WHO Prequalification of Medicines Programme

Ensuring quality medicines: a decade of prequalification

Reflections from A. J. van Zyl, First Programme Manager for the WHO Prequalification of Medicines Programme

In March 2001, United Nations partners initiated a project, managed by the World Health Organization, to facilitate access to quality medicines used in the treatment of HIV/AIDS. Partnering with WHO were UNICEF, UNAIDS, and UNFPA. The World Bank also supported this project. The first manager for the programme was appointed by WHO on a six-month contract to establish, implement and manage the pilot project. The project was principally funded by donations and grants from Member States.

Objectives of the WHO Prequalification of Medicines Programme (PQP) were to:

1. Propose a list of prequalified products manufactured in sites that meet WHO norms and standards.

2. Follow-up on products and manufacturing facilities for quality issues.

3. Ensure that prequalification and update of the original approved list is carried out periodically and that variations and changes are correctly controlled.

4. Assist national drug regulatory authorities to build capacity in assessment, inspection and control of medicines for priority diseases.

In designing the project, a quality system was established consisting of a Procedure for Prequalification that was adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), various guidelines, norms and standards, and standard operating procedures (SOPs). Prequalification (PQ) was based on existing WHO norms and standards approved by the ECSPP. In those cases where WHO did not have guidelines, relevant guidelines from ICH were used. A web site was also established to disseminate PQ vision, mission, procedures, guidelines, training material, results and information (1).

The initial focus was to prequalify medicines used in the treatment of HIV/AIDS. It was estimated that the number of people needing antiretroviral (ARV) therapy in 2003 was in the range of 100 000 with an ARV therapy coverage of only around 2%. It was further estimated that less than 10% of people in most African countries had access to ARV treatment (2). Figure 1 shows the number of deaths per 100 000 in the US population in the period 1982–1993 (3).

Later on, due to the pressing need for quality medicines in other disease areas, the project was expanded to include products used in the treatment of tuberculosis (TB) and malaria.

Prequalifying medicines is achieved through an extensive evaluation procedure that consists of assessment of product data and information that are voluntarily submitted by interested applicants and manufacturers expressing their interest to participate in the project. This is followed by inspection of manufacturing and testing sites. No fees have been charged by WHO since the beginning of prequalification but this practice is under
review. Sites are inspected to verify data submitted in the product dossiers and to assess compliance with WHO good manufacturing practices (GMP), good clinical practices (GCP) and other appropriate guidelines.

Reasons for initiating the PQ pilot project was concern about low quality products circulating in the international market, the prevalence of spurious products and also as a result of the recommendation in a report from a group of independent experts. The report found that many procurement organizations had no, or very limited, quality assurance systems in place to ensure that good quality products were procured.

Human resources
In terms of staff appointments, the PQP team slowly grew from one manager in 2001 to a manager plus one coordinator for assessments and one assistant during the first two years. One inspector was seconded from the French medicines regulatory agency in 2003, and in subsequent years the team expanded to include one manager, a coordinator for assessments and three inspectors. The organization chart in 2011 comprises:

- one PQP manager
- one head of inspections with five inspectors
- one head of assessments with seven assessors
- eight support staff
- one person each for liaison, capacity building and training, and sampling and monitoring (which includes prequalification of quality control laboratories).

Expansion of the programme after 2006 was possible due to the financial support from the Bill & Melinda Gates Foundation. Today, the programme is largely financed by UNITAID but is seeking a broader donor base.

External assessor group
From the initial one staff member with six external assessors present at the assessment meeting in June 2001, the group has grown over the past ten years to include on average seven internal assessors and more than 20 external assessors at a group session.
Assessments
Data and specifications are submitted and assessed by teams of assessors from national medicines regulatory authorities and WHO staff. Data and specifications include but are not limited to the active pharmaceutical ingredient (API), formulae, manufacturing process, stability (appropriate packaging and suitable for the intended market) and bio-equivalence data (for generic products).

Group assessment sessions are held every two months at the UNICEF offices in Copenhagen. Requirements for product data and information have also intensified over the years. In 2011, the recommendation is that manufacturers should submit a dossier in the common technical document (CTD) format (4–6).

To build capacity in developing countries, a unique three-month rotational post was established in the area of dossier assessment in 2006. Since then, 14 developing country regulators from nine countries have benefited from the arrangement.

During assessment, multisource (generic) drug products are expected to satisfy the same quality standards as those applicable to the originator/reference product. In addition, assurance has to be provided that they are clinically interchangeable with equivalent originator products (4).

Inspections
The inspection unit operates in accordance with an established quality system consisting of documented SOPs, formats for reports and letters, a training programme and related aspects as recommended in guidelines (7). Inspections are performed at the facilities of finished product manufacturers, API manufacturers, quality control laboratories and clinical sites including contract research organizations (CROs). Feedback on the implementation of norms and standards is given to the relative unit in WHO and recommendations are made for the development of new GMP guidelines (or revision of existing ones) as appropriate.

Complaints on prequalified products that are received in PQP are logged and investigated by the inspectors. Inspectors and assessors must comply with the confidentiality and conflict of interest rules of WHO.

Inspectors publish a quarterly newsletter available on the PQP web site as well as submitting articles to the WHO Pharmaceuticals Newsletter and WHO Drug Information (see “Further reading” on page 239).

Monitoring
Field sampling and testing projects have been carried out by PQP in order to monitor the quality of medicines (both WHO-prequalified and non-WHO prequalified) procured by UN agencies (8). Through cooperation with medicines regulatory authorities (MRAs), these projects also contribute to national quality control of medicines, to strengthening of health systems and capacity building. Samples are collected by MRA staff and tested at WHO-prequalified laboratories and results are published. Several reports and publications in scientific journals have become available over the ten-year period.

Brief overview
After the initial establishment of the project in 2001, the first list of prequalified products was published in March 2002. The project expanded to include prequalification of quality control laboratories and tuberculosis and malaria medicines in 2003–2004. Due to inspection findings of non-compliance with GCP, some products were withdrawn from the list in 2004. In order to improve patient compliance and ease of dosing, fixed dose combinations were developed. PQP was instrumental in providing the corresponding guideline. As the applicant of a prequalified medicinal product invariably makes changes to a supplied product during the product’s life cycle, a variation guideline was also developed to ensure appropriate oversight of such changes.
As the PQP become successful, it was extended to include HIV/AIDS, TB and malaria, reproductive health products, zinc sulphate for the treatment of diarrhoea in children, products used in treatment of influenza and diethylcarbamazine (DEC).

Mutual confidentiality agreements were signed in 2005 between the US Food and Drug Administration (FDA), PQP and the Quality Assurance and Safety: Medicines Unit of WHO and in 2011 between the European Directorate for the Quality of Medicines (EDQM) and WHO.

Within the biopharmaceutical classification system, PQP assisted in the development of a guideline on comparative dissolution for biowaiver applications.
Due to cases of non-compliance identified during inspections at CROs, it was decided to facilitate the development of an additional guideline for CROs to assist in better understanding the application of GCP for bioequivalence studies.

Due to reporting of low quality reproductive health products and problems in procuring good quality products, PQP expanded its scope and included reproductive health products within the PQP in cooperation with UNFPA.

In September 2008, the USA issued an import alert against Ranbaxy, a pharmaceutical company based in India. As there were several of their products listed in PQP, a joint inspection with Canada, Australia and the United Kingdom was undertaken at Ranbaxy to investigate impact. At that time, to respond to World Health Assembly Resolution 57.14 and the request by Member States and international procurement organizations to enhance transparency, PQP published a first Notice of Concern (NOC) for manufacturing sites. Provision was also made for issuing Notices of Suspension (NOS) for products. Resolution 57.14 requested WHO, among other actions to “ensure that the prequalification review process and the results of inspection and assessment reports of the listed products, aside from proprietary and confidential information, are made publicly available”.

As a consequence, publication of WHO Public Inspection Reports (positive outcomes of site inspections) and WHO Public Assessment Reports (positive outcomes of dossier assessment) and the list of prequalified products provides the public and regulators with extensive information on the PQ evaluation of products and sites.

The structure of PQP changed in 2007 with the appointment of a new Programme Manager, appointment of a Head of Inspections, and a Head of Assessments. In the same year, the launching of the PQP web site in Chinese followed, as well as implementation of the biowaiver procedure. All NOC and NOS were also published. In keeping interested parties informed of the activities of PQP, an inspection newsletter was regularly published as well as articles in publications. To further ensure transparency and better serve clients, PQP undertook a manufacturer’s survey in 2009.

In an effort to expedite registration of prequalified products, prevent duplication, and promote harmonization, PQP established and implemented a joint assessment programme with the East African Community (EAC) for product dossiers and a collaborative procedure for inspections (joint inspections and recognition of inspection reports among regulators). Both initiatives deserve more in depth clarification. It is anticipated that activities will be described in more detail in future publications.

With an increasing number of product dossiers containing comparative dissolution data, the inspection unit began inspections at sites to verify reliability of dissolution data and GMP compliance (biowaiver applications).

A major step forward in assisting MRAs to obtain information on the quality of APIs and API manufacturing sites, was implementation of the procedure for prequalification of APIs in 2010. This procedure is based on the assessment of API Master Files (also known as a Drug Master Files) and inspection of the sites.

In further attempting to ensure the quality of products purchased, a model quality assurance system for procurement agencies was developed. This guideline was adopted by the ECSPP and the Interagency Pharmaceutical Coordination group (IPC) and is used by different organizations including the World Bank. Following publication of the first Expression of Interest for HIV/AIDS products, more than 90 product dossiers were
received for assessment in the first group assessment session in Copenhagen. The number of product dossiers submitted for assessment has varied from year to year, and between disease groups.

Since 2001, more than 60 training workshops have been organized or co-organized in countries including Austria, Belgium, Brazil, China, Estonia, India, Kenya, Pakistan and Tanzania. Twenty quality control laboratories (QCLs) have been prequalified and four sampling and testing projects have been undertaken.

In 2008, PricewaterhouseCoopers was appointed to assist in the development of a business plan. Recommendations for improvement were made and it was calculated that the return on investment in PQ was 170.1 in the period 2009–2013.

Outcomes of the manufacturer survey carried out in 2009 (11) were presented to a manufacturers’ meeting in Copenhagen in April 2010 and at the PQP Annual Stakeholders meeting in 2011. The report concluded that both PQP assessors and inspectors are meeting or exceeding manufacturer expectations for service delivery. The structure of PQP generally delivers levels of service at, or above, those expected by manufacturers.

However, the service process is falling short of manufacturer expectations with respect to review/reply time for product dossiers; opportunities for in-person communication during the assessment process; question/problem resolution during assessment; consistency of membership in the team of assessors throughout the process, and local/national representation in on-site inspection teams. Most manufacturers view PQP GMP requirements as more stringent than those of the US FDA or European Medicines Agency. The findings from this survey indicate that pharmaceutical manufacturers consider PQP to be a well-designed, well-executed programme. PQP assessors and inspectors are meeting or exceeding manufacturer expectations for service delivery in all processes.

Table 2 reflects the number of inspections by site, over the years, including for APIs, finished pharmaceutical products (FPPs), CROs and quality control laboratories. By 21 June 2011, a total of 253 finished products had been prequalified by WHO. This included 190 HIV/AIDS products, 31 TB; 17 malaria; seven influenza, and eight RPH products.

**Conclusion**

The establishment and implementation of a prequalification procedure for pharmaceutical products, especially in the area of HIV/AIDS, has significantly facilitated access to quality medicines. Moreover, it has also triggered harmonization between quality assurance policies of various organizations involved in procurement of medicines for the developing world such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, UNFPA, UNITAID, and beyond.
Several publications reflect the increase in number of patients on antiretroviral treatment over the last decade, as well as the reduction in price of these medicines (see figure 2 below) (12). For example, in 2005 it was reported that the cost of highly active antiretroviral therapy (HAART) decreased from US$ 778 per month in 1996 to US$ 100 per month in 2000, and further to US$ 33 per month in 2003 after the first generic ARVs were made available. Where only 13% of patients were able to afford therapy in 1996, the number increased to 44% in 2003. The most common ARV regimen was 3FDC (lamivudine, stavudine, nevirapine) which was administered to 56% of patients receiving HAART (13). This is supported by the Global Fund’s quality assurance policy (supporting procurement of prequalified products) and Global Fund reports on procurement in countries (14).

Figure 2: Number of people receiving ARV therapy

The majority of products on the list of prequalified medicines are multisource/generic products. Generic manufacturers are the main suppliers of essential medicines in developing countries: 67% of medicines produced in India are exported to developing countries. Also, according to PEPFAR – 73% of ARVs delivered in focus countries are generic medicines (17).

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16. Medecins sans Fontières (MSF). Examples of the importance of India as the “Pharmacy of the developing World” (2007) at http://www.msfaccess.org/main


Further reading


WHO Drug Information


WHO Pharmaceuticals Newsletter

1. Inspection of manufacturing sites for active pharmaceutical ingredients within the WHO Prequalification of Medicines Programme. Number 1, p. 12 (2011).

2. Collaborative participation of inspectors from medicines regulatory authorities (MRAs) in inspections coordinated by the WHO Prequalification of Medicines Programme. Number 3, p. 12 (2010).

