ANNUAL REPORT 2012
GLOBALIZING QUALITY

WHO PREQUALIFICATION
OF MEDICINES PROGRAMME
A United Nations Programme managed by WHO
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ACRONYMS

ACT ......................... artemisinin-based combination therapy
API ......................... active pharmaceutical ingredient
ARV ......................... antiretroviral
ERP ......................... Expert Review Panel
FPP ......................... finished pharmaceutical product
Global Fund ........................ Global Fund to Fight AIDS, Tuberculosis and Malaria
GMP ......................... good manufacturing practice
HIV/AIDS ..................... human immunodeficiency virus/acquired immune deficiency syndrome
NAFDAC ............... National Agency for Food and Drug Administration and Control
NMRA ............................... national medicines regulatory authority
PQP ....................... WHO Prequalification of Medicines Programme
QCL ...................... quality control laboratory
TB ............................ tuberculosis
UNFPA .................. United Nations Population Fund
UNICEF ................. United Nations Children’s Fund
WHO ..................... World Health Organization

Text: Daniela Bagozzi
Design: messaggio
As we move towards the 2015 deadline for the Millennium Development Goals, the WHO Prequalification of Medicines Programme (PQP) continues to make a tangible difference in the fight against priority diseases and to the harmonization of medicines quality. The Programme is a unique contribution to the World Health Organization (WHO) priority functions of norms and standards setting and health system strengthening, and an excellent example of international stakeholder partnership. Its role as trusted and unbiased global partner in scaling up access to quality treatment benefits patients, countries, international health agencies and emerging market manufacturers. It ensures that billions of US dollars’ worth of medicines purchased by international agencies meet international quality standards. And by increasing the number of quality-assured products it has fostered competition and helped drive medicines prices down. But in an age of budget cuts and increasing emphasis on quick wins, sustaining progress made to date will demand increased effort.

In 2012 we continued to ensure that medicines procured for developing country priority conditions meet international standards of quality and safety, to lay the groundwork for global unified standards, and to build in-country know-how in medicines quality assurance. In addition, we stepped up our efforts to speed up faster delivery of medicines in countries through an innovative collaboration with national medicines regulatory authorities (NMRAs) aimed at accelerating national registration of prequalified medicines.

48 medicines and 20 active pharmaceutical ingredients (APIs) were added to WHO’s lists of prequalified products, making 2012 one of the most dynamic years in terms of availability of quality-assured products. The numbers of malaria and tuberculosis (TB) medicines prequalified were particularly high, significantly increasing the choice of quality treatment for those two diseases. We also continued our in-house training of developing country regulators, conducted 84 inspections of manufacturing plants, quality control laboratories (QCLs) and contract research organizations, and prequalified four medicines QCLs.

But with the good news there are also some present and future hurdles. The area of TB continues to pose challenges with too few manufacturers interested in developing the needed medicines, resulting in the use of poor-quality products, which are often the only drugs readily available on the market. The same can be said for reproductive health products, where the demand for cheapest buys discourages manufacturers from seeking prequalification and results in poor-quality medicines reaching women, with serious consequences for their health. Slow national registration of prequalified medicines also contributes to poor availability of quality products; if there is no market demand, manufacturers are less likely to improve the quality of their production and seek prequalification as a means of entering international markets.

In short, there is still work to do to ensure better coordination between quality assurance activities, procurement, and country capacity to absorb new products and develop the required technical capacity to monitor their quality. These are areas that I would encourage the global health community to address in a serious manner. Without universal access to quality medicines there can be no public health progress, lives will be lost unnecessarily and precious health investments will be wasted. Countries and the international community have made enormous advances in providing effective quality treatment, as demonstrated by the fact that 9.7 million people living with HIV/AIDS in low- and middle-income countries now have access to such treatment. We must build on that success, replicate it in other priority areas, and strive for countries’ greater ability to address their health challenges.

Kees de Jonchere
Director, Department of Essential Medicines and Health Products
The WHO Prequalification of Medicines Programme (PQP) aims to ensure that medicines bought for priority diseases meet global standards of quality, safety and efficacy, in order to optimize use of health resources and improve health outcomes. It was established in 2001 to address two broad challenges: insufficient in-country capacity to assess medicines quality; and the limited choice of affordable treatment for diseases affecting poor populations. By conducting a comprehensive quality assurance evaluation of priority medicines, validating numerous generic products and strengthening local capacity, PQP ensures that national and international agencies make sound public health and cost-effective choices when purchasing medicines and supplying them through countries’ health systems.

The Programme has sought constantly to respond to emerging global and developing country health priorities: first by assessing medicines to treat HIV/AIDS, malaria and TB, and then gradually expanding its activity to reproductive health, neglected tropical diseases, and APIs (the ingredient(s) of a medicine that ensure its therapeutic effect).

Effective medicines quality work spans a wide range of activities and is dependent on many different actors who, ideally, have equal knowledge, skills and a unified sense of direction. Such harmony among the different actors has still not been reached today. For that reason, PQP has engaged increasingly in activities that go beyond product assessment, to support pharmaceutical quality across the full spectrum of processes needed to deliver quality medicines to patients. These include technical assistance and training for national regulators, guidance for manufacturers, faster registration and post-procurement quality control. The main objective is to disseminate sound knowledge and ensure that all the actors concerned work according to international quality standards. This work has been especially appreciated by low- and middle-income countries as they evolve towards stronger health systems, local quality assurance and local manufacturing capacity.

Through PQP’s work for over 10 years, quality is now widely considered an integral part of treatment access: medicines need to be available and affordable, but public health results can be achieved only if those medicines are also of good quality, adapted to patients’ needs, with as few side-effects as possible.
Major achievements since 2001

Since its inception, the programme has played a central role in increasing access to medicines for priority diseases, harmonizing quality standards for generic manufacturers and transferring skills to developing countries. Top-line examples include:

- **HIV/AIDS** — made quality HIV/AIDS treatment possible by evaluating generic medicines. Four-fifths of the eight million people in low- and middle-income countries receiving treatment today are taking WHO-prequalified antiretrovirals (ARVs).

- **malaria** — had a major impact on the market for the best malaria treatment available, with sales of WHO-prequalified artemisinin-based combination (ACT) medicines exceeding 280 million individual treatment courses in 2011 (Figure 1).

![Figure 1: ACT deliveries, including contribution from the Affordable Medicines Facility – malaria](image)

Figure 1: ACT deliveries, including contribution from the Affordable Medicines Facility – malaria

![ACT deliveries graph](image)

Source: The data was provided by 8 manufacturers who are eligible for procurement via WHO and UNICEF. They reflect deliveries of four recommended artemisinin-based combination therapies (artemether-lumefantrine, artesunate-amodiaquine, artesunate-sulfadoxine-pyrimethamine, and artesunate-mefloquine) as fixed-dose combinations and co-blisters. Companies did not indicate the source of funds for these deliveries, but the vast majority were purchased with international funds.

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2. The Affordable Medicines Facility – malaria is an innovative financing mechanism designed to expand access to the most effective treatment for malaria, ACTs. It is hosted and managed by the Global Fund. See: http://www.theglobalfund.org/en/amfm/
■ TB — helped to improve treatment outcomes in TB, for which mortality rates have fallen across the board, including in most of the 22 highest-burden countries. 

■ manufacturers — prequalified over 350 finished pharmaceutical products (FPPs) (Figure 2), but assessed close to 1000 products (mostly produced by emerging market companies), provided guidance and information on good manufacturing practice (GMP) to numerous companies and increasingly supported capacity-building for local production.

■ national regulators — increased local quality-monitoring capacity through hands-on training of developing country medicines regulators, including by inviting their participation in PQP assessment and inspection activities.

■ APIs — launched a new activity to assess the quality of API to ensure finished product quality.

■ reproductive health — advocated for the need to improve this market sector, worked with UN partners, especially UNFPA, to harmonize procurement policies across the UN spectrum, and continued to push for better quality contraceptives by providing technical advice to manufacturers.

■ post-procurement quality monitoring — ensured quality of medicines all the way to the end user in conjunction with a sister programme that carries out assessments of QCLs in the countries where prequalified medicines are procured.

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“Contraceptives constitute a big market but there has been little attention given to quality — this is perhaps one reason why family planning is not always successful in a number of countries. Prequalification is helping to change that by constantly pushing for better quality in medicine and medical device manufacturing and procurement.”

Morten Sørensen
Deputy Chief, Procurement Services Branch, UNFPA

“One of the many ways that the World Health Organization makes an enormous difference in the fight against AIDS, tuberculosis and malaria is by facilitating access to quality medicines on a tremendous scale, through prequalification.”

Christopher Game
Chief Procurement Officer
Global Fund to Fight AIDS, Tuberculosis and Malaria

“There is no way we could be treating 8 million people for HIV/AIDS without prequalification’s impact on the generic market for ARVs.”

Jonathan Quick
President and CEO
Management Sciences for Health

“From practically no paediatric medicines for AIDS, TB and malaria 10 years ago, today we have a good number of products prequalified and children are receiving appropriate treatment. This would not have happened without prequalification’s stimulation of generic market innovation.”

Shanelle Hall
Director, UNICEF Supply Division

STAKEHOLDER VIEWS
ACTIVITIES IN 2012

Highlights

- 48 medicines prequalified, including the first zinc product
- Largest ever number of malaria and TB products prequalified, including some paediatric and 2nd-line medicines
- 20 APIs prequalified, including the first two APIs from a Chinese manufacturer
- Four QCLs prequalified, including the first Chinese QCL
- New initiative aimed at fast-tracking country registration of WHO-prequalified products piloted
- Fast response system for product complaints through the use of WHO-prequalified QCLs
- Market incentive work to encourage manufacturers to enter priority disease markets in low- and middle-income countries and provide affordable quality-assured products.

Products prequalified

In 2012 WHO prequalified 68 products (Figure 3), 20 of which were APIs. In the disease categories, 18 medicines were prequalified for HIV/AIDS, 10 for malaria, 19 for TB and a first zinc product, a substance that reduces the severity and duration of diarrhoea in malnourished children (Figure 4). Of particular note were the malaria and TB products: in terms of number, but also because they included some important new malaria medicines and extended the range of quality-assured treatment options.
Figure 4: FPPs by therapeutic area prequalified during 2008–2012
Malaria

Out of the full list of 28 anti-malarial products prequalified since 2001, 10 were added to the list in 2012. These included several firsts:

- **artesunate + mefloquine combination** — expected to become the 1st-line treatment of choice in a number of malaria endemic countries, in South-east Asia and South America, once the prequalified product receives national registration.

- **generic fixed-dose amodiaquine + artesunate combination** — adopted as 1st-line treatment in over 20 countries, mainly in central and western Africa. The co-blistered loose combinations are rapidly losing ground to the one-pill combination, which is increasingly popular as it is easier to administer and may be easier to tolerate.

- **artesunate + [sulfadoxine + pyrimethamine]** — adopted as 1st-line treatment in 12 countries in the Eastern Mediterranean Region, India and South America.

HIV/AIDS

Several of the HIV/AIDS products prequalified in 2012 are used in the treatment of the opportunistic infections that occur in patients because of weakened immunity due to the HIV virus. They are very welcome because prior to 2012 the list contained few such medicines. Some of these, and a number of ARVs were prequalified for the first time:

- **Gancyclovir** — the preferred antiviral drug used in the treatment of a herpes virus in HIV-infected adults and children with severe immunodeficiency.

- **Azithromycin** — an antibiotic used in treatment of non-TB mycobacterial diseases in HIV-infected adults and children, in combination with other anti-mycobacterial drugs. It can also be used in the treatment of other pulmonary and urinary bacterial infections.

- **Diazepam** — a hypnotic drug for symptomatic and palliative care of HIV.

- **Darunavir and etravirine** — preferred 3rd-line ARVs. These are used to treat patients for whom 2nd-line regimens are no longer proving effective. Darunavir has also been recommended as an alternative 2nd-line option in some situations.

- **Paediatric lamivudine tablet** — a preferred drug option in 1st- and 2nd-line treatment of children, when combined with other medicines.

- **Dispersible efavirenz tablets** — a preferred option in 1st-line treatment for children over 3 years of age, for use in combined formulations.
The increase in the number of prequalified antimalarials is largely attributable to a recently introduced, rapid quality risk assessment mechanism, which uses a risk rating approach to assessing medicines that are urgently needed but not yet prequalified. The mechanism provides a significant incentive for manufacturers, especially those producing antimalarials and TB treatments, to progress to full prequalification (see insert on the mechanism on p.11).

Prequalified APIs for malaria medicines were also abundant in 2012, accounting for 12 of the 20 ingredients that were listed over the year. This means that 2012 saw a significant increase in the choice of both prequalified antimalarials for procurement and prequalified antimalarial APIs. The latter will give manufacturers a much broader choice of quality-assured ingredients for their products and should contribute to increased production of quality medicines. This in turn should promote competition and reduced prices. A second important benefit resulting from a greater choice of quality antimalarials at reduced prices could be less incentive to buy cheaper but poor-quality medicines, which have insufficient or no therapeutic effect and provoke drug resistance.

Another important development for the malaria portfolio in 2012 was a submission from Sanofi of the first source of semi-synthetic artemisinin. Artemisinin is the vital chemical compound used to prepare several APIs used in ACTs, which are the WHO-recommended treatment for malaria and the best medicines known to stave off drug resistance. This landmark event was significant for patients and global health as the shortage of plant-derived artemisinin has often created gaps in the sustainable production and provision of recommended malaria medicines.
TB
An unprecedented number of TB products (19) were prequalified in 2012, including some paediatric and 2nd-line formulations. These are of particular importance for several reasons. First, the market for TB medicines has so far failed to provide the medicines needed due to a paucity of research and development of better medicines, for both simple TB and the multidrug-resistant strains. Second, WHO treatment guidelines only recently updated recommendations for fixed-dose combinations and dosage forms for children. Third, due to difficulties in diagnosing multidrug-resistant TB, countries and international agencies have been unable to give manufacturers a clear idea of the volume of medicines needed; the result is that few manufacturers are willing to enter the market, leading to stock-outs of medicines to treat this deadly and complex disease. Because of these combined factors, medicines markets in low- and middle-income countries have been characterized by a prevalence of sub-standard TB products. The newly-prequalified medicines should give procurers greater confidence in supplying quality treatment and hopefully contribute to reversing the negative trends observed in the TB drug market.

APIs
An important recent addition to PQP’s work is the assessment of APIs for HIV/AIDS, malaria, TB and reproductive health products. The 20 APIs prequalified in 2012 included the first prequalification of 8 API types (dihydroartemisinin, emtricitabine, ethambutol, lamivudine, nevirapine, piperaquine phosphate, rifampicin and zidovudine) and of more than one source in some cases. They also included the first two APIs from China — zidovudine, used in the treatment of HIV/AIDS, including as prevention of mother-to-child transmission, and lamivudine, also used in the treatment of HIV/AIDS. Quality-assured APIs are the building blocks of good-quality medicines and PQP provides a unique service in this respect: even stringent regulatory authorities do not publish a list of API-sources that are of assured quality and verified GMP. Since the majority of API manufacturers involved in PQP are located in India and China, and most medicines manufactured globally use APIs produced in Asia, PQP is helping to ensure that imported APIs meet international standards of quality across the board.
While much progress has been made in expanding the availability of quality-assured priority medicines, there are still too few WHO-prequalified or stringently authorized products on the market to ensure a sustainable supply of all medicines needed by treatment programmes. To promote greater availability, the WHO Department of Essential Medicines and Health Products has for the last three years hosted and coordinated a novel programme that intersects with prequalification. It operates a quality risk assessment mechanism in the form of an Expert Review Panel (ERP) that assesses the quality risks of medicines needed by grantee countries of the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), or procured by UNFPA, but which have not yet been fully evaluated for stringent quality requirements. Based on standardized and transparent criteria, the ERP advises whether each product would be acceptable for procurement, for up to 12 months, pending WHO prequalification or approval from a stringent regulatory authority. The ERP can assess as many as 150 medicines a year. The outcomes so far have been crucial to securing a sustained supply of missing medicines, especially TB medicines and some antimalarials. In 2012, 37 out of 74 HIV, TB, malaria, and reproductive health products submitted were deemed fit for procurement. 19 TB products out of 34 submissions were considered fit for procurement only if their benefits outweigh their risks, taking into account the circumstances of the specific country or treatment programme. For example, stock-outs of medicines lead to treatment interruption, the impacts of which can be much more severe than the consumption of a medicine that does not yet fully adhere to international quality standards.

Given the as yet low number of reproductive health medicines that have been prequalified, the 12 reproductive health medicines that ERP assessed as being fit for procurement significantly increased the choice of products that procurers could select from. The ERP process has been well accepted by manufacturers and procurement agencies, and promoted progression of medicines to prequalification. Of 134 eligible products assessed by the ERP during the period 2009–2011, 82 were subsequently prequalified by WHO or approved by a stringent regulatory authority. Other international agencies have adapted their quality assurance policies to WHO standards and are using the mechanism jointly with the Global Fund. This has resulted in unified quality standards and efficiency gains for all stakeholders.

Rapid quality risk assessment mechanism
SPOTLIGHT ON EMERGING MARKETS AND THEIR ROLE IN EXPANDING ACCESS

China — enormous potential for scaling up treatment

China has become a major exporter of medicines to the developing world and to Africa in particular. However, only recently has China taken steps towards reviewing its pharmaceutical production processes and applying internationally accepted standards to manufacture and quality assurance. 2012 saw WHO prequalification of the first Chinese API and the first Chinese QCL. This was important on several fronts. First, as the Chinese Government progresses towards universal health coverage it will see increased demand for quality-assured medicines for its large population; second, the fact that a Chinese API manufacturer has shown itself capable of meeting international standards could encourage many other Chinese manufacturers to seek prequalification of their products. Since the API is the most expensive part of a medicine, more quality-assured sources of APIs should increase competition and drive down API prices. This should eventually lead to further price reductions of FPPs, whether for export or local use. Equally, if more QCLs are prequalified, improvements in the quality of medicines produced in China can be anticipated. China, like India, has been supplying its own TB drug market for some time and some Chinese TB medicines, following technical assistance through PQP, are in the pipeline for prequalification and international procurement.

Nigeria — building quality local manufacturing

As an emerging economy and large provider of goods and services to countries in West Africa, Nigeria is poised to expand its pharmaceutical production in the coming years. To that end, both government authorities and local manufacturers have asked PQP for technical assistance to produce FPPs and APIs according to international quality standards. PQP is already auditing a number of Nigerian manufacturers and guiding them in preparing technically sound submissions for prequalification. In 2012 programme staff met with Nigeria’s health authorities, its pharmaceutical manufacturers association and individual companies interested in improving their manufacturing practices, particularly for malaria medicines. An important outcome of the meeting was the decision that PQP, in cooperation with the Nigerian authorities, will intensify its support of selected local manufacturers, with capacity building in quality production. In parallel, the programme will continue to provide hands-on training and transfer of knowledge to Nigeria’s regulators. Given the importance of Nigeria in its geo-economic region, the country’s ramped up production of quality medicines could lead to the expansion of regional markets, harmonized quality standards in West Africa and reduced prices for the needed treatments.

See: http://www.wpro.who.int/countries/chn/SICHNpro2011_finaldraft.pdf
India — 10 years of priority medicines supply

Dubbed the pharmacy of the developing world, India has steadily provided much-needed generic medicines to international markets, at very competitive prices, during the past decade. Of the 312 medicines on the WHO List of Prequalified Medicines at the end of 2012, 231 (74%) were generic, of which 200 (87%) were manufactured in India.

Indian generic manufacturers have played a key role in the scale-up of HIV/AIDS treatment programmes: first by offering more affordable alternatives to the expensive brand-name ARVs in the early 2000s, and then by regularly applying for prequalification, improving their manufacturing practices and developing innovative formulations specifically indicated for developing country conditions, such as paediatric medicines and fixed-dose combinations.

The majority of people on ARV treatment today in low- and middle-income countries are taking WHO-prequalified Indian generic medicines. According to a study published in the Journal of the International AIDS Society in 2010 (“A lifeline to treatment: the role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries”) — Indian-produced generic ARVs have accounted for more than 80% of the donor-funded developing country market since 2006, and for 87% of ARV purchased volumes in 2008. In the paediatric AIDS area, Indian-produced generics accounted for 91% of the whole volume purchased in 2008.

India has also provided some innovative malaria formulations and is becoming a major producer of APIs, which it exports to numerous countries, including the United States and Europe.

7 In volume 13(35).
SUPPORT TO COUNTRIES

Accelerated registration mechanism

Providing medicines that are quality-assured in the quantities needed by a population is not just a matter of pricing and creating market demand but also of ensuring that the medicines can legally enter a specific market. If a medicine is not registered nationally, then neither local nor international procurers can bring that medicine to the people who need it. National registration is therefore a determining factor in access to both medicines and other health technologies.

2012 saw the launch of the pilot phase of a collaborative procedure between PQP and NMRAs aimed at fast-tracking registration of WHO-prequalified medicines in countries where the medicines are needed. Ten countries participated in the pilot phase (Botswana, Ghana, Ethiopia, Kenya, Namibia, Nigeria, Tanzania, Uganda, Zambia and Zimbabwe) which saw faster registration of a hormonal contraceptive and an ARV.

Under the procedure, manufacturers of a prequalified product can authorize PQP to share its assessment and inspection reports, in full, with NMRAs in countries where registration is sought. If the NMRA agrees to apply the procedure to the specific product, it commits to issuing its independent decision within 90 days. If the decision is positive, then the product can be marketed immediately for the benefit of patients.

Thus the initiative offers several benefits. It gives manufacturers greater incentive to apply for WHO prequalification. In most countries with low-capacity regulatory authorities registration can take several years. This discourages manufacturers from seeking prequalification as there is no business incentive to invest in the WHO assessment scheme without assurance that they can enter a market. With a significantly shorter registration time of 90 days, the new mechanism will provide manufacturers with greater market opportunities for their products, create competition, and, once registration is granted, provide international procurers with more products from which to select.

A further important benefit of the initiative is capacity building in countries and the saving of internal resources. The detailed data from prequalification assessments and inspections will give NMRAs an inside view of international quality control standards and registration processes, and serve as models that they can replicate. In addition, the initiative will ensure that a medicine is registered under the same conditions in participating countries, which will facilitate assessment and approval of post-registration variations, and quality control. The procedure will also serve as a model for those situations in which a medicine is tested and registered in a reference country. Other NMRAs from the region may thereafter choose to forego their own assessment and manufacturing site inspection, and proceed directly with national registration, based on the neighbouring country’s assessment.

For procurers of these medicines, the greatest benefit of the mechanism is that it ensures that prequalified medicines reach end-users much more quickly. Second, it allows PQP to work closely with regulatory authorities and advise them on international quality standards and practices, thereby ensuring a continuum in knowledge transfer and training.

The procedure is completely voluntary and will see full implementation in 2013. It is hoped that other African and some South-East Asian countries will also participate in the future.
PQP rotational fellowships

Aside from organizing training workshops in countries and advising regulatory authorities on quality issues, PQP provides regulatory capacity building through rotational assessor fellowships. During the period 2006–2012, 18 assessors from 9 countries completed a rotation. Some of these have progressed to more senior positions within their organizations.

The rotational fellows work alongside PQP assessment staff at headquarters. This gives them exposure to a wide range of medicines quality issues. Generally this does not occur within their regulatory authority to the same extent. As they follow some of the debate concerning the development and the interpretation of a comprehensive set of WHO guidelines, the assessors gain awareness of the main risk areas and learn skills to adopt risk-based strategies in medicines regulation, including dossier evaluation, in context and in more depth.

The rotational assessors also gain access to WHO experts on pharmacovigilance, quality control testing and development of The International Pharmacopoeia, and participate in GMP inspections as observers, working in close collaboration with the PQP inspectorate and other experts.

So in addition to increasing technical skills and knowledge, rotational fellowships help to create or strengthen networks since they enable the assessors to know “the faces behind the scenes” and who the right contact is to get technical advice. Most importantly, having worked together, WHO staff and regulators “speak the same language”: they understand technical questions in the same way and can identify the best possible solution to the issue at hand.

WHO and PQP are well known in countries where prequalified medicines are funded because prequalified products meet internationally accepted standards. Assessors returning to their countries generally find that the advice they offer as “a WHO expert” and as “someone who has written pre-qualification reports” is trusted and respected. By improving regulatory practice in their countries, the regulators improve the conditions in which all medicines are produced, distributed and provided to patients.
QUALITY CONTROL TESTING
AND RESPONDING TO PRODUCT COMPLAINTS

Ensuring medicines quality starts with the right choice of active ingredients, continues with correct dosage forms and GMP practices and goes all the way through to quality testing of the finished product once it arrives at its destination. While PQP approval already gives a strong validation of a product’s quality, it cannot guarantee that the specific batches of medicines purchased have adhered to the manufacturing procedure that achieved prequalification. The quality testing of medicines is therefore an inherent part of ensuring quality treatment for patients and is practised in all countries with strong medicines regulation.

Since 2004 PQP has assessed QCLs in countries where PQP-validated medicines are supplied. If a laboratory is found to comply with international quality standards it is prequalified, which means that it is fit to carry out quality checks on medicines procured internationally or purchased nationally. Out of 26 WHO-prequalified laboratories globally, four were prequalified in 2012: in Belarus, China, Russia and Thailand (Figure 5).

As well as increasing countries’ capacity to test medicines locally, the scheme provides a second step in the quality assurance services offered by PQP. If quality problems arise with batches of prequalified products once they reach the country of destination, the local prequalified laboratories are alerted and requested to check the product; if non-compliance with standards is detected, PQP investigates further, in cooperation with procurers and/or NMRAs.

Figure 5: Distribution by WHO region of prequalified QCLs and QCLs working towards prequalification at the end of 2012

<table>
<thead>
<tr>
<th>Region</th>
<th>QCLs working towards prequalification</th>
<th>QCLs prequalified</th>
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</thead>
<tbody>
<tr>
<td>AF</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>AM</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>EM</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>EU</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
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<td>3</td>
<td>2</td>
</tr>
<tr>
<td>WP</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

AF = Africa
AM = Americas
EM = Eastern Mediterranean
EU = Europe
SEA = South-East Asia
WP = Western Pacific
For instance, in 2012 a study claimed to have found quality problems following some sample testing of WHO-prequalified malaria medicines procured through the Global Fund distributed in a number of countries in Africa. PQP activated its networks to verify the claims and reassess the medicines’ quality by working with a WHO-prequalified QCL in South Africa. By late 2012, all of the results obtained by the PQP investigation indicated that samples of the allegedly defective batches fully met their approved shelf-life specifications. In every case, the retention samples of the batches, which had been described as containing less than 75% of the artemisinin component, actually contained more than 90%.

A second crucial role of PQP’s QCL function is to provide assistance to countries in the event of adverse drug reactions. In 2012, it assisted the Punjab health authority in Pakistan to check the quality of two medicines for which serious adverse effects had been reported. The medicines, Tyno, a cough syrup, and Isotab®, used for cardiac disease, were not WHO-prequalified products.

In both cases, several deaths had occurred (60 for Tyno and 107 for Isotab), as well as severe adverse reactions in other patients. PQP worked with other parts of WHO, and with partner laboratories in Europe, to investigate the root cause of the deaths, which was linked to specific batches of the medicines. In the case of Tyno, quality control tests revealed that one of the active ingredients, dextromethorpan, was contaminated in a limited number of batches. In the case of Isotab, tests showed that the medicines in one batch contained pyrimethamine (used in the treatment of malarial) in quantities large enough to result in a substantial overdose.

As well as assisting in the quality control testing, WHO issued public alerts regarding the two products. In both cases the Punjab health authority took steps to contain the supply of the suspected medicines.
In addition to its day-to-day operations focusing on assessment of pharmaceutical products, PQP seeks to analyse and share the data and information that it accumulates regarding those products. In 2012 it published two important papers.

"Deficiencies in generic product dossiers as submitted to the WHO Prequalification of Medicines Programme”, reviews the type and extent of deficiencies in generic product documentation provided by manufacturers in the therapeutic areas of HIV/AIDS, malaria, TB and reproductive health. One important outcome of the paper is the wealth of information it provides for manufacturers to improve their product quality documentation, which is a crucial element of quality assessment.

To the authors’ knowledge, the study is the first comprehensive review of the quality and efficacy/safety sections of generic product dossiers that originate from pharmaceutical manufacturers in emerging markets, and the first comparison of dossier deficiencies across four critically important therapeutic areas. Similar studies by the United States Food and Drug Administration and the European Medicines Agency investigated quality and/or efficacy/safety deficiencies relating to new drug applications, but did not indicate the therapeutic areas studied or the origin of the dossiers.

A second paper published in 2012 — “Statistical approaches to indirectly compare bioequivalence between generics: a comparison of methodologies employing artemether/lumefantrine 20/120 mg tablets as prequalified by WHO” — is based on a study to compare the bioavailability of different generic products, with a focus on artemether/lumefantrine, used to treat malaria. From a clinical viewpoint and of most interest to treatment providers, the study showed that not only are WHO-prequalified generic artemether/lumefantrine 20 mg + 120 mg tablets bioequivalent with the reference product (Coartem; Novartis), but, more importantly, bioequivalent between themselves. For public health programmes, these results suggest that the different generic products can be interchanged safely without any safety or efficacy concerns.
BETTER INFORMATION MANAGEMENT — THE NEW IT SOLUTION

In 2012 PQP and an IT company completed development of a new data management system that will significantly streamline PQP’s operations and customer relation management. The new IT solution enables integration of web-based data management, integration of email-based communication, document management and rapid information exchange. Based on the new solution, complex processes and information-intensive workflows have been computerized. This includes communication between applicants and numerous professional and administrative staff, as well as with external partners, across a wide range of geographic locations. Using the new IT solution, activities can now be carried out in a shorter time span, with a greater level of transparency.

The new IT solution will also provide managers with better visibility, help ensure the accountability of day-to-day operations through its recording and monitoring of service performance levels (stop clock time, input/output comparisons, etc.), and minimize process delays and human input errors.

PQP is actively promoting and sharing the solution with other WHO departments and partners, including NMRAs. This will facilitate cost sharing of future enhancements and also promote best practices for regulatory core processes and procedures. Several NMRAs have approached WHO about the possibility of sharing medicines regulatory information management solutions, particularly with respect to dossier assessments and site inspections.
HIGHLIGHTS OF MAIN MEETINGS IN 2012

An important aspect of PQP's work involves information and knowledge sharing with stakeholders to ensure coordination of activities and objectives. A portion of senior PQP staff time is therefore devoted to meetings with manufacturers, national regulators, UN agencies and other partners. Of note in 2012 were the meetings described below.

**UNICEF-WHO-PQP meeting with manufacturers and procurers in Copenhagen, Denmark** — In 2012, PQP joined with UNICEF to host a meeting attended by pharmaceutical suppliers and procurers. As well as presenting projected demand for quality essential medicines, UNICEF and PQP described international procurement quality requirements and how manufacturers can ensure that their products meet these. But for many manufacturers the highlight of the meeting was the opportunity to meet individually with the PQP assessment, inspection and technical assistance teams, to discuss issues relating to current or proposed dossier submissions, and to obtain information regarding PQP requirements for pharmaceutical quality, efficacy and safety.

**International Conference of Drug Regulatory Authorities, Tallinn, Estonia** — This biannual meeting, organized by WHO, is an important platform for regulators to exchange information on recent developments and build partnerships. In 2012, the conference discussed the novel idea of a global network of low- and middle-income country NMRAs that would gradually take over medicines prequalification activities in certain countries and regions. Such an initiative would provide a sustainable alternative to the current quality assurance landscape and enable responsibility for prequalification of medicines to be transferred from WHO to national regulators, with whom the responsibility rightfully belongs. WHO would then be able to refocus efforts carried out to meet its pharmaceutical mandate on provision of scientific expertise and generation of pharmaceutical consensus. The concept is aligned with a number of high-profile regulatory capacity building initiatives (including the African Medicines Registration Harmonization Initiative, which is working to support African countries to harmonize medicines regulations and expedite registration of essential medicines), and with the global trend towards harmonization of medicines regulation.

**WHO Expert Committee meeting, WHO Headquarters** — The norms and standards developed and approved via the WHO Expert Committee on Specifications for Pharmaceutical Preparations underpin all of PQP’s activities. At its 47th meeting, the Committee adopted 14 monographs for inclusion in The International Pharmacopoeia and recommended for use a number of new guidance documents that it had reviewed.
Meeting with the China Chamber of Commerce for Import and Export of Medicines and Health Products, Beijing, China — This meeting’s purpose was to identify Chinese manufacturers who are capable of submitting both finished products and APIs to PQP for evaluation, including those who export their products to developing countries. The growing number of API applications received from Chinese manufacturers indicates that this type of outreach activity is worthwhile for the Programme (Figure 6).

WHO/Indian Pharmaceutical Association, Mumbai, India — The objective of this meeting was to maintain the interest of Indian manufacturers in API prequalification. The majority of API’s prequalified to date are from manufacturers who were already involved in FPP prequalification. PQP is therefore keen to encourage additional Indian API manufacturers to submit applications for evaluation.

Meeting with Nigeria’s National Agency for Food and Drug Administration and Control (NAFDAC), and manufacturers, Abuja, Nigeria — A response to interest in achieving prequalification in order to improve local manufacturing capacity, this meeting was notable for its decision that PQP, in cooperation with NAFDAC, will intensify its support of selected local manufacturers and inspectors with capacity building in quality production and monitoring, through hands-on training and transfer of knowledge.

![Figure 6: Country of origin of applications for API prequalification](image-url)
PARTNERS AND DONORS

Many partners contribute to the work and outcomes of PQP. They include manufacturers, regulators, procurement agencies, WHO disease programmes and donors. The successes of PQP are dependent on the combined input of all of these partners. At the same time, many of PQP’s partners are dependent on the Programme’s outputs. For instance, the recipients of Global Fund and UNITAID funding who procure medicines are required to purchase medicines prequalified by PQP (or approved by a stringent regulatory authority), as are UN procurement agencies such as UNICEF and UNFPA. In addition, many developing countries and nongovernmental organizations use the WHO List of Prequalified Medicinal Products as a key reference for the purchase of quality-assured medicines. The manufacturers themselves have often benefitted greatly from technical assistance and training organized by PQP.

PQP’s principal donors in 2012 were UNITAID and the Bill & Melinda Gates Foundation, with UNITAID providing 85% of overall funding (Figure 7).

→ Figure 7: PQP’s funding sources in 2012
PQP’s major donors in 2012

UNITAID — As a health financing initiative for the supply of medicines for the three priority diseases, UNITAID needs a sound technical basis to guide its grantees’ purchasing decisions — PQP provides that basis by proactively seeking to prequalify the products UNITAID prioritizes for procurement, provided they comply with WHO treatment recommendations. In addition, UNITAID has, since its inception in 2006, assumed the role of ‘creator’ of market demand for neglected products, such as paediatric formulations and adapted medicines (i.e. fixed-dose combinations) that are better suited to developing country populations. These medicines, often developed without a reference originator product, need rigorous quality assurance but also the developing country know-how that only WHO can provide.

Bill & Melinda Gates Foundation — In 2012, the Foundation provided funding for quality assurance activities focusing on reproductive health products, which form part of the foundation’s priority agenda on maternal and child health. Earlier funding enabled PQP to expand significantly: from a pilot initiative to a fully-fledged programme.
FUTURE DIRECTIONS

PQP will continue to prioritize evaluation of products that address current and emerging public health needs, such as:

- new ARVs for combating resistance
- new HIV/AIDS medicines, including “missing” paediatric formulations
- new TB medicines, including paediatric formulations
- APIs for TB medicines.

Following successful dialogue in 2012 with Chinese and Indian manufacturers, one important direction for the near future will be a greater focus on the quality of APIs. This area represents a win-win proposition for both public health and companies. Increased volumes of quality-assured APIs will lead to better-quality and cheaper products, benefitting patients, while for manufacturers, WHO prequalification status enables them to compete for international procurement funds and enlarge the markets to which they supply their products.

In terms of new FPPs, PQP will increasingly seek to liaise with organizations such as the Patent Pool, who are involved in development of new medicines, in order to anticipate and plan assessment needs. Another important development for the future is greater country ownership of quality assurance activities, in line with the growing trend of quality standards harmonization. Following the successful meeting of NMRAs in Estonia in 2012, PQP is building the basis for a network of NMRAs to whom prequalification activities can be transferred. The initiative responds to calls to ensure the sustainability of prequalification activities, as does the decision taken in 2012 to set up a fee structure for manufacturers seeking prequalification. The fees will be carefully calibrated taking into account, for example, the turnover of the applicant manufacturer, and the number of other prequalified versions of the product in question. A wider range of donors will also be sought in the future.

Greater advocacy efforts are also planned. Due to the technical nature of pharmaceutical quality assurance, donors and the international community are often unaware of the complexity of the work involved and the importance of coordinating treatment access activities.

For instance, some donors’ and countries’ quest for the lowest price is starting to have a negative impact on the availability of quality medicines and destabilizing developing country medicines markets. This is a well-known problem for reproductive health and TB products but is also becoming visible in the area of HIV/AIDS. In some instances prices have dropped so low that quality-assured manufacturers are finding it difficult to produce medicines without financial loss. A logical consequence of this would be that manufacturers cease production of urgently needed products. PQP therefore plans to intensify advocacy and educational activities towards global health stakeholders involved in or financing medicines supply. Unless the global community and countries work in a coordinated manner to ensure both affordability and quality, the future for the treatment of AIDS and other priority conditions could present new challenges and progress made in the last decade could be reversed.