WHO Prequalification

Ensuring global availability of quality-assured vaccines

WHO supports Member States in providing safe, effective, high quality vaccines against diseases of public health importance. The WHO prequalification programme ascertains that products meet acceptable standards for use in national immunization programmes. Its activities are coupled with regulatory capacity-building to help develop sustainable mechanisms for vaccines quality assurance in Member States. WHO prequalification also facilitates international harmonization of vaccine production standards.

This article gives some background about this long-standing programme and outlines progress and challenges encountered in recent years.

Background

Immunization is key to protecting children from diseases, including polio, measles, diphtheria, and tetanus. Vaccination is one of the most cost-effective health interventions.

To increase access to vaccines of assured quality and safety in Member States, WHO introduced a vaccine prequalification programme in 1987 as a service to UNICEF and other UN purchasing agencies. The norms and standards used for vaccine prequalification are developed in consultation with a wide range of stakeholders. In the 25 years of its existence the prequalification programme has adjusted its procedures to the changing needs (1).

As more countries routinely immunize children and develop more ambitious national vaccination programmes, the demand for quality products is growing. From 2000 to 2013 the value of the global vaccine market has quadrupled from USD 5 billion to almost USD 24 billion (2). The number of prequalified vaccines has also grown. The online list on the WHO website (3) includes more than 120 products of 36 different vaccine types, including those that have been in use for a long time – such as diphtheria/tetanus/pertussis vaccine combinations, yellow fever vaccine and oral polio vaccine – as well as new ones, such as pneumococcal conjugate vaccine, rotavirus and human papillomavirus vaccine. Each year, WHO-prequalified vaccines are used to immunize 65% of the world’s birth cohort.

Regulatory oversight

Vaccines are complex biological products. To ensure that all vaccines used by national immunization programmes meet the required standards of quality, safety and efficacy, WHO works in partnership with national regulatory authorities (NRAs) to provide lot-to-lot oversight. In 1996 WHO launched an initiative to strengthen NRAs. An assessment tool was developed to monitor progress and to provide a benchmark for vaccine prequalification for purchase by United Nations agencies. Over the years the tool was revised several times with input from more than one hundred countries. The current version dates from 2011 (4).
Assessment of NRAs using this tool gained a new significance in 2002, when the decision was adopted that the WHO prequalification programme will accept submissions from vaccine manufacturers only if the NRA of the producing country has been assessed as functional against the indicators defined in the assessment tool. This decision has greatly supported WHO efforts to strengthen capacity for vaccine regulation in developing countries.

For the last five years, WHO’s regulatory capacity-building measures have been targeted strategically to emerging economies which impact global vaccine supply. This strategy has a dual goal: to sustain existing functionality of NRA in countries with already prequalified manufacturers, and to strengthen the NRAs of countries with manufacturers interested in vaccine prequalification.

At the end of 2013, 35 of 43 vaccine-producing countries around the world were assessed as functional according to WHO indicators. Of these, 22 supplied at least one WHO-prequalified vaccine, thus broadening the supplier base for safe and effective vaccines of good quality. For example, maintaining functionality, since early 2011, of the China Food and Drug Administration (CFDA) was the catalyst for WHO prequalification of the first vaccine from China in 2012, a live attenuated Japanese encephalitis vaccine. Prequalified vaccines are produced in seven other low- and middle income countries: Brazil, Bulgaria, Cuba, India, Indonesia, Senegal and Thailand.

Engagement with manufacturers
As increasing numbers of vaccines come from countries with NRAs recently declared as functional, there is a need to familiarize manufacturers with the quality standards required by the WHO prequalification programme. In addition to providing detailed online guidance on prequalification requirements and processes, the prequalification team is engaging with manufacturers before submission of applications. This activity has grown significantly in past years. The number of one-on-one meetings with manufacturers increased from 40 in 2008 to 131 in 2012.

The improved guidance has helped to decrease the average time spent by WHO assessors on evaluating dossiers substantially. From 2007 to 2013 the average time from application to prequalification – excluding periods spent waiting for additional data – has almost halved, from 350 to 138 days.

Streamlined procedures
A major revision of the vaccines prequalification process was adopted in 2010 and came into force in January 2012 (5). The revised procedure introduced two significant changes.

Firstly, taking into account the increasing need for regulatory collaboration and risk-based approaches, the revised procedure provides the option for fast-tracked assessment. This option is used if WHO has an official agreement for information-sharing with a mature NRA responsible for the product, usually that of the producing country. The fast-track process shortens the average assessment time. In 2013 WHO assessors spent an average of 82 days on dossiers submitted under this process, compared to 138 days for the standard process.

Secondly, the revision also introduced written criteria defining programmatic suitability for prequalification (6). This addresses a previously unmet need to provide manufacturers with clarity on the desired product design features for use.
in immunization programmes receiving vaccines through UN procurement. Manufacturers now routinely consult WHO at an early stage of developing products for prequalification. This interaction has reduced the time taken by WHO assessors to consider products with non-compliant characteristics.

**Post-prequalification activities**

Even if dossier assessment can be fast-tracked for products from countries with mature regulatory authorities, WHO remains responsible for ensuring compliance with UN tender specifications and programme needs, monitoring product quality and safety, and conducting a targeted testing programme. If there are quality concerns, the supply of prequalified vaccines can be suspended, or the product can be delisted from WHO’s prequalification list. A complete record of issues relating to prequalified vaccines is published on the WHO website (7).

WHO’s post-prequalification work consists of both planned and unplanned activities, which have been increasing over the years as more vaccines have become prequalified (*Figure 1*). Regular maintenance causes a significant workload; for example the 53 product reviews done in 2012 gave rise to assessment of 448 variations (changes) to prequalified vaccines. In addition, unplanned but urgent activities arise whenever complaints or reports adverse events following immunization (AEFI) are received from the field.

**Prequalification of immunization equipment and devices**

WHO prequalifies not only the actual vaccines but also a comprehensive range of cold chain equipment, injection devices and other products needed for safe and effective immunization delivery. The Performance, Quality and Safety (PQS) scheme for the prequalification of equipment and devices for immunization was introduced in 2006 and became functional gradually during a transition

---

**Figure 1:** Planned and unplanned post-prequalification activities for vaccines

![Graph showing planned and unplanned post-prequalification activities for vaccines](Image)
period from the previous PIS (Product Information Sheet) system.

The PQS approach to equipment and device prequalification encourages the continuous improvement of existing products whilst remaining open to innovation. The scheme is based on three key criteria for products:

- Performance characteristics that meet the relevant specification standards;
- Quality and reliability characteristics that are appropriate for field conditions, and
- Safety characteristics that ensure that no harm is caused to users, patients or the environment over the course of the product’s life cycle.

In recent years the number of accessory products prequalified through the PQS scheme has increased more than fourfold, from 55 in 2008 to 245 at the end of 2013 (8). As more and more countries are now including requirements for PQS prequalification in their tenders, the scheme goes far beyond UN purchasing. It provides procurement agencies around the world with a list of reliable immunization equipment and devices, each proven to meet user needs.

**Regulatory capacity-building**

The prequalification programme uses two strategies to promote the implementation of WHO norms and standards for vaccines in countries.

Firstly, regulators from a wide range of WHO Member States are invited to participate in expert meetings to develop WHO standards. The focus is on the review of scientific evidence for clinical evaluation of vaccines. In this way, participating regulators acquire the specific expertise needed to drive the implementation of the agreed standards actively in their own regulatory environments.

Secondly, WHO organizes implementation workshops for new written WHO standards, using practical examples and case studies. Vaccine lot release, stability evaluation, safety of cell substrates for vaccine production and Good Manufacturing Practice (GMP) are examples of priority topics covered.

**Vaccine safety**

Post-approval surveillance is essential to confirm that vaccines are safe to use in the target populations. To follow up on the safety of vaccines used in Member States WHO created a functional network of countries, including some of the most advanced in terms of vaccine pharmacovigilance.

The participating countries have played a key role in advancing vaccine safety worldwide. They contributed to the Global Vaccine Safety Blueprint objectives (9), leading to the launch of the Global Vaccine Safety Initiative in November 2012 (10). They also proposed implementation models to achieve these objectives and shared their experience with other countries. Regional vaccine safety networks in line with the globally recommended model are being established in three WHO regions: the Eastern Mediterranean Region, the Region of the Americas and the South-East Asia Region.

A key outcome from the network was the definition of a minimum core data set to be collected for AEFI (11). A standard AEFI reporting form was designed and implemented in network countries. In parallel, a simple, vaccine-specific electronic user interface was developed and has meanwhile been pilot-tested successfully in one country.

The network has provided a good understanding of the opportunities and challenges of managing vaccine safety in
low- and middle-income countries. Each of the network countries has faced major hurdles. Nevertheless, most have made significant progress in detecting and reporting AEFI, and some are now moving beyond minimal capacity to participation in epidemiological risk assessment studies. Valuable lessons have been learned that can be used to improve safety management programmes for other health technologies.

Conclusion
WHO has prequalified a wide range of vaccines and related products, and has developed streamlined, risk-based processes to assess products in line with current, stringent regulatory principles. This has enabled faster access to a wide range of needed products for WHO Member States and has promoted international norms and standards for vaccines among manufacturers, regulators and procurers.

A significant challenge facing the WHO vaccine prequalification team is the expanding workload to oversee an increasingly complex range of prequalified products. This expansion has not been matched by a similar increase in funding and resources.

In this context it should be noted that the prequalification service provided by WHO is not intended to be a permanent mechanism to ensure the quality, safety and efficacy of vaccines globally. It is therefore crucial for WHO and Member States to continue their regulatory collaboration and capacity-building initiatives, as urged in May 2014 by the Sixty-seventh World Health Assembly (12).

References and further reading
2 WHO. Vaccine market [web page].
3 WHO. WHO prequalified vaccines [web page].
6 WHO. Immunization standards. Assessing the programmatic suitability of vaccines candidates for WHO prequalification [web page].
7 WHO. Issues relating to prequalified vaccines [web page].
8 WHO. PQS Catalogue [web page].
10 WHO. The Global Vaccine Safety Initiative (GVSI) [web page].
11 WHO. Global vaccine safety. Core variables for AEFI [web page].
Bringing quality-assured in vitro diagnostics to WHO Member States

The success of treatment programmes and the rational use of medicines depend critically on diagnostic products. In the absence of fully functioning regulatory mechanisms for in vitro diagnostics (IVDs) in many countries, the WHO prequalification of IVDs programme generates independent technical information that can be used by UN agencies, governments and other organizations when selecting IVDs for use in their health programmes.

Since its creation in 2008, the programme has undergone some changes as WHO strives to identify quality-assured IVDs for use in Member States where they are needed most. This article describes the prequalification of IVDs programme, its processes, and how it fulfils its unique role.

Background

Good quality in vitro diagnostics (IVDs) are crucial for informed treatment decisions. Incorrect diagnoses can have profound implications for the individual patient, potentially delaying life-saving treatment, subjecting people to unnecessary medication that can be harmful, and impacting their lives in significant ways. IVDs also play a central role in public health, enabling governments to prevent transmission of communicable diseases, to safeguard blood supplies against contamination, and to allocate limited resources effectively. Quality-assured IVDs are therefore critically important for health systems in WHO Member States.

IVDs are challenging to regulate. Unlike medicines and vaccines they are often produced in significantly different versions for different target markets. They also have fast innovation rates and frequent changes of manufacturer ownership.

Although regulatory systems for IVDs have been evolving globally in recent years, there are still many countries where they are virtually non-existent or limited to purely administrative procedures. This regulatory vacuum has resulted in low cost, but low quality, IVDs being introduced into some markets.

By prequalifying IVDs for use in treatment programmes, WHO aims to promote and facilitate access to safe, appropriate and affordable IVDs of good quality in an equitable manner. The WHO prequalification status, together with other criteria, is considered by UN agencies, WHO Member State governments and other interested organizations in making procurement decisions. It is important to understand, however, that it is not WHO’s mandate to issue approvals, certificates or licenses for IVDs. This responsibility lies with the national regulatory authority of each country.

A recent review has resulted in a streamlined approach to prequalification of IVDs1, taking into account the lessons learned in the programme’s early years and the evolving environment in which it operates. The changes introduce more efficient, transparent and consistent processes, better technical support to manufacturers, and greater integration with

---

1 For details, refer to: [http://www.who.int/diagnostics_laboratory/streamlining/en/](http://www.who.int/diagnostics_laboratory/streamlining/en/)
the work of other WHO programmes and partners.

**Prioritization**

Prequalification focuses on IVDs for priority diseases and for use in resource-limited settings. Principles and criteria have been defined to prioritize submissions for review, with the overall aim to make needed technologies of good quality available where regulatory mechanisms are lacking (Box 1). The criteria are periodically reviewed in consultation with other UN agencies, WHO programmes and technical experts.

**Box 1. Prioritizing submissions for review**

**Prioritization principles:**
- Need for the IVD in managing a particular disease or disease state;
- Appropriateness of the product for use in resource-limited settings;
- Requests from WHO Member States for particular IVDs;
- Performance characteristics of particular IVDs;
- Availability of other WHO prequalified products that are of a similar test format and/or test principle.

**Prioritization criteria:**
- Products already listed on the WHO procurement scheme and procured by UN organizations in significant volumes;
- Products which assist in:
  - diagnosis and/or monitoring of infection with HIV-1/HIV-2,
  - diagnosis and/or monitoring of infection with hepatitis C, and
  - diagnosis of infection with malaria parasites;
- Products in a rapid test format and/or technologies that can be used at or near to point-of-care (POC);
- Products manufactured by original product manufacturers;
- Products of categories for which there are few other prequalified products.

**Prequalification assessment**

WHO assesses IVDs through a standardized procedure, which includes three components: product dossier review, manufacturing site inspection and laboratory evaluation (Figure 1). The assessment can be terminated at any time if the manufacturer fails to provide required information or take corrective actions as requested by WHO, or if the product does not meet the acceptance criteria for laboratory evaluation.

**Product dossier review**

The product dossier provides evidence in support of the safety and effectiveness of the product. It includes information on product performance, product design and manufacture. An important component is the manufacturer’s quality management system, a hallmark of any quality-assured product. It provides assurance that manufacturing is done under stringently controlled oversight, so that all lots produced over time can be expected to perform consistently.

The prequalification dossier format is based on a model developed by the Global Harmonization Task Force (GHTF), a group of representatives from the mature regulatory systems of Australia, Canada, the European Union, Japan and the United States. The expected contents of the dossier are described in a guidance text (2).

**Manufacturing site inspection**

WHO inspectors visit the sites where IVDs are manufactured to assess

---

2 GHTF generated a series of documents identifying best regulatory practice for medical devices that can be applied globally. GHTF was replaced in 2012 by the International Medical Device Regulators Forum (IMDRF), which continues to promote GHTF goals and maintains the guidance documents produced by GHTF.
compliance with the applicable ISO quality management standard (3) and with other relevant international standards and guidelines, notably those produced by GHTF/IMDRF. The WHO inspections focus on verifying whether the manufacturing processes are suitable to ensure a reliable supply of products to WHO Member States. Importantly, the inspectors will also cross-check the content of the product dossier by reviewing reports and raw data on site and by interviewing the personnel involved.

**Laboratory evaluation**

The purpose of the laboratory evaluation is to assess the performance and operational characteristics of the product. The latter are important in understanding how well-suited a product is for use in the destination country.

The laboratory evaluation is carried out by specified WHO Collaborating Centres or designated laboratories under the instructions of WHO. Products are evaluated against predetermined performance criteria established by WHO.

**Abbreviated prequalification assessment**

If a product has already passed a stringent assessment by a mature regulatory system – i.e. a GHTF founding member – then WHO considers that another full assessment would unnecessarily duplicate efforts on the part of both the manufacturer and the assessing entities. For such products the programme offers an abbreviated pathway to prequalification (Figure 2). A product qualifies for abbreviated assessment if:

1. A stringently assessed regulatory version is submitted for prequalification; or
2. A non-stringently assessed (“rest of world”) regulatory version is submitted for prequalification, but a stringently assessed regulatory version also exists and there are no substantial differences between the two regulatory versions.

Under the abbreviated procedure no formal dossier is required. Instead, manufacturers have to maintain a current technical file of which WHO will review certain elements during inspection. However,
WHO will always perform an inspection – in abbreviated form unless there are recent reports of serious concerns – and a laboratory evaluation. This is done because regulatory approval in a given country does not necessarily provide assurance that the product will have the same quality, safety and performance when it is used in other jurisdictions.

**Prequalification outcome**  
Once a product meets WHO prequalification requirements it is added to the list of WHO-prequalified IVDs, stating the specific product name, product code(s) and regulatory version as manufactured at the specific manufacturing site(s) that have been inspected. The list is published on the WHO website along with a public report for each product summarizing the prequalification assessment findings.  

After prequalification the manufacturer has to keep WHO informed of any changes to the product and/or to the quality management system under which it was manufactured at the time of prequalification.

**Post-market surveillance**  
While a comprehensive pre-market assessment goes a long way to ensure that a product is well designed and is manufactured under controlled conditions, it does not guarantee safety and performance at the point of use. The successful use of an IVD also depends on a host of downstream factors, from manufacture and transport of products to their storage, maintenance and use by health workers. Detecting, understanding and addressing any shortcomings is crucial for IVD technologies to have the expected impact in treatment programmes.

The purpose of post-market surveillance is to verify that the IVDs supplied to treatment programmes continue to comply with WHO prequalification requirements. This is done proactively through lot verification testing (verifying whether each lot manufactured meets set criteria) and proficiency testing (verifying that valid test results are obtained at the point of use), as well as reactively through systematic reporting of complaints and adverse events, followed by appropriate action. Manufacturers on their part must fulfill their post-market surveillance responsibilities as a condition for WHO prequalification.

**Achievements and challenges**  
Since 2010, when the prequalification of IVDs programme became fully operational, WHO has prequalified a total of 26 IVD products including HIV and malaria rapid diagnostic tests, HIV virological technologies and CD4 technologies.  

The programme has experienced a number of challenges in setting up effective prequalification processes for IVDs, which are produced and used in a complex, fast-moving and relatively unregulated environment. Following the implementation of a streamlined approach, work will continue among all stakeholders to shorten the time to prequalification decisions with the overall aim of contributing to faster market access for needed IVDs of good quality.

**Conclusion**  
The WHO prequalification programme fills a niche by assessing IVDs developed for use in resource-constrained settings, where the capacity for regulation and quality assurance of IVDs is often limited. WHO’s independent assessment provides Member States, their procurers and other implementing partners with access to a
list of WHO-prequalified IVDs that meet internationally recognized quality, safety and performance standards, along with detailed technical information for each product in public reports. Given the scarcity of regulatory systems for IVDs in many parts of the world, this information represents a significant global public good.

References

1. WHO Prequalification of In Vitro Diagnostics Programme: Overview of the prequalification of in vitro diagnostics assessment. PQDx_007 v5; 30 May 2014.
2. WHO Prequalification of In Vitro Diagnostics Programme. Instructions for Compilation of a Product Dossier. PQDx_018 v2; 30 June 2014.