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WHO PREQUALIFICATION: ASSURING THE QUALITY OF KEY PRODUCTS

The World Health Organization’s Prequalification Programme ensures that key health products are safe, appropriate and meet stringent quality standards for international procurement. It does so by assessing product dossiers, inspecting manufacturing and testing sites, organizing quality control testing of vaccines and medicines, validating the performance of diagnostics, and verifying that the products are suitable for use in the destination countries.

### VACCINES

The Prequalification of Vaccines Programme was created in 1987 to assure the quality of vaccines distributed by UN purchasing agencies.

- It prequalifies a wide range of traditional as well as combination and novel vaccines, and identifies other possible future candidate vaccines.

### MEDICINES

The Prequalification of Medicines Programme was created in 2001 to prequalify antiretrovirals (ARVs) meeting WHO norms and standards, as a contribution to combating the HIV epidemic. The Programme’s mandate was later extended to also cover medicines for malaria, tuberculosis, reproductive health, neglected tropical diseases, influenza and diarrhoea.

### DIAGNOSTICS

The Prequalification of Diagnostics and Medical Devices Programme evolved from the test kit evaluation programme created in 1988. It became operational in 2010 and is aligned with current regulatory requirements.

- It covers diagnostics and medical devices for priority diseases, such as HIV/AIDS, malaria and hepatitis B and C.

#### Prequalification creates global competition for quality-assured products.

- Every year, more than 2.5 billion doses of vaccines are used globally to immunize children under 10 years old.

- Prequalified vaccines are used to immunize 65% of infants worldwide.

- The majority of the 9.7 million people currently on HIV treatment in low- and middle-income countries are taking prequalified ARVs. Over 280 million treatment courses of prequalified artemisinin-based combination therapies (ACTs) were sold in 2011 to treat malaria.

- In 2012, prequalified HIV rapid diagnostic tests (RDTs) accounted for 85% of the 58.7 million tests procured by key stakeholders. Prequalified CD4 technologies suitable for district and point-of-care level represent the vast majority of the global market for such products.

#### Prequalification detects and addresses quality failures.

- Outcomes of a WHO site audit led to a supply suspension of a vaccine through UN systems in 2012.

- The manufacturer proactively quarantined products in transit and developed a corrective action plan. Alternative sources of prequalified vaccine were available to ensure continued supply.

- In September 2011, falsified copies of a prequalified ARV product were found in an African country. WHO immediately investigated the matter and published full information and recommendations for procurers and treatment providers.

- The Programme works closely with regulatory and other partners to monitor the quality of prequalified products.

#### Prequalification provides assurance that products meet consistent quality standards, every time.

Comprehensive information on prequalification and quality issues is available at:


- [www.who.int/prequal](http://www.who.int/prequal)

Vaccination is one of the most cost-effective health interventions.

Prequalification of vaccines aims to facilitate universal access to vaccines of assured quality to National Immunization Programmes in countries in most need.
Prequalification of vaccines is linked to the maturity of regulatory oversight and to the availability of international standards. Due to the inherent variability of biological products, standardization is key, as is the need for strong regulatory oversight. On the other hand, constant technical advances present continuous challenges for all stakeholders in assuring the quality of vaccines to the highest attainable standards.

The Programme prequalifies a wide range of vaccines according to a biennial prioritization list which takes into account the demand in UN-supplied markets, programmatic needs and strategies, and supply security.

A wide choice of prequalified vaccines is produced in 21 different countries, including some emerging economies. The top five countries by number of products prequalified are India, Belgium, France, Indonesia and the Republic of Korea.

A streamlined procedure was introduced in 2012 to reduce assessment timelines and make best use of limited resources through the following approaches:

- Recognition of regulatory assessment and inspection reports and test results for vaccines approved in USA, Europe, Canada, France, Belgium, Italy or Australia, or by the European Medicines Agency under Article 58
- Review of manufacturers’ Vaccine Product Annual Reports for each prequalified vaccine
- Risk-based re-assessment schedule taking into account NRA functionality, QC test results, complaints and adverse events history, and the number and scope of variations.

Evaluation principles
- Functionality of the national regulatory authority [NRA] of the producing country
- Dossier assessment
- Assessment of suitability for use of the vaccine in the intended settings
- Good manufacturing practice [GMP] inspections
- Random quality control (QC) testing
- Monitoring of complaints and adverse events

Fees
- As specified on the Programme’s website

Prequalified vaccines
- 129 prequalified vaccines listed on the Programme’s website

Pipeline
- Total of 14 vaccines under assessment
- 7 new submissions in 2012 — one completed, six ongoing

Variation control
- 53 manufacturers’ annual reports reviewed in 2012, giving rise to review of 448 variations
- Guidance on variations and variation reporting by manufacturers published for comment in February 2013

Re-assessment
- 12 prequalified vaccines reassessed in 2012

(as of June 2013, or for full years as stated)
The quality of prequalified products is monitored on an ongoing basis through QC testing as well as monitoring of complaints and adverse events following immunization (AEFI). Serious issues are fully investigated and followed up as appropriate by additional lot testing, site audits and other measures; if they are not remedied the vaccine may be removed from the prequalification list. Investigation outcomes are published on the web, providing safety signals to the Global Advisory Committee on Vaccine Safety.

Manufacturers are encouraged to meet with the Prequalification Programme before submitting applications for prequalification to gain a clear mutual understanding of product characteristics and development plans, maximizing the chances for success in prequalification.

In addition, detailed guidance on prequalification processes is provided on the Internet. Meetings with manufacturers are also held to ensure continued supply and to identify alternative sources where needed.

The Programme collaborates closely with responsible NRAs that oversee the quality of prequalified vaccines. It conducts regular consultations, and concludes collaboration agreements with the NRAs of countries exporting prequalified vaccines.

Representatives of the Developing Country Vaccine Regulators Network (DCVRN) — funded by member countries with donor support, and coordinated by the Prequalification Programme — participate in clinical reviews for prequalification, with significant benefits for harmonization and capacity-building.

Since 2006 a facilitated procedure exists for national registration of imported WHO-prequalified vaccines such as MenAfriVac®, a vaccine developed to address the yearly meningitis epidemics in the meningitis belt.

Through its emphasis on NRA functionality in the producing countries the Programme is promoting effective regulatory oversight of prequalified vaccines in the long term.

ACHIEVEMENTS

RESULTS

(as of June 2013, or for full years as stated)

Random testing
- 154 vaccine lots tested by WHO-contracted laboratories in 2012

Follow-up of potential quality issues
- 15 complaints investigated in 2012
- 9 reports of AEFI communicated to WHO in 2012 (7 in 2011), of which 7 were serious. None was linked to a quality defect, 3 were due to programmatic error

Consultations
- 119 one-on-one meetings held with manufacturers in 2012 (71 in 2011)
- Consultative meeting with IPV/OPV manufacturers held in October 2012
- Briefing workshops in India and China for a total of 18 new manufacturers in 2012

Guidances
- Guidance on Master Formulae and on environmental monitoring of clean rooms published in 2012

Collaboration with NRAs
- 109 meetings with NRAs in 2012
- Confidentiality and collaboration agreements with 6 NRAs in 2012

Developing Country Vaccine Regulators Network (DCVRN)
- One meeting held in Thailand in 2012
- One webex-based meeting held in 2012
- Annual 3-month secondments of 2 DCVRN representatives to Geneva (from Thailand and Indonesia in 2012)

Facilitated national registration
- 26 NRAs trained in 2011 using the example of MenAfriVac® in 2012 and 2013
- Support in target countries for introduction of MenAfriVac® in 2012 and 2013
Good quality medicines are a key element of global efforts to combat the pandemics of HIV infection, tuberculosis, malaria and other diseases which threaten public health, yet some products are still out of reach of patients in countries with limited resources.

Prequalification of medicines aims to facilitate access to medicines that meet unified standards of quality, safety and efficacy for all who need them.
**Prequalification of medicines** is underpinned by comprehensive WHo norms and standards, combining stringent harmonized regulatory standards as used in Europe, Japan and the United States with a practical focus on the technical aspects that are most relevant in developing countries. The Programme’s small team of 30 works with an external pool of regulatory assessors and inspectors from all settings. The Programme invites Expressions of Interest for prequalification of key medicines identified by WHO disease programmes. Since 2001, the programme has assessed close to 1000 products.

A competitive market for prequalified finished pharmaceutical products (FPPs) is now in place for most needed HIV-related and antimalarial medicines, and the prices of some products have reached minimum sustainable levels. Prequalification has been extended to reproductive health products and other categories. 2012 saw the prequalification of the first zinc product to help treat diarrhoea in malnourished children. In July 2013 the Programme released an Expression of Interest for medicines to treat neglected tropical diseases such as lymphatic filariasis, soil-transmitted helminthiasis and schistosomiasis.

Prequalified products of additional medicines are continuously needed. To bridge the gaps until prequalified or otherwise stringently assessed products become available, the Expert Review Panel (ERP) — coordinated by the Programme since 2009 — gives risk-based technical advice to procurers about products which can be procured while still under stringent assessment. A recent example is the first ERP-reviewed generic linezolide — a product for treatment of drug-resistant tuberculosis — that became available in June 2013 at 10% of the originator price.

### ACHIEVEMENTS

**Prequalified APIs (since 2011)**
- 39 prequalified APIs from India (31), China (7) and Italy (1) listed on the WHO website
- 20 APIs prequalified in 2012 (8 in 2011)
- Important “firsts” in 2013:
  - Prequalification of a contraceptive API (June)
  - Acceptance of semi-synthetic artemisinin (May)

### RESULTS

(as of June 2013, or for full years as stated)

**Evaluation principles**
- Prequalification of products and services at several stages of the production chain
- Dossier assessment and variation control
- Inspection of manufacturing sites, contract research organizations (CROs) and quality control laboratories (QCLs)
- Recognition or consideration of other stringent assessment outcomes

**Fees**
- To be introduced for selected services in 2013

**Prequalified FPPs (since 2001)**
- 397 FPPs prequalified over time
- 347 prequalified FPPs listed on the Programme’s website
- 48 FPPs prequalified in 2012 (35 in 2011), including 16 “firsts” i.e. product types not previously prequalified (20 in 2011)

**Re-assessment and variations**
- 44 prequalified FPPs undergoing requalification review
- 521 variation submissions to prequalified FPPs and 80 variations to API master files assessed in 2012

**Pipeline**
- Over 150 products under assessment
- 82 new applications received in 2012 (68 in 2011), 73 accepted after screening
- 21 ERP-reviewed products listed on Global Fund website in June 2013

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**Pipeline**
- 38 applications received in 2012
- 42 APIs under assessment

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An increasing choice of prequalified active pharmaceutical ingredients (APIs) has opened up new opportunities for production of affordable, good quality medicines, and has shortened the time to prequalification for the finished products that use them.

Similarly, acceptance of the first semi-synthetic (non-plant-derived) artemisinin in May 2013 is expected to stabilize the supply of starting material for the ACT market, making treatment available to more patients.
Prequalification of QCLs throughout the world supports regulators, procurement agencies and specific public health programme implementers in testing whether pharmaceutical products meet the specifications defined for them. Relationships with prequalified laboratories greatly stimulate collaboration on medicines quality issues such as investigating substandard medicines or combating counterfeit medicines.

Prequalification helps to detect and protect patients from poor medicines quality, which can occur at any time and may be linked to problems in manufacture, storage or distribution. The Programme follows up quality issues as part of its own evaluations and on behalf of other stakeholders. Its extensive network and the high number of inspections conducted annually provide added opportunities for on-site follow-up: in 2012 the Programme inspected 25 FPP manufacturing sites; 34 API manufacturing sites; 9 CROs and 7 QCLs in a total of 15 countries.

"Capacity building was almost universally considered a major positive impact of the PQ Programme." [Presentation of WHO-PQP external review results at the 6th consultative stakeholders meeting, April 2011]

In 2013 WHO approved a collaborative procedure for registration of prequalified products in participating countries: manufacturers can request the Programme to share full prequalification information with a participating NRA, which will then issue its independent registration decision within 90 days. This is a bonus for prequalification holders and a relief for overloaded NRAs.

Prequalification has profoundly changed the global markets of some key medicines. The prequalification model can be used by regulatory authorities of all WHO Member States to evaluate other nationally important medicines, such as life-saving antibiotics, to international standards.
In what has been termed “the decade of diagnostics”, access to quality-assured products, adapted to resource limited settings, will be decisive for the success of health programmes.

Prequalification of diagnostics and medical devices aims to promote and facilitate access to safe and appropriate products of good quality in an equitable manner.
Prequalification of diagnostics and medical devices is in line with international standards fostered by the Global Harmonization Task Force, a group of regulatory and industry representatives from Europe, Japan, Australia and North America, now succeeded by the International Medical Device Regulators Forum (IMDRF).

Regulatory best practice for in-vitro diagnostics and other medical devices is evolving and converging in high-income countries, but remains virtually non-existent in many low- and middle-income countries.

Diagnostics, in particular point-of-care tests, are composed of a number of diverse components, and the quality of each component, as well as the composition of the product, need to be understood and assessed.

The WHO prequalification process was redesigned from the predecessor evaluation mechanism in order to address new challenges, be more closely aligned with international regulatory principles, and ensure a fair and transparent process for all applicants.

**Evaluation Principles**

- Dossier assessment, to gain an understanding of the design, its validation and manufacture of the product
- Variation control and review of different regulatory versions
- Site inspections to assess the quality management system (QMS) under which the product is manufactured
- Laboratory evaluation by WHO Collaborating Centres to assess performance, lot-to-lot variation and ease of use characteristics
- Focus on customers in intended use settings, appropriateness for point of care and lower levels of the health care system
- Recognition or consideration of other stringent assessment outcomes under the fast-track procedure
- Monitoring of complaints and adverse events

**Fees**

- As specified on the Programme’s website

**Prequalified diagnostics — medical devices**

- 25 prequalified products (with a total of 107 catalogue numbers) listed on the Programme’s website
- Important “firsts” in 2013:
  - Adult male circumcision device
  - Test for HIV early infant diagnosis
- The fast-track procedure has been applied to 10 of the 25 prequalified products
- Inspections/re-inspections of the site of manufacture of 24 products were conducted in 2012 (21 products in 2011)

**Pipeline**

- Applications for 180 products received since 2010, of which 120 were accepted for assessment
- 77 products currently under assessment
- 21 new applications received, in the first six months of 2013 (12 in 2012)
- Evaluation of new product categories (HBsAg and HCV) commenced in 2012
- Advisory visits for new innovative diagnostics, i.e. point-of-care CD4 and HIV viral load/early infant diagnosis starting July 2013

**ACHIEVEMENTS**

**RESULTS**

*(as of June 2013, or for full years as stated)*
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<td>The Programme's review of quality management systems in manufacturing provides assurance, in principle, that products continue to conform to agreed international standards. In some circumstances, WHO inspections have revealed poor manufacturing practices for diagnostics, leading to public issue of a WHO Notice of Concern, with all products in the prequalification pipeline produced at the respective sites on hold until issues are rectified in a satisfactory manner. In such cases the Programme follows up quality issues on site and maintains public information and Notices of Concern on its website.</td>
<td>Identification of quality risks</td>
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<td>Quality monitoring in the field is carried out through a mechanism for complaints reporting, with appropriate follow-up action by the Programme and possible issuance of Field Safety Notices. Capacity for lot testing at country level is being increased.</td>
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<td>Prequalification is conducted in collaboration with external consultants, regulatory and diagnostics production specialists and WHO Collaborating Centres. A small group of 11 core staff coordinates the Programme’s activities, which require a wide range of expertise, including a thorough understanding of Quality Management Systems, auditing skills against ISO 13485 and other standards, expertise in immunology, microbiology, market dynamics, public health issues and other fields.</td>
<td>Participation by regulatory experts</td>
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<td>Being collaborative, most of the Programme’s activities have a capacity-building effect for regulators, assessors, inspectors and manufacturers.</td>
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<td>Collaboration and harmonization are being stepped up as international procurement agencies globally harmonize their quality assurance mechanisms and more clearly communicate the requirements and outcomes. This will incentivize manufacturers to ensure a sustained production that meets transparent, stringent quality requirements. The Programme’s role as a technical reference group is essential in this regard. The updated technical information on the Programme’s website supports partners in product selection (including accessories and regulatory versions), and tracking quality issues.</td>
<td>Stakeholder information and consultation</td>
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<td>As a quality-assured supply of key donor-funded diagnostic product types is emerging, international organizations are expanding their quality policies to additional product categories, such as tuberculosis and syphilis diagnostics, which will also be assessed by the Programme.</td>
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“By ensuring that products are acceptable for use in all WHO Member States, prequalification of diagnostics and medical devices fills a significant gap that regulatory review cannot fill.”
WHO prequalification was established to assure the quality of health products supplied to patients in all WHO Member States. It has achieved this goal: prequalification has significantly increased the availability of health products that meet unified quality standards, enabling international organizations to procure unprecedented volumes of key products meeting international quality standards.

After a major expansion of funding for health in the past decade, resources are now shrinking, since governments have competing priorities. The budget constraints of WHO Member States also affect WHO’s financing and ability to obtain expert support. This means that both the WHO prequalification programme and NRAs globally are faced with growing challenges in sustaining their operations, and are seeking new ways to achieve the greatest possible impact with limited resources.

The demand for quality-assured products is expanding. For vaccines, technical advances and evolving national and global strategies will guide priority-setting. For medicines, beyond infectious diseases, reproductive health, and neglected and tropical diseases, potential focus areas include treatment of non-communicable diseases such as cardiovascular conditions, cancer, asthma and diabetes, which are taking an increasing toll on developing countries. For diagnostics, there will be a wave of innovation with a greater range of products for use at point-of-care.

With available resources, prequalification will not be able to cover all these needed products. Its impact has been greatest in those markets where the large majority of buyers enforce harmonized stringent quality policies. For example, it has enabled the creation of a competitive market for quality-assured ARVs, which are now priced at lowest possible levels and in fact need to be protected from further downward pressure on pricing. On the other hand for other essential products, while there may have been some positive spill-over effect, quality assurance can represent a competitive disadvantage for manufacturers and can pose serious dilemmas for buyers who are forced to balance product quality against cost.

Prequalification is not intended as a permanent mechanism to replace regulatory control of health products. Its most durable contributions to global public health are the unified quality norms and standards which underpin it, and the practical guidance for their implementation, which has promoted regulatory convergence among WHO Member States. At a time of global economic crisis, regulatory work-sharing has become a must. The most important continued role of WHO is to support regulators in all WHO Member States to jointly assume the full range of their regulatory functions.

WHO has an assessment tool for regulatory authorities, and effective regulatory oversight by functional authorities is a prerequisite for vaccines prequalification. Building on these approaches, the establishment of regional networks for specific regulatory functions — such as inspection capacity close to major production sources, assessment of generic essential medicines to international standards and vigilance systems to identify and address quality failures — could be first steps on the way towards transferring full responsibility for stringent quality assurance to the national authorities.

Ultimately, a supply of safe and efficacious products at fair prices can be sustained only with effective regulatory oversight, countering the effects of purely price-driven markets and incentivizing both manufacturers and buyers to invest in product quality. Whether that will succeed depends on how highly the quality of health products is rated as a common good.