt the PQT’s decision about the variation, it may also deviate from it. In this case the NMRA has to inform the PQT about its deviation and the underlying reasons. As soon as there are different outcomes of a variation procedure, the prequalified product and the national product are no longer identical. Consequently, the national drug is deleted from the CRL and its lifecycle can no longer be synchronised with the prequalified product using the CRP. Although the status of the national MA is not affected at all, the NMRA alone is now responsible for all post-approval maintenance concerning this product. This in turns requires the respective resources since work-sharing is no longer possible.

The practice for suspensions or withdrawals is similar. If a prequalified drug is delisted from the PQL, the WHO informs all NMRAs that issued an MA for this respective medicine in their country. Again the authority is not obliged to follow the PQT’s decision. Depending on the reasons for delisting provided by the WHO, the NMRA can decide sovereignly if it suspends or withdraws the national MA or if it remains unaffected. In case the NMRA decides not to change the approval status, it is solely responsible for its regulatory maintenance in future.

Post-registration maintenance also includes regular re-inspections and re-assessments by the WHO (71). Nevertheless, this is regulated by the PQP, not by the CRP process. Re-inspections

of manufacturing sites take place every one to three years to verify GMP-compliance (28). In analogy to renewals at NMRAs a prequalified product has to be requalified every five years (28). Therefore, the manufacturer submits current product-related data that are assessed by the PQT (28).

Besides the lifecycle management of a medicinal product, pharmacovigilance (PV) is a major post-registration issue of tremendous importance. PV enables monitoring of safety and efficacy of a registered drug circulating in the market. Thereby, substandard, counterfeit or generally low-quality drugs can be detected and consequently eliminated from the distribution chain (6). Furthermore, signals with regard to adverse events are detected by PV measurements and can be analysed subsequently. Unfortunately, up to now the issue of collecting pharmacovigilance information proactively has not been addressed, not by the PQP and consequently neither by the CRP. Nonetheless, the PQP considers generally available pharmacovigilance data as part of prequalification maintenance. The underlying problem is that PV systems differ widely between countries or do not exist at all (7). While PV systems of the ICH region are quite developed and harmonised, there are some African countries with only very elementary systems with manual methods of reporting of adverse events (82). Consequently, PV systems should be established and harmonised in the future.

5.7 Sovereignty

An important factor of the CRP is the sovereignty of the participating NMRAs throughout the procedure. Regardless of its general agreement to apply the CRP and to follow its provisions, an NMRA may reject an application that has been submitted according to a CRP at any time. It is still the NMRAs' right and privilege to regulate medicines within their jurisdiction in line with local conditions and needs of the individual country (69). This cannot and must not be taken over by the WHO. The WHO itself does not intend this and stresses that it is not a regulatory authority. On the one hand this is certainly true since it cannot issue MAs for example. On the other hand in terms of prequalification it functions exactly as a regulator except that no MA is granted.

The participation in the CRP programme is voluntary for manufacturers as well as for NMRAs. Hence, all participating NMRAs proactively choose to apply this procedure. Moreover, according to the WHO a CRP does not interfere with national drug legislation. The NMRA still decide independently if an MA for a prequalified product is granted. As aforementioned the NMRA may decide if and how thoroughly to evaluate the dossier submitted when a CRP is initiated. Nonetheless, the WHO strongly recommends to exclusively assess data that may be of specific relevance for the respective country, such as disease burden, the prevalence of other diseases and comorbidities, to avoid duplication of work (69). Thereby the NMRA's sovereignty is not restricted. Furthermore, the NMRAs' sovereignty is fully kept with respect to regulatory fees. These are determined locally and are charged directly by the NMRA.

Variations have to be submitted in parallel to the PQT and all concerned NMRAs. Thereby *“variations should respect national requirements”* (69). Nevertheless, there is no definition of the kind of national requirements meant. Furthermore, the variations are assessed principally by the PQT. The respective reports are shared afterwards with the NMRAs which have to decide within 30 days if they agree or disagree with the outcome. However, the NMRAs are strongly encouraged to stick to the PQT’s decision (69).

In principle sovereignty of concerned NMRAs is respected throughout the process: The authorities decide for each product if they want to apply a CRP to it, how comprehensively provided data are assessed, if additional obligations are imposed and finally if they adopt the PQT outcome fully or partially.

5.8 Drawbacks

The CRP accelerates drug registration in some countries tremendously and thereby saves time and money for the authority as well as for the applicant. The PQP achieved that the production of generic medicinal products became again more interesting for manufacturers. Nevertheless, pharmaceutical companies are still not particularly interested in registering their products in small developing countries due to the small markets. The CRP already provides new incentives for manufacturers: The prequalified product as well as all national ones registered via CRP are continuously synchronised, which reduces the workload of lifecycle management tremendously. Hence, manufacturers are somewhat more motivated to have their product authorised in smaller markets. Nonetheless, to date several participating NMRAs have not yet received any application according to the CRP.

To the regret of the NMRAs, the restriction to products of certain therapeutic areas is another disadvantage. *“I would like to see more product categories included in the CRP because diseases like diabetes and hypertension are quite common now in Nigeria. Unfortunately, these categories are not included in the collaborative procedure.”* says Moronu from the NAFDAC (22). Certainly, this is due to the fact that the CRP is based on the PQP which focuses on priority diseases. Nevertheless, the list of essential medicines is adapted regularly and already includes medicines for cancer or chronic diseases such as diabetes. Therefore, in future there will presumably also be invitations to EoI for additional therapeutic areas. However, it remains to be seen when this is going to happen since the WHO’s resources are restricted too. Therefore, it is forced to prioritise some conditions over others depending on the current disease burden.

Manufacturers would appreciate the possibility to also apply the CRP to products that were not assessed by the PQT but by an SRA (15). Currently this is impossible because for those products there is no WHO assessment report. The eligibility of prequalified products evaluated by an SRA could further decrease duplication of work for applicants as well as NMRAs and

accelerate the access to medicines for patients in LMICs. Therefore, a process of information sharing between the SRA, the WHO and the NMRA would have to be defined.

The short timeline of the CRP is intended to be beneficial for all stakeholders. Nevertheless, it could also lead to further resource restrictions at the NMRA. One NMRA mentions that it would be helpful if the submission of an EoI by the manufacturer was announced earlier (78). Thereby, the NMRA could prepare for the upcoming submission of the dossier. In Kenya for instance it is mandatory to perform an analysis of product samples before the drug can be registered (78). However, this may not always be possible within the expected timeline of the CRP. If problems involving resources necessary for a timely processing of the CRP persist, the establishment of “slots” might be an option. Thereby, the NMRA determines when submissions of applications for an MA according to CRP are possible.

In practice there are also some technical difficulties that complicate communication and inhibit smooth processes. Information such as WHO assessment reports, variation outcomes or withdrawals are communicated to the NMRAs via the restricted access website. However, some NMRAs in developing countries have to cope with unstable internet connections and obsolete technical equipment. Furthermore, there are some problems with regard to the technical handling of submitted applications. Those were not always recognised instantly by the NMRA and there were also difficulties with regard to information sharing: EoIs, feedback and decisions were not communicated in a timely manner (15). To date this has caused delays in the handling of MA applications according to CRP. To avoid this in the future, the WHO plans to establish best practice guidelines (15).

6 Outlook

The CRP is based on the longstanding and successfully applied WHO prequalification programme (PQP). The PQP is the only global quality assurance system that improved tremendously the availability of high-quality, safe and efficient medicines in developing countries. Consequently, the PQP provides an excellent starting base for the CRP programme. All in all this collaborative registration programme is judged very positively by participating NMRAs. Solange from the DPML: *"I know the WHO Collaborative Registration Procedure will help us to accelerate the process of registration in Cameroon"* (18). He further states: *"we are grateful for everything that helps to put forward our country."* (18).

Unfortunately, some NMRAs in resource-restricted countries have not yet benefited from the CRP, since to date no applications were submitted. Therefore, it may require additional incentives for manufacturers to enhance registration of medicines in currently unattractive markets. An option to address this problem in the future could be the grouping of several countries into clusters and to apply some kind of "centralised procedure" within such a cluster. A centralised procedure could promote the registration of lifesaving medicines in very small and thereby uninteresting markets. Therefore, the application of the procedure should be mandatory for essential medicines or drugs used in the treatment of life-threatening or chronic diseases and specified other serious conditions, similar to the European CP. The major advantage of the CP is that subsequent lifecycle management is centralised, consequently all national MAs are synchronised and the regulatory burden for authorities as well as for pharmaceutical companies is reduced. Furthermore, patients can access these medicines all over the region. Maybe the application of a similar model as extension to the CRP could support the registration of urgently needed essential medicines in additional developing countries. The clustering of countries could be done according to already existing communities and associations such as the EAC. Certainly, a prerequisite would be the participation of all concerned NMRAs in the CRP.

Although the CRP is still in its infancy, the first 2.5 years went very well and indicate a promising future of the programme. Due to this development, the programme will be extended. In July 2014, a revised draft of the CRP was published for comments in which also prequalified vaccines are eligible for CRP (86). This follows the fusion of the prequalification programmes of medicines, vaccines and diagnostics in 2013 (54). Moreover, it is envisaged to include *in vitro* diagnostics into the CRP (87). It is further planned to make the CRP eligible for medicines that have not been assessed by the WHO PQP itself, but by SRAs like the EMA or the FDA (87). Therefore, consultations with representatives of pharmaceutical companies, associations of industry and SRAs take place to achieve the most beneficial outcome for all stakeholders (87).

Additionally, the EMA currently plans a pilot programme in cooperation with the WHO to foster medicines registration in resource-restricted countries based on Art. 58 procedures (88) (89). Similar to the CRP, this pilot includes the sharing of full assessment and inspection reports

instead of only providing an opinion and a relatively short European Public Assessment Report (EPAR) (32). Furthermore, now also centrally authorised medicines are eligible for this kind of assessment (88) (89). It remains to be seen if this increases the usage of the procedure. However, more drugs assessed according to Art. 58 could lead to more drugs on the PQL. If these also become eligible for CRP, more medicines are available for accelerated national registration.

Another collaboration could take place with MSF which developed its own qualification system for assuring the appropriate quality of drugs not approved by an SRA or prequalified by the WHO (6). Since this system was established in accordance with WHO standards, cooperation with the PQP could be a beneficial option for the MSF as well as for the PQT (6).

Currently, only a small fraction of essential medicines are prequalified and consequently the number of products that can be nationally registered via the CRP is still very restricted. This is regretted by some NMRAs of developing countries. However, the bundling of programmes such as those mentioned above could create further synergies and thereby increase the number of prequalified drugs. Consequently, more drugs would be eligible for registration via a CRP.

The CRP programme demonstrates that it is able to facilitate and accelerate drug registration in developing countries tremendously. If the promising start is followed by a sustainable future, remains to be seen. Nonetheless, the current development gives reason for an optimistic view of the future.

7 Summary

Medicine regulation is a challenging, sophisticated and resource-demanding task. However, NMRAs in developing countries have to cope with very constrained resources regarding adequately trained staff, expertise and funding. Hence, circulating substandard and counterfeit medicines are not detected and consequently commonly distributed and dispensed. Furthermore, some urgently needed drugs are not available on the local market for the patient population. Due to the fact that neither the government nor the people can afford high-priced medicines, innovative pharmaceutical companies are rarely interested in marketing their medicinal products in developing countries. Additionally, in the past the quality of several generic products was doubted. Unfortunately, this could not be addressed and monitored adequately by the NMRAs because of their restricted resources.

To enable UN agencies to purchase high-quality, safe and efficient medicines at reasonable prices address, the WHO established the prequalification programme in 2001. This approach improved the situation in developing countries tremendously. Nevertheless, prequalification does not result in a national marketing authorisation and consequently required medicines are still not accessible for all patients via the regular distribution chain. This approach improved the situation in developing countries tremendously. That is why the WHO started a pilot project in 2012 to foster drug registration in developing countries. This collaborative registration procedure (CRP) not only aims to accelerate the authorisation process but also focuses on capacity building at the NMRA. Trainings, workshops and joint activities extend expertise as well as experience of local assessors and inspectors. Furthermore, the CRP programme promotes harmonisation and thereby the reduction of regulatory burden for the NMRAs as well as for the manufacturers.

This thesis describes the historical context that led to the establishment of the CRP. It further summarises experiences and achievements of the first 2.5 years and discusses advantages and drawbacks as well as the potential development of the programme in the future.

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

Regensburg, den 12. Februar 2015

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