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Benefits of WHO Prequalification of Pharmaceutical Product to Developing Countries

			
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ABSTRACT

WHO prequalification review is very well adapted to the needs of developing countries. It takes into account, for example, specific stability/temperature conditions and pediatric needs. These don't apply in the same way in all countries. Some regulatory authorities, therefore, have less experience in evaluating medicines from these perspectives. No other evaluation system takes developing countries' needs into account in the way that WHO does. WHO also monitors any variations (to content or manufacture) occurring after the prequalification of a product. This is crucial if the continuous quality of the medicines distributed to users is to be guaranteed. WHO medicines prequalification primarily benefits populations requiring treatment for priority diseases. It also supports procurers, regulators, medicines quality control laboratories (QCLs), manufacturers, and donors, in reaching their public health objectives.

INTRODUCTION

The Indian pharmaceutical market is the third-largest in terms of volume and thirteenth-largest in terms of value. Indian manufacturers are the key contributors to the WHO Prequalification Programme (PQP) for medicines and vaccines. It was observed that 64% of Finished Pharmaceutical Products are from India. Of the WHO prequalified Active Pharmaceutical Ingredients, 59% are from Indian manufacturers in the segments of HIV-AIDS, Tuberculosis, Malaria, Reproductive Health, etc. The government's Make in India campaign is encouraging the manufacturing of medicines and devices to foster public health goals.

India has emerged as a world leader in generic pharmaceutical production, supplying 20% of the global market for generic medicines. The vast majority of people in low- and middle-income countries have been treated with generic medicines produced by Indian manufacturers' unhampered by a patent and other intellectual property restrictions.

History of Prequalification¹:

The WHO Prequalification Team: medicines (PQTm) was first established as the then Prequalification of Medicines Programme in 2001, in response to the HIV/AIDS pandemic. It aimed to guide UN agencies and other international organizations concerning the quality of antiretroviral medicines, for supply to low-income countries. Its services now cover assessment, not only of a range of finished pharmaceutical products, in several therapeutic areas, but also an assessment of active pharmaceutical ingredients, and quality control laboratories. It also provides technical assistance, conducts extensive training activities (In 2013, the former Prequalification of Medicines Programme was merged with the WHO programs for prequalification of diagnostics and vaccines, to create the WHO Prequalification Team).

UNAIDS, UNICEF, UNFPA and the World Bank and many other organizations consider WHO medicines prequalification to be a concrete contribution to the United Nations' priority goal of addressing high-burden diseases in countries with limited access to quality medicines.

Introduced in 2001, the WHO Prequalification Programme was equally revolutionary. The program responded to an urgent need. Generic manufacturers, largely concentrated in India, were producing large quantities of low-cost treatments for HIV, tuberculosis, and malaria, but

those products were coming on the market without authorization from a stringent regulatory authority. The WHO program stepped in to meet the need for stringent assessment by sending expert teams to inspect manufacturing facilities and ensure compliance with WHO Good Manufacturing Practices and testing to see if the quality and efficacy of generic products matched those of patented originator products.

The program satisfied an urgent and unmet need at a time when the three epidemics were still rapidly expanding. It eventually extended its remit to include the prequalification of active pharmaceutical ingredients and drug-testing laboratories. Today, the WHO “prequalified” stamp of approval means that medicines and vaccines are considered safe, effective and of high quality, and thus recommended for bulk purchase.

After years of stepwise improvements urged by WHO, China’s National Regulatory Authority was assessed as fully functional for the regulation of vaccines in 2011, when WHO certified that the authority’s oversight of vaccine quality met rigorous international standards. That assessment paved the way for the prequalification of individual vaccines and opened the door to exports from the country that had the largest vaccine manufacturing capacity in the world.

The first vaccine made in China, for Japanese encephalitis, was prequalified by WHO in 2013. The vaccine was not only less expensive than vaccines already on the market, it was also a better product. The vaccine is easier to administer, being effective after a single dose, and can be safely given to infants, greatly simplifying the logistics of vaccine delivery and cutting costs even further. The prequalification of this vaccine by WHO was welcomed as a true game-changer for a disease that is the leading viral cause of disability in Asia. Japanese encephalitis kills or causes neurological disabilities in 70% of those infected.

In February 2017, WHO assessed India’s National Regulatory Authority as fully functional, reporting 100% compliance with a roadmap, set out by WHO in 2012, for strengthening the national authority. That seal of approval is expected to go a long way towards securing international confidence in medical products manufactured in India, often referred to as the “pharmacy of the world”.

Prequalification of Medicine²⁻³:

The availability, quality, safety, and efficacy of medicines is a major concern of WHO. To ensure that quality pharmaceuticals are available, WHO sets norms and standards, develops

guidelines, and advises on issues related to quality assurance of medicines for national and international markets. WHO assists countries in building national regulatory capacity through networking, training, and information sharing. These activities have been endorsed and supported through numerous World Health Assembly resolutions. WHO medicines prequalification is an important component of these activities and mandate. Until 2000, poor quality medicines were available for the poor but due to the establishment of prequalification of medicines, millions of people suffering from HIV/AIDS, tuberculosis (TB), or malaria in low-income countries have access to world standard treatment.

Prequalification is a service provided by WHO to assess the quality, safety, and efficacy of medical products for priority diseases and which are intended for UN⁴⁻⁶ and international procurement to developing countries. Currently, the program evaluates in-vitro diagnostics, medicines, and vaccines. In 2017 it has introduced assessments of vector control products (insecticides).

Manufacturers interested in entering the global procurement market have their products assessed based on expressions of interest WHO issues periodically. Once evaluated, if the products are deemed compliant with international standards they are listed as eligible for procurement on a public web platform. Large medical products suppliers, such as the Global Fund, GAVI, UNITAID and UNICEF, rely on the list when selecting products for procurement to countries. By guaranteeing acceptable standard levels for the products, WHO helps procurement agencies to buy quality-assured products, and to save money on otherwise expensive evaluations they would have to contract to private companies.

The prequalification of vaccines began in 1987 to ensure that vaccines used in national immunization programs were of assured quality. Later, with the creation of the GAVI vaccine fund, WHO vaccine prequalification became even more relevant as GAVI mainly purchases products that have been scrutinized by WHO.

Medicines prequalification started in 2001, at the height of the AIDS epidemic, and the beginning of major global efforts to tackle priority infectious diseases. Prequalification has been instrumental in broadening access to medicines for HIV/AIDS, malaria, and tuberculosis by prequalifying a large number of the less expensive Indian generic medicines. The lower prices have allowed more people to be treated for the same money. In time, medicines prequalification also began to include other products pediatric medicines,

reproductive health products, treatments for neglected diseases, and active pharmaceutical ingredients.

Diagnostics prequalification began with the assessment of in vitro HIV tests in 2008 and soon expanded to include malaria tests. Today, the diagnostics team also works on emergency-prone pathogens for which few or no medical products exist, such as Ebola and Zika.

Many low- and middle-income countries also use WHO's lists of prequalified products to guide national procurement of medical products.

Benefits of WHO Prequalification

WHO medicines prequalification primarily benefits populations requiring treatment for priority diseases. It also supports procurers, regulators, medicines quality control laboratories (QCLs), manufacturers, and donors, in reaching their public health objectives.

Since its inception WHO medicines prequalification has:

- Improved public health outcomes and value for money through quality assurance of generic medicines, which has stimulated price competition and as a result enabled more medicines to be procured with the funds available so that millions of patients suffering from HIV/AIDS, tuberculosis, or malaria can be treated. About 70% of WHO prequalified medicines are generic.
- Increased uptake of medicines designed specifically to meet low-income country needs including pediatric formulations for HIV/AIDS, TB, and malaria, combination therapies to prevent HIV transmission from mothers to their new-borns, affordable antimalarials, and second-line medicines for drug-resistant HIV and TB.
- Strengthened regulatory capacity in low-income countries (LIC)⁷⁻⁸ by providing professional development and training for their national medicines regulators, and opportunities to participate in innovative regulatory initiatives.
- Developed an effective mechanism that significantly reduces registration time for prequalified finished pharmaceutical products (FPPs) that helps minimize the time it takes to get medicines to those who need them. A similar procedure is now being piloted for medicines with stringent regulatory authority approval).
- Improved capacity to manufacture FPPs and active pharmaceutical ingredients to

international standards by providing effective feedback and guidance during a prequalification evaluation, and organizing training and technical assistance. The improved capacity applies not only to the FPP or API that has been submitted for evaluation but to any FPP or API that the manufacturer produces.

- Increased availability of medicines testing services through the prequalification of QCLs. Prequalified QCLs now exist in every WHO geographic region and can work together with their national medicines regulatory authority to monitor the quality of medicines on the national market, be these manufactured locally or imported.*

WHO prequalification review is very well adapted to the needs of developing countries. It takes into account, for example, specific stability/temperature conditions and pediatric needs. These don't apply in the same way in all countries. Some regulatory authorities, therefore, have less experience in evaluating medicines from these perspectives. No other evaluation system takes developing countries' needs into account in the way that WHO does. WHO also monitors any variations (to content or manufacture) occurring after prequalification of a product this is crucial if the continuous quality of the medicines distributed to users is to be guaranteed.

WHO prequalified products are urgently needed products, supplied to treatment programs in low-income countries. They have saved and radically improved the quality of life for millions of people. This achievement is the result of not only of the efforts of WHO prequalification staff and WHO colleagues, but also those of its partner organizations and manufacturers who submit products to WHO for evaluation, and who work hard to improve product quality, under WHO guidance.

Recognizing the value of WHO prequalification's contribution to meeting global public health goals, several donors have continued to provide financial support, without which this activity could not have achieved so much.

Prequalification activities relating to medicines for treating HIV/AIDS, TB, and malaria UNITAID's mission is to increase access to treatment for HIV/AIDS, TB, and malaria for people in low-income countries by leveraging price reductions of quality-assured medicines and diagnostics, and to accelerate the pace at which they are made available. So for UNITAID, WHO prequalification's role in increasing the supply of quality-assured medicines, and building a more efficient market place for safe medicines, is vitally important.

Need for Prequalification of Medicines:

Nearly 2 billion people have no access to basic medicines, causing a cascade of preventable misery and suffering. Since the landmark agreement on the Global Strategy and Plan of Action on Public Health, Innovation, and Intellectual Property, WHO and its partners have launched several initiatives that are making market forces serve the poor. The WHO prequalification program is now firmly established as a mechanism for improving access to safe, effective, and quality-assured products.

WHO has struggled to improve access to medicines throughout its nearly 70-year history, and rightly so. Good health is impossible without access to pharmaceutical products. Universal health coverage depends on the availability of quality-assured affordable health technologies in sufficient quantities.

Lack of access to medicines causes a cascade of misery and suffering, from no relief for the excruciating pain of a child's earache to women who bleed to death during childbirth, to deaths from diseases that are easily and inexpensively prevented or cured. Lack of access to medicines is one inequality that can be measured by a starkly visible yardstick: the number of preventable deaths. Many people have no access to essential medicines, effectively shutting them off from the benefits of advances in modern science and medicine.

Substandard and falsified products

WHO has recently stepped up its efforts to combat yet another threat to the life-saving and health-promoting power of medicines. The health harms caused by substandard and falsified medical products. These products flood the markets in countries with weak drug regulatory authorities or circumvent regulatory controls through sales via the internet. The complex web that characterizes the global production and distribution of pharmaceutical products, including a long and convoluted supply chain, places all countries at risk. Products that enjoy lucrative commercial markets are particularly susceptible to falsification, as are badly needed medicines and vaccines that are in short supply. Substandard and falsified medicines not only steal income from consumers who pay for products that have little or no medical value. They cause harm by not resolving a medical problem and have sometimes caused hundreds of deaths, especially when the products contain toxic ingredients.

The WHO Global Surveillance and Monitoring System for Substandard and Falsified Medicines were launched in West Africa in July 2013. Since then, more than 400 regulatory

personnel from 126 countries have been trained to use this system for the rapid reporting of substandard or falsified products. Reports from national regulatory personnel are immediately uploaded to a secure WHO website. If the investigation confirms harm to health, the WHO responds within 24 hours, providing coordination and technical support in the event of an emergency.

When warranted, WHO issues a global Medical Product Alert to warn countries and populations of the existence of a dangerous medical product. The alerts, which include photographs of falsified products, also encourage increased vigilance and regulatory action to protect populations and supply chains. In the past two years, alerts were issued for falsified yellow fever vaccines, hepatitis C medicine, meningitis vaccines, anti-malaria medicines, and treatments for epilepsy. Information gathered by the surveillance and monitoring system can have broader policy implications. For example, many anti-malaria tablets, sold at street markets in common countries, contain no active pharmaceutical ingredients at all.

Regulatory Authorities⁹⁻¹⁰

Since its inception, regulatory agencies have both supported WHO medicines prequalification and benefited from it. They can be seen as an important community that joins forces to help make quality priority medicines available for those who urgently need them.

Stringent regulatory agencies (SRAs)

SRAs provide critical expertise for the evaluation of finished pharmaceutical products (FPPs) and active pharmaceutical ingredients (APIs) for prequalification.

This includes:

- Participating in the WHO Prequalification Team (PQTm) assessment sessions that take place every two months in Copenhagen, Denmark, to share their expertise and work with PQTm to resolve technical pharmaceutical issues relating to dossier assessment.
- Participating in WHO inspections of manufacturing sites, contract research organizations, and quality control laboratories, helping PQTm to ensure that its inspection standards and approaches are fully aligned with current practice.
- Working with PQTm to develop prequalification guidance that will help manufacturers to

understand and meet prequalification requirements.

- Participating in individual meetings with manufacturers, and in training workshops for manufacturers, to provide technical advice that will enable them to meet prequalification requirements more quickly and more efficiently.
- Participating in training for low- and middle-income country medicines regulators to facilitate understanding of WHO prequalification requirements and enhance their expertise in applying international standards for assessment and inspection.

Much of the support has been and continues to be provided at no or little cost to WHO, reflecting recognition of the public health value that WHO prequalification brings. PQTm welcomes expressions of interest from SRAs regarding possible participation in prequalification activities.

Regulatory agencies of low- and middle-income (LMIC) countries

For regulatory agencies of low- and middle-income countries (LMICs), WHO prequalification is a source of rich learning and training opportunities. These include:

- Participation in the annual assessment training session
- Participation in the WHO Prequalification Team (PQTm) assessment sessions that take place every two months in Copenhagen, Denmark, Participation in PQTm inspections as an observer, The opportunity to work with PQTm as a rotational assessor or inspector, Participation in training workshops on prequalification requirements and current regulatory issues of relevance to prequalification and regulation of priority medicines, Participation in the WHO Collaborative Procedure for Accelerated Registration.

The usefulness of WHO technical outputs of medicines prequalification

LMIC regulators also appreciate both the technical underpinning (the norms and standards on which it is based) and the outputs of WHO prequalification. The latter can enable savings to be made in time and resources when conducting regulatory activities.

WHO Listed Authorities

The term ‘Stringent Regulatory Authority’, defined as original ICH member/observer, was developed to promote reliance and guide procurement decisions - widely used and recognized

Concerns with term SRA; with the fact that ICH is a harmonization initiative for pharmaceuticals, not a body with a remit or competence to assess regulatory capacity; coupled with expanding membership WHO Expert Committee (Oct 2017) considered new WHO proposal and made several recommendations.

The expert Committee recommended Term SRA be replaced by “WHO-Listed Authority” (WLA) currently identified “SRAs” will be regarded as WHO-Listed. The designation of additional NRAs is based on the WHO Global Benchmarking Tool (GBT) and the completion of the ‘confidence-building process. The procedure for listing is developed through the usual public consultation process.

Process of Prequalification of Medicines

In 2001, so that the United Nations (UN) procurement would select medicines of assured quality, WHO established the PQP. Most international procurers doubted that Indian drug regulatory authorities could verify the quality of medicines. Yet India produced the most generic medicines used in developing countries. Moreover, fixed-dose combinations (FDCs) of antiretroviral (ARVs) medicines and paediatric ARV formulations from India had no originator equivalents (medicines made and regulated in high-income countries), constituting another regulatory assessment challenge. Often national and international procurement organizations could not guarantee quality because their quality-assurance systems were limited in scope. WHO member states requested WHO to assist procurement organizations by assessing the quality of increasingly available low-cost generic medicines. Given its mandate to set international pharmaceutical norms and standards, WHO was suited for this role. Initially WHO focused first on low-cost generic versions of medicines to treat HIV, tuberculosis (TB), and malaria.

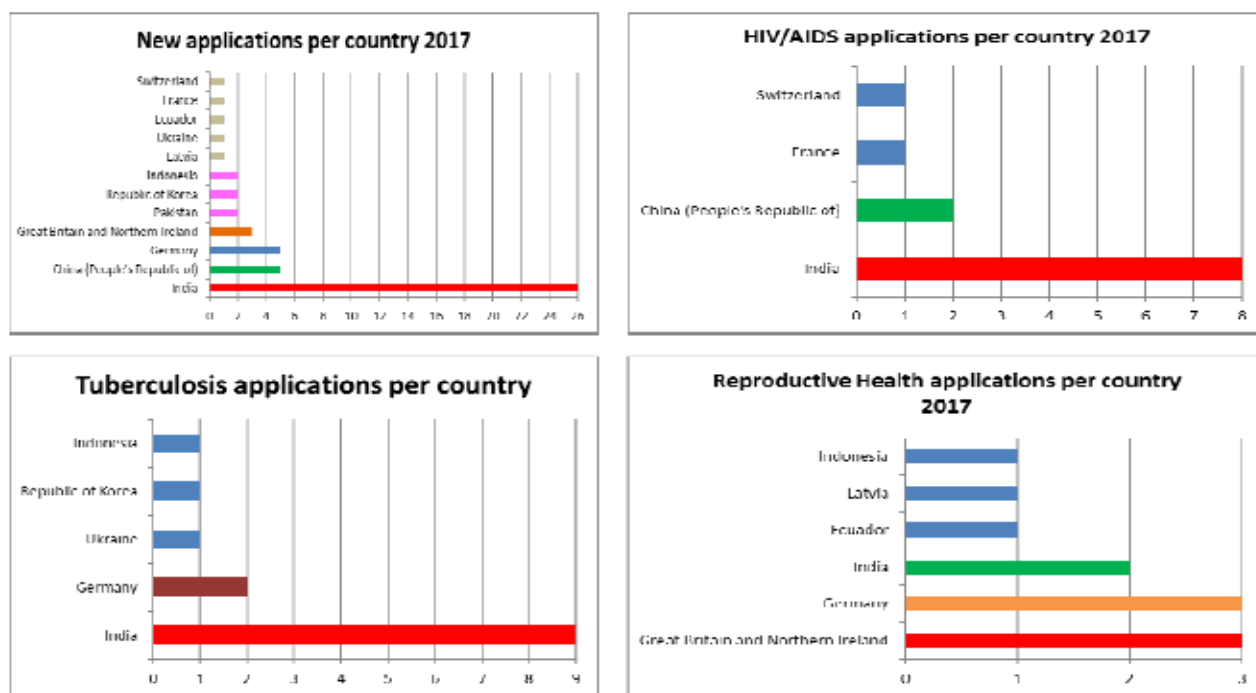


Figure No.1: Contribution of Indian Pharmaceutical Industries to PQ

Working of Prequalification Programme:

1. Invitation

The WHO Prequalification of Medicines Programme (PQP), other UN agencies (UNAIDS and UNICEF) and UNITAID, issue an invitation to manufacturers to submit an expression of interest (EOI) for product evaluation. Only products included in an EOI are eligible for prequalification.

2. Dossier Submission

WHO recognizes the scientific evaluation of multisource (generic) products by regulatory authorities, which apply similarly stringent standards for quality, safety and efficacy as those recommended by WHO.

3. Dossier Assessment

The product information submitted in the dossiers will be assessed by teams of experts (assessors) having the relevant qualifications and experience in the fields of pharmaceutical development, quality assessment of pharmaceutical products, quality assurance, biopharmaceutics and other relevant fields.

4. Inspection

A team of inspectors verifies that the manufacturing sites for the finished pharmaceutical product and its active pharmaceutical ingredient(s) comply with WHO good manufacturing practice.

5. Decision

If the product is found to meet the specified requirements, and the associated manufacturing site(s) and contract research organization(s) are compliant with WHO standards, the product is added to the WHO list of prequalified medicinal products.

6. Maintenance of Pre-qualification Status

Inclusion in the list of prequalified products does not mean that the prequalified status of a product lasts forever. Every five years from the date of prequalification, or when requested to do so by the WHO Prequalification of Medicines Programme, the holder of a prequalified product is required to submit data and information about the product to WHO for assessment.



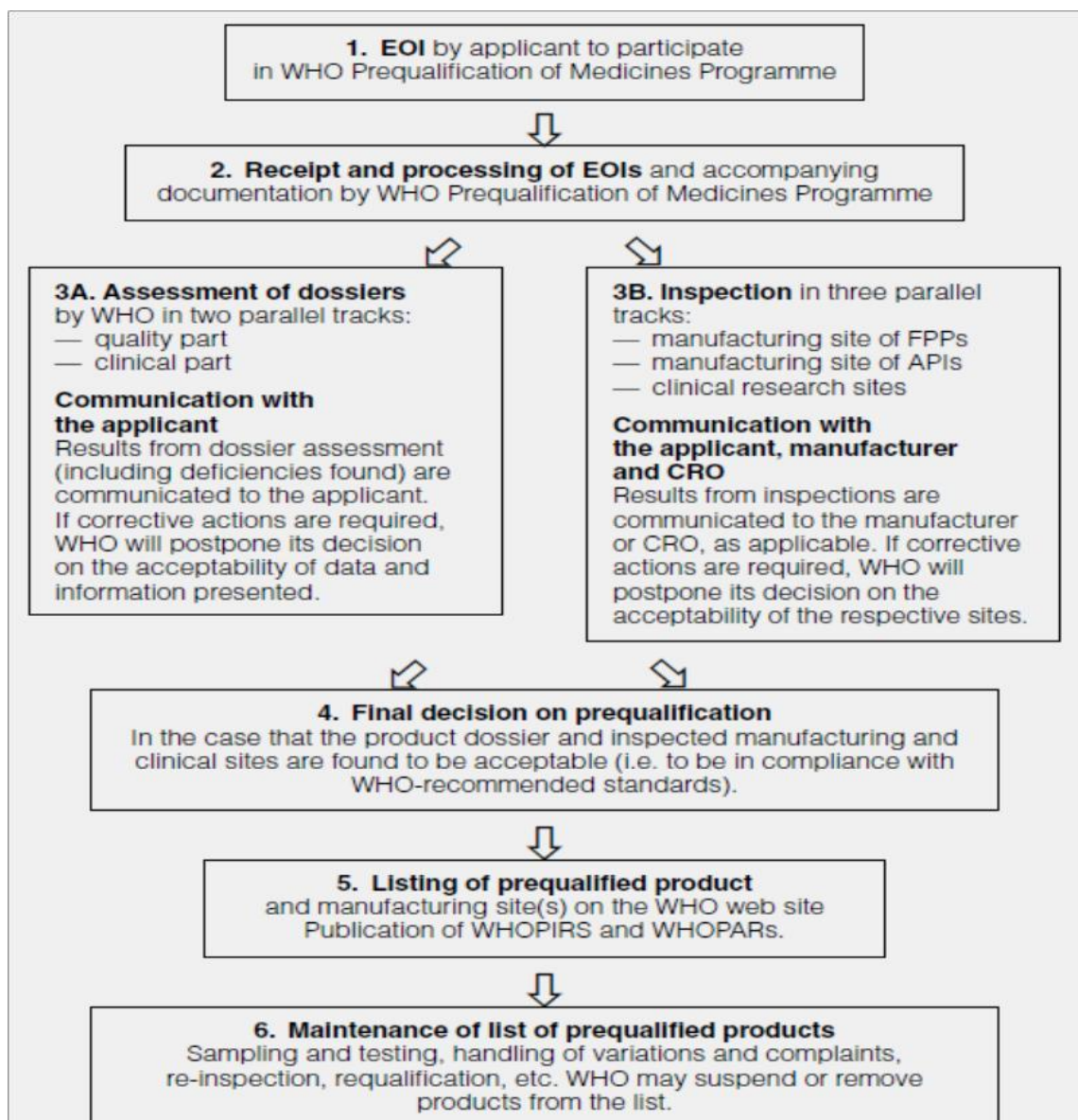


Figure No. 2: Flow chart of Prequalification of Pharmaceutical product

SUMMARY

WHO medicines prequalification primarily benefits populations requiring treatment for priority diseases. It also supports procurers, regulators, medicines quality control laboratories (QCLs), manufacturers, and donors, in reaching their public health objectives.

WHO prequalification review is very well adapted to the needs of developing countries. It takes into account, for example, specific stability/temperature conditions and pediatric needs. These don't apply in the same way in all countries. Some regulatory authorities, therefore, have less experience in evaluating medicines from these perspectives. No other evaluation system takes developing countries' needs into account in the way that WHO does. WHO also

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