Original Article

A quiet revolution in global public health: The World Health Organization's Prequalification of Medicines Programme

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Abstract Problems with the quality of medicines abound in countries where regulatory and legal oversight are weak, where medicines are unaffordable to most, and where the official supply often fails to reach patients. Quality is important to ensure effective treatment, to maintain patient and health-care worker confidence in treatment, and to prevent the development of resistance. In 2001, the WHO established the Prequalification of Medicines Programme in response to the need to select good-quality medicines for UN procurement. Member States of the WHO had requested its assistance in assessing the quality of low-cost generic medicines that were becoming increasingly available especially in treatments for HIV/AIDS. From a public health perspective, WHO PQP's greatest achievement is improved quality of life-saving medicines used today by millions of people in developing countries. Prequalification has made it possible to believe that everyone in the world will have access to safe, effective, and affordable medicines. Yet despite its track record and recognized importance to health, funding for the programme remains uncertain.
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Introduction

In 1977, the World Health Organization (WHO) published the first Model List of Essential Medicines (Essential Medicines List, EML). The EML assisted health authorities in selecting products for primary health

care. It introduced the idea that some medicines are more important than others. Many later considered the first EML 'a revolution in public health'.[1] After 25 years, WHO made an equally important decision to prequalify medicines. WHO Prequalification of Medicines Programme (PQP)'s greatest achievement is sustained improved quality of life-saving medicines used today by millions of people in low- and middle-income countries. The historical background of this WHO programme, how it developed over the last 13 years, its main achievements, and some of the challenges ahead are the subject of this article. We conclude with recommendations for the programme's future.

The quality of medicines can help ensure effective treatment, maintain patient confidence in treatment, and prevent development of resistance. These problems are particularly prevalent in countries where regulatory oversight is weak (in about one third of low- and middle-income countries), where prices make medicines largely unaffordable to patients, and where official supply channels fail to reach patients.[2]

In 2001, so that United Nations (UN) procurement would select medicines of assured quality, WHO established the PQP. A review of the regulatory and procurement environment at that time helps one understand why such a programme was needed.

Most international procurers doubted that Indian drug regulatory authorities could verify the quality of medicines. Yet India produced most generic medicines used in developing countries. Moreover, fixed-dose combinations (FDCs) of antiretroviral (ARVs) medicines and paediatric ARV formulations from India had no *originator equivalents* (medicines made and regulated in high-income countries), constituting another regulatory assessment challenge. Often national and international procurement organizations could not guarantee quality because their quality-assurance systems were limited in scope. WHO Member States requested WHO to assist procurement organizations by assessing the quality of increasingly available low-cost generic medicines.

Given its mandate to set international pharmaceutical norms and standards, WHO was suited for this role. Initially WHO focused first on low-cost generic versions of medicines to treat HIV, tuberculosis (TB), and malaria. The programme evolved and expanded to increase the availability of safe and effective medicines of quality by covering:

- essential medicines for reproductive health, diarrhoea, and neglected tropical diseases (NTDs);

- quality control laboratories;
- active pharmaceutical ingredients (APIs);
- review of clinical research used to prove equivalence of generic medicines with their comparators; and
- capacity of medicines regulators and pharmaceutical manufacturers in developing countries of Africa and Asia;

The WHO PQP has prequalified over 200 products for treatment of HIV/AIDS.[3] Of 8 million people receiving treatment for HIV in 2012, 6.5 million were receiving WHO-prequalified ARVs[4] (Box 1).

Box 1: Timeline: WHO PQP.

2001 (February): The Indian generic medicines manufacturer Cipla announces triple-ARV AIDS treatment for $350 ppy

2001 (March): WHO establishes the PQP

2001 (November): WTO adopts the Doha Declaration on TRIPS and Public Health

2002 (January): Global Fund to fight AIDS, TB, and malaria created

2002 (April): WHO publishes first list of 41 approved formulations of ARVs and other medicines used in the treatment of HIV, and at the same point WHO includes for the first time 12 ARV medicines in its EML

2003 (January): US PEPFAR approved by Congress

2003 (December): the first triple FDC for HIV treatment prequalified

2003 (December): WHO and UNAIDS announce the 3 by 5 Campaign

2004 (January): US FDA's Tentative Approval mechanism established

2004 (April): WHO PQP expands to include testing sites

2004 (April): Scientific and technical principles for fixed dose combination drug products drawn up at the meeting of interested parties held in Botswana

2004 (May): WHO PQP delists an ARV for the first time

2005 (June): The WHO Expert Committee on Pharmaceutical Specifications adopts a regulatory guideline for assessment of fixed-dose combinations.

2006 (September): UNITAID established as a new mechanism for the purchase of medicines for HIV,TB, and malaria financed by a tax on airline tickets

2006: WHO PQP includes medicines for reproductive health

2007: WHO PQP includes one medicine for use in pandemic influenza

2008: WHO PQP includes zinc for the management of acute diarrhoea

2008: UNITAID decides to fund the WHO PQP with a 5-year grant

2010: WHO PQP begins to prequalify APIs

2011: WHO and US FDA, also WHO and EDQM confirm confidentiality agreements that enable the exchange of confidential information and avoid repetition in assessments and inspections

2013: WHO prequalifies first medicine for treatment of a NTD (lymphatic filariasis)

2013: WHO merges its prequalification activities for diagnostics, medicines, and vaccines into one programme

The Global Health Environment Around the Turn of the Century

Neither national governments nor donors placed quality assurance of essential medicines high on their agendas. WHO estimated that only one third of regulatory agencies met standards; the rest lacked resources, procedures, and enforcement capacity. UNICEF, the International Dispensary Association (IDA), and Médecins Sans Frontières (MSF), were large international not-for-profit suppliers of essential medicines for national programmes and faith-based facilities. Their supplier selection

and quality assurance mechanisms were generally considered adequate, and many bilateral donors and WHO programmes used their services.

In 2000, only one in a thousand people living with HIV in Africa had access to treatment.[5] Highly active ARV treatment was available in wealthy countries. Thus AIDS changed from a death sentence into a manageable chronic disease. However, the drugs (ARVs) were available only from originator companies, who controlled the patents. They produced small quantities carrying paralysing price tags – US$10 000–$15 000 per person per year (ppy).[6]

Civil society and health professionals joined forces and campaigned for access to HIV treatment, adequate resources, and flexibility in patent rules – the last to enable production of generic ARVs. Controversies ensued over patents on ARVs following the introduction of new global rules on intellectual property (IP), international requirements to tighten national patent law. These patent restrictions largely prevented UNICEF, IDA, and MSF from distributing generic ARVs made in India.

In 1995, following creation of the World Trade Organization (WTO), the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) came into force. TRIPS is a WTO agreement and laid out minimum standards for IP protection, including an obligation to provide pharmaceutical product patents of at least 20 years.[7] Such patent protection did not exist in most developing countries. In 2001, the WTO Ministerial Conference, to facilitate access to low-cost generic medicines, discussed making implementation of IP standards in developing countries flexible. In November 2001, the Ministerial Conference adopted the Doha Declaration on TRIPS and Public Health. Could TRIPS obligations be rebalanced with the need to protect public health, particularly with respect to affordable medicines?

The Doha Declaration affirmed the sovereign right of governments to take measures to protect public health, including the use of *compulsory licensing* and *parallel importation*. Compulsory licensing enables a competent government authority to license the use of a patented invention to a third-party or government agency without the consent of the patent holder. The holder of the compulsory license pays a royalty (adequate remuneration) to the patent holder. Parallel imports are cross-border trade in a patented product, without the permission of the manufacturer or publisher. Parallel imports take place when there are significant price differences for the same item in different markets.

The Declaration also allowed least developed countries not to grant or enforce pharmaceutical product patents before 2016, taking away patent barriers to importing generic medicines from India. In 2002, this implementation deadline was extended to July 2021. These measures have become known as the 'TRIPS flexibilities'. When the Indian drug firm Cipla announced in 2001 that it could supply triple-therapy ARVs for less than a dollar a day, it was evident that the role of emerging generic medicines producers would grow and become a key element of the response to demand for greater access to HIV treatment.

In January 2002, the Global Fund to fight AIDS, TB, and malaria was established after the endorsement of the G8 in 2001. It struggled to use its funds wisely. For new generic medicines, the Fund and other donors needed assurance that quality was acceptable. Although not yet a high-profile issue, Fund staff understood the dangers for their new organization if large sums were spent on medicines of unknown or substandard quality or used for expensive branded products only.

The case of TB medications was especially alarming. In 1999, WHO had received the disturbing results of a small pilot study by a research group in South Africa on the quality of FDCs for first-line (directly observed treatment, short-course, (DOTS)) treatment of TB (PB Fourie, personal communication 11 December 2013). Simple quality control tests had showed that the FDC tablets contained rifampicin, the key component of the combination, leading programme managers to believe that tablets met quality standards. Sophisticated testing, however, showed that in 6 out of the 10 samples, the rifampicin was not absorbed by the intestines of the patient, and was therefore clinically useless. If representative, the results suggested that more than half the world's TB patients were receiving DOTS treatment without its most important component. Poorer treatment outcomes and increased resistance would result. The results were never published but passed on under confidential cover to the relevant regulatory agencies to act upon. The studies convinced WHO staff that there were serious problems with the quality of TB drugs used in public programmes. Better quality assurance was needed, although most donors and health workers were unaware of the problems. These findings underlay WHO's critical decision to start a quality assurance programme for essential combination medicines for TB.

The new fixed-dose combination AIDS tablets produced by generic companies in India needed quality assurance. Most regulators in generic drug manufacturing countries – India, South Africa, and China – and

in potential recipient countries had no experience with these 'new' products. This problem demanded a quick solution as the originator medicines were extremely expensive and the recommended treatments were not available in patient-friendly combination tablets. In India, patents did not prevent generic companies from developing fixed-dose combination of ARV drugs from different originators. Could inexpensive and more convenient products from India be trusted and did they have the same efficacy and safety profile as the originator products? National regulators in recipient countries, UNICEF, and non-governmental organizations (NGOs) wanted to know. They requested WHO's expert opinion.

WHO could not immediately answer these questions. Thus WHO created a review process to apply assessment criteria used by stringent regulatory agencies to determine product safety, efficacy, and quality. The term 'prequalification' (PQ) refers to the outcome: after WHO approval, a product is deemed 'prequalified' to participate in UN procurement tenders. Products that have received approval by a stringent regulatory agency are already eligible for procurement.

The Development of the WHO PQP

Since 1996, the senior pharmaceutical advisers of all UN agencies – WHO, UNICEF, and Word Bank – had met every 6 months in the 'Interagency Pharmaceutical Coordination' (IPC) group, to coordinate their medicine policies and to ensure that their agencies complement rather than duplicate each other in the medicines components of their country support programmes. A recurrent IPC discussion topic was the wide divergence between UN agencies in quality requirements.

The new prequalification programme fit this interagency environment. In 2001, the IPC accepted and endorsed the WHO/UN PQP as a UN interagency collaboration project. IPC wanted to streamline quality standards and policies on medicine procurement at WHO, UNICEF, World Bank, and later the Global Fund and UNFPA.

The medicine prequalification programme approach was not new. The Expanded Programme on Immunization established proof of concept over 30 years. WHO tested and approved all children's vaccines supplied by UNICEF. Prequalification was new for medicines and new in that WHO decided to approve medicine products even from countries where regulatory agencies were not up to international standards. (For vaccines

to be prequalified, the national regulatory agency had to be pre-qualified as well).

The new prequalification programme first took on fixed-dose combination medicines for TB, responding to the alarming rifampicin study. However, the global TB community and the Global Drug Facility that focuses on TB were slow to accept the study's results. They continued to procure medicines without sufficient quality assurance procedures. In the meantime, the Global Fund had been established and global attention shifted towards HIV/AIDS. WHO too decided to shift prequalification attention to medicines for HIV/AIDS (Box 2).

Verifying quality of medicines may appear a non-controversial activity, but early on the WHO PQP was criticized harshly, especially by high-income countries. Its principal critics maintained that WHO should not help commercial generic producers gain access to new markets, presumably at the expense of 'research-based companies'.

In 2002, WHO published its first list of 41 approved formulations of ARVs and other HIV medicines. The International Federation of Pharmaceutical Manufacturers, a trade organization representing the interests of large pharmaceutical companies, was quick to question whether WHO's assessment standards were sufficiently strict. They warned against counterfeit and substandard medicines.[8]

On 1 December 2003, WHO and UNAIDS declared the lack of HIV/AIDS treatment to be a global public health emergency. They launched the '3 by 5' campaign, to get three million people on antiretroviral treatment (ART) by 2005. The political momentum of the campaign, combined with new funding from governments, the Global Fund, and President's Emergency Plan for AIDS Relief (PEPFAR), and later from UNITAID, allowed countries to begin purchasing HIV/AIDS medicines in large volumes. Yet to optimize buying power and cover all patients needing treatment, the price of the ARVs would have to be lowered.

Everyone recognized FDCs as an important advance in HIV/AIDS treatment, particularly for resource-poor settings where the 'one pill twice a day' regimen would help increase adherence to treatment, reduce the risk of developing resistance, and simplify the supply chain.[9,10] Indian firms were the first to produce a FDC of a WHO-recommended first-line combination, although not the only ones to produce triple FDCs.[11] The price of the first generic triple combination by Cipla was less than $140 ppy. The combination of lamivudine, stavudine, and

Box 2: WHO prequalification of medicines process.

1. WHO lists for possible prequalification specific products with their recommended strength and presentation (tablet, injection, syrup). A product may be listed if it appears on the biennial WHO EML, or when a product is recommended in a new WHO treatment guideline and the maker has applied to put it on the next EML. (These are typically reviewed every 3–4 years).
2. WHO then includes the product on an Invitation to Manufacturers to Submit an Expression of Interest (EOI) List for Product Evaluation that it publishes on the WHO/PQP Website.
3. Any manufacturer of a product on that EOI may apply to have the product evaluated for inclusion in the WHO List of Prequalified Medicinal Products. To apply, each manufacturer must submit information to enable the international assessment teams convened by WHO to evaluate the product's quality, safety, and efficacy. Submissions include comprehensive data on quality, safety, and efficacy, including details about the purity of all ingredients used in manufacture, stability of the finished products – tablets, capsules, oral liquids – in tropical climates, plus results of *in vivo* bioequivalence tests. These tests in healthy volunteers must prove that the product has the same absorption in the body as the originator product. The manufacturer must also open its manufacturing sites to inspection to assess compliance with WHO Good Manufacturing Practices (GMP). (To avoid duplication, WHO also recognizes recent inspections carried out by stringent regulatory bodies).

   The WHO Expert Committee on Specifications for Pharmaceutical Preparations adopts standards and procedures for prequalification based on the principles and practices used by the world's leading regulatory agencies.
4. A global team of assessors from developing and developed countries evaluates the data presented, and if satisfactory, dispatches a WHO inspection team of experts (also from developing and developed countries) to inspect the manufacturing site for compliance with GMP. If applicable, the team also examines the contract research organization that performed clinical testing relating to the product. The clinical testing must have been conducted in compliance with GCP and GLP. If the manufacturer's

product made at the inspected site meets all these standards, it may be added to the WHO List of Prequalified Medicinal Products. (*Source*: http://apps.who.int/prequal/)

nevirapine – compounds developed by three different originators – was sold under the name 'Triomune'.

Brand-name companies set the price of a similar combination, using single tablets – six pills per day – at a minimum of $562 ppy in developing countries (http://www.healthgap.org/HGAP_PEPFAR_EDITORS_NOTE.doc). Because a three-in-one ARV product for first-line treatment, as recommended by WHO, was not manufactured by any research-based company, it had never been assessed or approved by any stringent regulator. Research-based companies were testing and producing only combinations of their own patent-protected products – not necessarily the best combinations from a medical perspective. The triple FDCs, produced only by generic companies, came to symbolize the great savings that generics could achieve. WHO's prequalification of Cipla's first generic FDC of three ARVs, a ground-breaking move, brought an important innovation to resource poor countries.

Prequalification of a first generic FDC provoked a global debate about WHO's role in making generic HIV/AIDS medicines accessible in developing countries. The new combination lacked an originator equivalent as a reference. Regulatory standards for FDCs, in general, were also lacking. WHO found itself in uncharted territory. A number of industry-based groups were quick to condemn the prequalification of triple FDCs, arguing that because triple FDCs did not exist as originator products, safety and efficacy comparisons could not be made and new clinical trials should be performed.[12,13] As the three compounds in the FDC were still under patent in many countries, this provoked further criticism. Some questioned the legality of WHO's move.[14]

The US administration of George W. Bush insisted on buying only originator branded products for its programmes. It defended this policy by referring to concerns about the quality of generics approved by WHO.[15] The head of the United States PEPFAR, Randall Tobias, a former CEO of Eli Lilly, publicly questioned the rigour of WHO's PQP. He told the Associated Press: 'Maybe [FDC] drugs are safe and effective. Maybe these drugs are, in fact, exact duplicates of the research-based

drugs [sold in the United States]. Maybe they aren't. Nobody really knows'. He added that the United States does not want to contribute to an increase in ARV drug resistance because of 'widespread or inappropriate' use of the treatments.[16] US refusal to accept WHO-prequalified AIDS medicines provoked responses from care providers dependent on access to lower-cost generic ARVs, as well as from politicians seeking to make life-saving medicines available in the developing world.[17,18]

A breakthrough on the use of FDC ARVs came in March 2004 at a conference in Gaborone, Botswana. Co-sponsored by UNAIDS, WHO, the Southern African Development Community, and the US Department of Health and Human Services, it focused on the safety, efficacy, and quality of FDCs, whether from innovator or generic sources. It tried to provide urgently needed guidance on the development, evaluation, and/or use of combination products for HIV, malaria, and TB. It also tried to encourage development of paediatric FDC formulations.[19] Drug regulators of 23 countries, care providers, NGOs, government officials, industry, treatment advocacy groups of people living with HIV, and UN agencies, gathered to draw up this guidance.

In a great success for WHO, the conference's guidance for the future regulation of FDCs confirmed the regulatory principle, proposed by WHO, that if three separate medicines have successfully been used clinically in combination therapy, there is no need for new clinical trials of an FDC of the same medicines in the same dosages.[20] The only proof needed is that each of the compounds in the combination tablet achieves the same serum levels as did the original products when given separately. This principle, subsequently confirmed by WHO's expert committee, implied that establishing bio-equivalency (BE) in such cases would be sufficient to determine interchangeability with the originator products given separately. This agreement between the leading regulators of the world paved the way for rapid approval of ARV combinations based on product quality and BE grounds alone. Had new clinical trials been required, market entry of generic FDCs would have been delayed for several years, (or even a decade for TB, where the relapse rate is an essential measure of efficacy). The meeting also gave many stakeholders the opportunity to rally and secure US Government support of procurement and use of generic ARVs.[21,22]

The July 2004 report of the United States General Accounting Office (GAO) helped change US policy on the use of generic ARVs. The GAO

identified serious problems for PEPFAR funding recipients caused by a lack of procurement guidance. Thus GAO recommended that the US Global AIDS Coordinator explicitly specify what activities PEPFAR was permitted to fund in national treatment programmes that use ARV drugs not approved for purchase by the Office.[23] Unfortunately, the US Government was not yet ready to accept the WHO PQP and announced, with the support of the US Global AIDS Coordinator's Office, that it would establish its own review process for generic and other ARV drugs to be procured with PEPFAR money.

This 'United States Food and Drug Administration (US FDA) Tentative Approval mechanism' duplicated the WHO PQP. The global community quickly recognized it as a competitor to the WHO PQP that could undermine further development of WHO PQP.[24] For most developing countries, however, WHO remained the only international agency with a global mandate to establish pharmaceutical standards for quality, efficacy, and safety, including the scientific justifications necessary to establish the bioequivalence of products. In 2004, supporters of WHO PQP sought to bolster the programme through a World Health Assembly resolution on HIV/AIDS that included a paragraph calling for strengthening of WHO's prequalification project. The resolution asked that inspection and assessment reports on the listed products, aside from proprietary and confidential information, be made publicly available.[25] Transparency of the WHO PQP has proved essential in creating and maintaining confidence among buyers, funders, and users of the approved medicines.

A Crisis of Confidence

Days after the heated debate in the Assembly, and while the WHO Executive Board was still meeting to discuss next steps, WHO was confronted with information that threatened to inflict severe damage on WHO PQP's credibility. Following an informal warning and a follow-up inspection at Cipla's manufacturing plant in India, inspectors reported to WHO's headquarters by telephone from India that the bioequivalence studies for a key prequalified ARV product were seriously deficient. The inspectors suspected them to be fraudulent. Inspectors had not found proven lack of bioequivalence, but there was simply no good evidence of bioequivalence. WHO's strict standards for bioequivalence studies, including inspection of the organizations that had performed the studies on the maker's behalf, tracked recently adopted

European guidelines. At the time, these were stronger than those of any other regulatory body. The subtle difference between 'proof of lack' and 'lack of proof' later created confusion among regulators, health workers, and patients.

The information created a difficult situation for WHO. Only four originator and four generic ARV products had been prequalified. Besides pressure from some rich countries that objected to prequalified generic products, the activist community criticized WHO for having colluded with industrialized country interests to make the quality standards so high that generic products manufactured in low- and middle-income countries were largely excluded from prequalification.

Technically, it was clear that the Cipla product had to be delisted until its bioequivalence had been properly established. However, immediate publication by WHO, during the Board meeting, risked inflaming and derailing on-going political discussions as the evidence appeared to show that generic products might be inherently unreliable. Was the justification for the entire prequalification programme flawed? *Not* publishing the information immediately, and later being exposed as having withheld damaging knowledge to protect a generic product, despite lack of proof of its quality and efficacy, would support allegations that WHO promoted generic medicines without regard to quality problems.

WHO postponed publication of its findings until it received written confirmation from the inspectors. This gave WHO just enough time for the Executive Board to complete its meeting and for the delegates to travel home, avoiding an immediate and almost certainly acrimonious debate. Then, before publicly delisting the Cipla product, WHO informally told the treatment activist community and civil society organizations, asking them not to use the information to further attack the programme (see, for example, a message from Hogerzeil, H., Director of the Department of Essential Drugs and Medicines Policy at the WHO to Internet mailing lists: http://lists.essential.org/pipermail/ip-health/2004-September/006896.html, accessed 18 November 2013). The medical humanitarian organization MSF commented that being told about the flaws in the prequalification process demonstrated the programme's strength. 'MSF supports the WHO Prequalification Project and believes that on-going monitoring by the WHO is a sign of an efficient process. The rigour of this process ensures that companies are always striving to improve their assessment of quality'.[26] MSF's statement helped

counteract those who saw the delisting as an opportunity to criticize the programme as a whole.

WHO described the decision to delist the Cipla product as 'short-time pain for long-term gain'. The public delisting sent a shockwave through the Indian generic industry, and gave a clear signal that quality standards would continue to be demanded of all products submitted for evaluation. In November 2004, insistent WHO requests for confirmation of the proper bioequivalence testing of its ARVs also led Ranbaxy Laboratories, another generic maker, to withdraw of several products from WHO's prequalified products list.

Very few prequalified generic products remained for the treatment of HIV. Cipla did not submit genuine bioequivalence studies for its products. (In later years, Cipla once again became an important supplier of quality-assured, low-cost ARVs.) Regulators, health workers, and patients found it difficult to understand why essential ARVs were withdrawn by WHO based on quality standards not yet applied to any other medicines in any jurisdiction. Many national AIDS programmes were seriously frustrated and confused by the withdrawal of essential products and struggled to find alternative solutions. UNICEF refused a consignment of specially labelled ARV products that had already been shipped. An editorial in *The Lancet* though, hailed WHO's move, stating that '…it shows that this little known part of WHO is effective and has teeth that can bite rapidly'.[27]

The strength and independence of WHO medicines prequalification seemed to gradually diminish political opposition to the programme. The only remaining opposition comes as occasional complaints from ministers of health that the WHO PQP is too slow or too strict, that it makes it hard for their national generic industries to meet requirements.

Ultimately, opposition to WHO PQP served to strengthen it. Yet two positive factors also helped it survive and grow: donor support and purchasing power. WHO began PQP with small amounts of donor funds not earmarked for a particular purpose. Then the Bill & Melinda Gates Foundation recognized the power of the prequalification concept and provided steady support for the programme. Since its inception in 2006, UNITAID has also supported the programme. Its generous 4-year commitment for 2009–2012, now extended into 2013 and perhaps further for 2014–2016, secured the programme when WHO's own resources were not equal to the demands from Member States and other stakeholders.

The most important factor in the survival and growth of the WHO PQP was the Global Fund's quality assurance policy for medicines procurement. Its policy restricts use of the Fund's immense purchasing power to products approved by stringent regulatory authorities or prequalified by WHO. This policy came out of the IPC process designed to harmonize international procurement quality standards among UN agencies. Later UNFPA adopted a similar policy. As a result, the public sector market for non-prequalified medicines for AIDS, malaria and, later, TB and reproductive health medicines shrank. Companies were obliged to get stringent regulatory approval or WHO prequalification to compete in the international market (Box 3).

Box 3: Relationship with the US FDA tentative approval programme.

Generic producers did not seek the approval of the US FDA for their ARVs because patents prevented them from marketing their products in the United States. Hence, the US rules that prevent it from spending PEPFAR money on medicines not approved by the US FDA were essentially a rejection of generic ARVs in favour of US companies' brand name products. However, some US politicians realized that PEPFAR's resources would not stretch far if they had to be spent on expensive branded medications.

In 2004, the US FDA, rather than providing expertise to the WHO PQP and in order to break through this deadlock, created its own mechanism for prequalifying medicines to be used for the treatment of HIV in developing countries and procured with US funds.[42] The so-called US FDA Tentative Approval System also assessed overseas generic products for use by US-funded programmes, and paved the way for PEPFAR procurement of generic medicines. No generic FDCs were approved until 2006, delaying by two years use of WHO recommended regimens by PEPFAR recipients.[43]

US FDA Tentative Approval was for HIV medicines only. No similar approval process was established for products to treat other diseases. In the President's Malaria Initiative, WHO prequalification is relied upon. Now USAID has agreed to accept WHO/PQ as a quality standard, aligning itself with the Global Fund and UN interagency quality policies. In 2011 and after long discussions, WHO and US FDA reached an agreement that enabled them to exchange confidential information and thus avoid repeated assessments and inspections.

Current Activities and Achievements of the WHO PQP

Since its establishment in 2001, the WHOPQP has prequalified more than 350 finished pharmaceutical products (FPPs). Only 20 products have been removed from the list, most upon request from the manufacturer. The original focus was prequalification of medicines for treating HIV/AIDS, TB, and malaria. In 2006, this range was expanded to cover medicines for reproductive health, in 2007 to cover a medicine for pandemic influenza, and in 2008 to cover zinc for the management of acute diarrhoea in children.[28] More recently, the Programme has started to evaluate the quality of medicines for treating NTDs. (For the 17 diseases identified as NTDs by WHO see: http://www.who.int/neglected_diseases/diseases/en/).

The time required for prequalification can vary enormously and depends on the quality of dossier and the manufacturer's experience with stringent evaluation. Today WHO prequalification of a medicine can take as little as 3 months, if the data presented are complete and demonstrate that the product meets all required standards. If a manufacturer responds quickly to questions from the assessment team, prequalification can be more rapid. WHO's fastest prequalification of a generic was 6 weeks.

In 2010, WHO started to prequalify APIs – the essential building blocks of medicines.[29] In 2013, the WHO PQP approved 23 APIs.

Testing sites – medicine quality control laboratories and commercial contract research organizations that perform bioequivalence studies – have been inspected since 2004. These inspections ensure that sites meet standards for good laboratory practice (GLP) and good clinical practice (GCP).

A complete listing of prequalified products by disease category is available on the WHO Website (http://apps.who.int/prequal/query/ProductRegistry.aspx). The programme's annual budget today is $15 million.

The list of prequalified medicines has become a vital tool for any agency or organization purchasing of medicines in bulk, whether at country or international level, as demonstrated by the Global Fund. The WHO PQP has prequalified 85–90 per cent of market of ARVs, malaria, and TB medicines for the Global Fund, UNICEF, and UNITAID. It is widely used by NGOs and others, such as national procurement agencies. It helps assure that scarce resources for health stretch further and are not spent on products of unknown quality, safety, and efficacy. (Table 1)

Table 1: WHO prequalified finished pharmaceutical products (FPPs) per year

	WHO prequalified FPPs per year					
	2008	*2009*	*2010*	*2011*	*2012*	*2013*
HIV	29	18	22	23	18	27
Tuberculosis	5	7	5	7	19	17
Malaria	6	3	1	1	10	7
Reproductive health	0	3	5	3	0	10
Influenza	0	6	1	0	0	0
NTD	0	0	0	0	0	1
Zinc	0	0	0	0	1	0

WHO Prequalification and National Regulators

The programme promotes interaction and close collaboration with and between national drug regulatory agencies, in both developing and wealthy countries. The legitimacy of the WHO PQP's decisions derives in part from this collaboration, and from its solid and transparent procedures and standards. The standards come out of an international consensus process conducted with Member States. The process concludes with review and adoption by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Transparency builds confidence. The WHO PQP goes beyond the current information-sharing practices of national drug regulators.

The Programme has raised the bar for quality assurance. Its standards are recognized and promoted by others, helping expand quality medicines production. Medicines Patent Pool (MPP) licenses, for example, oblige producers to play by the WHO PQP's rules.[30]

WHO PQP assessments have always been managed and led by WHO, but they are executed by designated assessors and inspectors from WHO Member States. The Programme also trains regulatory personnel and manufacturers from low- and middle-income countries. On-the-job involvement in dossier assessment and site inspections are offered each year to selected regulatory personnel from low-income countries. Training programmes for medicines regulators and manufacturers reach about 1300 participants annually, the most extensive in the world.[31]

In 2011, WHO developed a procedure to promote accelerated approval by national regulatory authorities of products already prequalified by WHO, reducing duplication of regulatory effort. The procedure speeds up access to markets and patient access to treatment. In total,

15 countries are now testing the procedure on two products.[32] The East African Community (EAC) relies on the WHO PQP regulatory format and standards for regional regulatory harmonization. The EAC medicines regulatory harmonization project serves as a model for the continent-wide African Medicines Regulatory Harmonization Initiative spearheaded by the New Partnership for Africa's Development.

To build capacity, especially for regulators from developing countries, in 2007 WHO created a rotating position at the WHO headquarters in Geneva. National regulatory assessors and inspectors work for 3 months in Geneva getting first-hand experience with WHO PQP, also interacting with other WHO units and departments that have roles in medicines regulation.

Prequalification and Innovation

WHO promotes and supports a public health approach to innovation in several ways. Recent editions of the WHO EML,[33] and the two WHO reports on Priority Medicines for Europe and the World of 2004[34] and 2013,[35] identified *missing* essential medicines, medicines that should exist but do not, such as ARV combinations for children, zinc tablets for the treatment of diarrhoea, and injectable long-term contraceptives. These reports encourage innovation in neglected areas.

Early in product development, the WHO PQP can specify what regulatory requirements will ultimately be applied to the newly developed products – data on safety and product stability, for example – avoiding delays and conserving resources of not-for-profit drug development partnerships and others developing products.

Finally, WHO prequalification publishes an independent assessment of the product, making it eligible for procurement through international funding. It then supports rapid regulatory approval in recipient countries. Rapid uptake of a new product encourages innovation.

Saving Lives and Saving Money

From a public health perspective, WHO PQP's greatest achievement is improved quality of key medicines used by millions of people in developing countries. In a study of 12 958 ARV purchase transactions between 2002 and 2008, Brenda Waning concluded that five ARVs recommended by WHO in 2003 constituted 98 per cent of the ARVs purchased in 2004–2006. The price of the major FDCs decreased from

$484 per person in 2002 to $88 in 2008. Purchases of new ARVs recommended by WHO in 2006 increased 16–20 times in the 2 following years. By 2008, 85–88 per cent of the ARVs procured by PEPFAR, the Global Fund, and UNITAID were prequalified.[29]

The programme has saved money both directly and indirectly. In 2006, the Clinton Health Access Initiative and McKinsey estimated WHO PQP contribution to increased public access to low-cost quality generics. On the basis of the use of first-line ART in Africa since 2004, every dollar invested in the prequalification programme saved $200 in public medicine procurement.[36] The programme has maintained this positive benefit/cost ratio: in 2009 the estimated return on investment was $170 of savings for every dollar spent on prequalification.

Saving for PEPFAR from buying generics has also been sizeable. A report by PEPFAR, Supply Chain Management Systems (SCMS), and USAID concluded: '$1.1 billion in taxpayer money [had been] saved [over six years] by procuring generics rather than branded ARVs'.[37] Use of generics effectively doubled the number of patients who could be treated for the same funds. PEPFAR's products were qualified through the US FDA fast track system. Would the US FDA system have been created without WHO PQP? Perhaps the indirect impact of the programme may be as great as its direct impact.

All global health donors would seem to favour WHO prequalification. Yet WHO PQP's funding continues to depend on the Bill & Melinda Gates Foundation and UNITAID. The two contributed 80–90 per cent of the WHO PQP budget in 2013. Money strapped WHO could not help pay for the WHO PQP. A narrow funding base brings risks, including *donor-driven priority setting*. UNITAID's mandate, for example, to focus on HIV, TB, and malaria[38] is fine, but from a public health perspective, other priorities for prequalification exist, such as insulin and low-cost medicines for chronic diseases.

To establish financial sustainability for WHO PQP, WHO has introduced a fee-based system whereby companies applying for prequalification of their products may be charged a fee. However, will this fee-based mechanism jeopardize WHO PQP's full independence?

The Future of the WHO Prequalification Programme

The recent revision of the WHO HIV treatment guidelines, recommending treatment initiation when CD4 cell count falls to 500 cells/mm^3 or

less (instead of 350 cells/mm^3) means that 26 million people in low- and middle-income countries are eligible for ARV treatment compared with 10 million under the 2010 guidelines.[39] Continued access to low-cost quality ARVs in FDC formulation remains critical.

How long will the prequalification programme be needed, and how long will it need public funding? The simple answer to that question is: as long as UN agencies procure medicines for low- and middle-income countries; or until the WHO PQP is no longer needed to provide assistance to national regulatory agencies that lack capacity to assess the quality of the medicines their countries produce or import. However, that day is still far in the future.[40]

A more nuanced response is also possible. The WHO PQP has always improved both the quality of generic first-line ARVS produced in low- and middle-income countries, and the capacity of their national regulators to assess the quality of these products. A long list of internationally approved products indicates a mature market for these medicines. The WHO prequalification programme has become less urgent, as regulators in producing countries or in regional regulatory centres of excellence can now manage the assessment. This is where WHO PQP has taken us farthest. The situation is stable unless new domestic manufacturers enter the market or programmes recommend new first-line medicines.

Less far along are therapeutic groups for which very few products have been prequalified (for example, new first-line ARV combinations, second-line TB medicines, zinc, misoprostol, and oxytocin), or where unassessed or substandard products are still widely procured (for example, contraceptives). Here prequalification can help stimulate a mature market of quality-assured products. As long as very few products are prequalified, the WHO Expert Review Process can help UN agencies select the least risky products, pending their prequalification.

Least far along are therapeutic areas where hardly any good-quality generic medicines are available in low- and middle-income countries, and whose national regulators lack experience in evaluating those products. Examples include insulin for diabetes and anti-snake venom. WHO medicines prequalification has not begun, but could presumably make an important contribution. The same applies for 'new' products produced or marketed only in countries without stringent regulatory agencies, such as the dapivirine vaginal ring, a microbicide to prevent HIV transmission.

Creating a mature medicines market for first-line ARVs for use in developing countries took about 10 years of large-scale public procurement. The prequalification programme could continue for a long time, with a slowly changing range of essential medicines of great public interest, each in its own market development cycle. Future funding could then remain project-based and time-limited. Dedicated funds would be raised for certain medicines for the period necessary to create a mature market. Large-scale procurers and their funders could then contribute financially to the programme to assure the quality of the products and to work towards market sustainability.

Pressure on the Development of New Generics

The more widespread patenting of pharmaceuticals in countries traditionally suppliers of generic medicines may affect the work of the WHO PQP. Generic companies concerned about legal action by patent holders may find it too risky to develop generic versions of new medicines, slowing down availability of newer, second- and third-line ARVs. Will new results from the Medicines Patent Pool offer a solution? Patent licenses negotiated by the Patent Pool attempt to assure development of low-cost generic versions of new molecules. Similarly, generic medicines may be produced as a result of a compulsory license or a direct voluntary license agreement between the patent holder and a generic manufacturer.

Some of first generic companies to have WHO prequalify their early products (Cipla Ltd., Ranbaxy Laboratories) have improved quality performance to the point where industrialized country markets are open to them. Good-quality generic manufacturers may then be tempted to shift to markets where prices are more attractive, to the detriment of production of cheap generics for Africa. There may be a continued need to prequalified products from other, newer companies.

Conclusion

The last 13 years have underscored the importance of the WHO PQP for public health. Without it, the goal of WHO's '3 by 5' programme or reaching 10 million people with ARTs would not have been achieved as quickly and inexpensively or at all. Donor money would likely have been wasted on products of unknown quality with potentially devastating effects for public health. The Programme is a good example of

far-sighted concerted international action by the UN system, supported by NGOs and donors.

Donors and buyers of medicines must still demand quality assurance in their procurement and resist the primitive temptation to procure only the cheapest medicines. Failure to do so paralyses the effectiveness of the WHO PQP. TB programmes, for example, continued too long purchasing medicines of uncertain quality – thereby removing an incentive for manufacturers to invest in better quality. Users of medicines in the reproductive health and family-planning domains continue to buy products of unknown quality.

The WHO PQP has become a global public good that has helped save millions of lives. Most international organizations and many governments that procure and supply medicines depend on the WHO PQP. Yet very few choose to contribute financially to its work. The Global Fund spends around $610 million per year on medicines and other pharmaceutical products. (The Global Fund, 3 September 2013, personal communication). PEPFAR spent $1.2 billion on medicines procurement over 5 years.[41] The $15 million annual budget for the WHO PQP represents less than 2 per cent of the annual amount spent on medicines by these two organizations alone. Reliance on two donors is risky. It is time a consortium of public and private global health donors create a sustainable funding base. WHO PQP is essential to assure their products' quality. It is the strongest mechanism currently in place to create sustainable regulatory systems in low- and middle-income countries. This alone justifies investment in WHO PQP.

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