INVESTING IN WHO PREQUALIFICATION OF FINISHED PHARMACEUTICAL PRODUCTS

INFORMATION FOR MANUFACTURERS

World Health Organization

CONTENTS

WHY YOU SHOULD READ THIS OVERVIEW

WHO medicines prequalification, initiated in 2001, facilitates access to good-quality medicines through assessment of products and inspection of manufacturing facilities. Finished pharmaceutical products (FPPs) that meet WHO assessment criteria, and that are manufactured at sites that adhere to WHO Good Manufacturing Practice (GMP) are added to the WHO List of Prequalified Medicinal Products. UN agencies and other bulk purchasers of medicines use this list to guide them in their procurement decisions.

Any manufacturer who manufacturers FPPs included on WHO's Invitations to Manufacturers to Submit an Expression of Interest for Product Evaluation (EOIs) can apply for evaluation of those products. Each application must be accompanied by extensive information on the product submitted, to enable WHO's assessment teams to evaluate its quality, safety and efficacy.

Before submitting an application, manufacturers are encouraged to read this overview, which summarizes key information about WHO medicines prequalification, including the benefits it offers, the process itself, what it might cost a manufacturer to obtain prequalification of a product and assessing the market for a prequalified product.

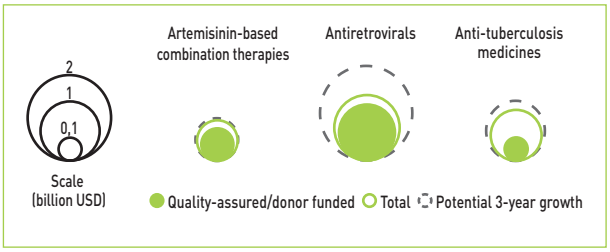
WHAT ARE THE BENEFITS OF PREQUALIFICATION FOR MANUFACTURERS?

Participation in WHO prequalification can bring significant benefits to manufacturers, including:

Access to donor-sponsored tenders: The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), Global Drug Facility (GDF), UNFPA, UNAIDS, Médecins Sans Frontières (MSF), UNICEF and other organizations are increasingly harmonizing their procurement policies to stipulate that medicines procured with their funds must meet international quality-assurance standards. Prequalification can increase access to medicines tenders financed by these donors. Key medicines worth USD 832 million were reported as financed by the Global Fund during 2011—2012.[1] Of these, 74% were WHO-prequalified, 22% were authorized by a stringent regulatory authority (SRA) only; 30% of the total had received both types of approval. Some manufacturers participating in prequalification therefore report a subsequent increase in sales volumes and revenue.

Faster regulatory approval: Prequalification can lead to faster regulatory approval, as some authorities accept prequalification approval or data for registration purposes. Currently, 15 medicines regulatory authorities (MRAs) in Africa and Central Asia are participating in a WHO procedure[2] to expedite the registration of prequalified products. This procedure was piloted in 2012. To date six prequalified products in different therapeutic categories have been registered in four countries. In 75% of cases, registration was achieved in less than 90 days. Moreover, more and more MRAs are working together and aligning their registration requirements with WHO guidelines. Manufacturers who have participated in WHO prequalification will enjoy a competitive advantage over manufacturers who have never developed a complete dossier for stringent regulatory scrutiny or undergone a stringent GMP inspection.

Illustrative market sizes



[1] *As per Global Fund Price and Quality Reporting (PQR) database as of August 2013.*

[2] *See: WHO collaborative procedure for registration of prequalified products, WHO Technical Report Series 981, Annex 4, at: www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/*

International, quality-assured product status: During product evaluation, the WHO medicines prequalification team often provides a manufacturer with valuable technical advice — for example, on how to meet WHO GMP requirements. Such advice is valid for all aspects of medicines production. Accordingly, prequalification can lead to improved overall product quality, strengthened organizational capabilities and an enhanced corporate image (both internal and external). These can all help a manufacturer to enter stringently regulated medicines markets (for instance, within Europe or the USA), secure higher profit margins in non-institutional markets, and win contracts for contract manufacture for local markets. In brief, increased understanding of and ability to meet stringent regulatory requirements can contribute to improved local and international market share.

Lower variable/commercial operating costs: Prequalification of a product can result in lower commercial operating costs. This is because large tenders mean greater volumes, giving manufacturers opportunities to make economies of scale and to negotiate better prices for active pharmaceutical ingredients (APIs).

Benefits for manufacturers of participating in WHO medicines prequalification

Increased sales/market access

- Access to donor-sponsored tenders
- Access to stringently-regulated markets, e.g. in Europe, USA
- Increased potential to compete successfully for contract manufacture for local markets

Improved image/brand

- Quality-assured product status
- Improved external and internal image
- Improved positioning in home country

Reduced manufacturing costs

- Improved capacity utilization
- Lower variable/commercial operating costs

Increased capacity/skills

- Development of human resources for ensuring and managing quality manufacture
- Capacity to ensure quality manufacture across range of products
- New or increased capacity to meet stringent regulatory requirements

Greater expertise: Participating in WHO medicines prequalification helps manufacturers to deepen their expertise in developing product dossiers and preparing manufacturing sites for inspection. As a result, they are not only better able to prepare for future product evaluation, but also to resolve current technical problems relating to quality-assured manufacture of a specific product.

WHO PREQUALIFICATION PROCESS

The first step in the prequalification process for any manufacturer is review of the EOIs to ascertain whether it manufacturers any of the products invited by WHO for evaluation. EOIs focus on products that the respective WHO disease departments consider to be vital to effective treatment and to expansion of treatment programmes. Currently, this means products for treating HIV/AIDS, tuberculosis (TB) and malaria, as well as for reproductive health. Some products for treating neglected tropical diseases, influenza and childhood diarrhoea are also invited for evaluation. Generally, every product contained in an EOI is already included on the WHO Model List of Essential Medicines and/or in WHO treatment guidelines.

For each application for product evaluation, a manufacturer must submit a covering letter, product dossier, product sample and site master file to the WHO Prequalification Programme. Thereafter the Programme undertakes comprehensive evaluation of the quality, safety and efficacy of the product, based on the information submitted by the manufacturer, and inspection of the corresponding manufacturing site(s).

Products submitted for prequalification are often multisource generics. In such cases, therapeutic equivalence with an innovator product is verified by performing a bioequivalence study. Such studies are generally carried out by an independent clinical research organization (CRO), which must therefore also be inspected and approved.

The results — both positive and negative — of dossier assessments and inspections are relayed to manufacturers and CROs, together with advice, if needed, concerning corrective actions that are required if prequalification is to be achieved.

WHO charges fees for applications to prequalify medicines, but with several important exemptions, including for first-time applications.

ELIGIBLE PRODUCTS

Individual EOIs generally remain current for some time; new EOIs are issued following a change in treatment guidelines, for instance. The single list of all FPPs (and APIs) invited for evaluation is updated frequently since it also gives the number of products already prequalified and/or under assessment per product invited for evaluation (thus providing manufacturers with some information about competitors).

ERP review — an entry point towards prequalification

Increasingly, international donors fund procurement of quality-assured products. However, products that have been WHO-prequalified and/or approved by an SRA are not yet available on the market for some needed medicines. Therefore, criteria other than "prequalified" or "SRA-approved" must be used for product selection. These criteria need to balance the benefit of treatment against the quality risks for patients of a product that does not yet meet stringent standards. This can be a complex process. WHO therefore hosts a mechanism — the Expert Review Panel (ERP) — which conducts an abbreviated product dossier review, using clear, transparent criteria, to advise procurers whether a product would be acceptable for procurement during the next 12 months.

To be eligible for ERP review, products must be included on the relevant EOI (issued, for example, by the Global Fund) and manufactured at a site that has already been inspected and found compliant with stringent (WHO or SRA or PIC/s*) GMP.

Urgently needed products fall into two groups:

- products that have entered the WHO medicines prequalification pipeline or which are being assessed by an SRA
- products not eligible for WHO prequalification, that are needed for short-term procurement only.

Further information

- Invitations to manufacturers to submit an expression of interest for product evaluation by the Expert Review Panel, including product lists and eligibility criteria, are posted at:
  - www.theglobalfund.org/en/procurement/information/
  - www.ungm.org/Notices/Notices.aspx
  - http://www.unfpa.org/public/procurement
- The description of the experience of the Expert Review Panel gives useful information about the ERP process, including its benefits for both manufacturers and procurers.

** Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S).*

ESTIMATED INVESTMENTS TO GET A PRODUCT READY FOR PREQUALIFICATION

Common expenses involved in preparing a product for evaluation by WHO, or other stringent evaluation, include those listed below.

Bioequivalence studies: These studies often account for the most significant expenditure. Many manufacturers choose to use external organizations, such as CROs, or bioanalytical services companies, to carry out the work for them.

Formulation development: If the formulation is not already being manufactured, the specific formulation has to be developed. The cost of developing a new formulation varies with its complexity.

Lot production: One of the critical steps in the WHO prequalification process is determining whether a manufacturer is able to consistently produce product that meets specifications and product claims. The manufacturer is required to produce two batches of the product at pilot scale (except under certain circumstances, when the second batch can be smaller). These materials are used for bioequivalence studies, stability studies, etc.

Stability studies: WHO prequalification requires two lots of material for stability studies of generic medicines. Stability analyses must be carried out at a prescribed frequency. In addition to the cost of the manufactured material, costs will be incurred for analytical laboratory work (performed by technicians) and possibly also to ensure an adequate analytical system (e.g. high performance liquid chromatograph (HPLC), mass spectrometer or other analytical tool).

Headcount: The administrative headcount required for application for prequalification approval consists of personnel responsible for developing the documentation according to WHO prequalification requirements.

Ongoing communications: Continuing communication with the WHO prequalification team to address questions represents a relatively small amount of resources.

Local regulatory and incidental expenses: With WHO prequalification approval, a manufacturer may be more able to win tenders. However, registration approval for the product, from each of the countries on the tender list, must still be obtained. In addition to the direct fees for registration, each application requires time and work and often an "unofficial fee". Sometimes local authorities request additional data, which may add cost to the local application. Incidental costs could include, for example, the cost of having a new facility remain idle during the approval process. However, as mentioned above, WHO has piloted a procedure to accelerate registration by national MRAs.

Capital investment required to meet WHO prequalification standards: This can vary widely, depending on a manufacturer's degree of experience and the current state of its facilities. Global companies with well-established infrastructure usually have little or no incremental capital investments to make. For less experienced companies, capital costs may consist of acquiring land for building or upgrading manufacturing facilities, purchase of analytical instrumentation, or systems upgrades.

Facilities and systems upgrades: Often, a manufacturer without SRA experience must upgrade its facilities to ensure consistent manufacturing at GMP level, that meets WHO prequalification requirements. In addition, packaging equipment may have to be purchased. Occasionally, an entirely new facility is required.

Laboratory equipment: A manufacturer may also have to invest in state-of-the-art laboratory equipment to develop and optimize its quality control procedures. This can include items such as equipment for carrying out HPLC, or software updates.

The table on the next page gives an indication of some investments that might be needed to adequately prepare a product for evaluation by WHO.

Approximate ranges of investment (in USD)*

Low level of investment: Global innovator manufacturer with WHO-GMP-compliant production and own research unit
Medium level of investment: Manufacturer with established development and production processes
High level of investment: Start-up manufacturer with little experience and few established processes

	High level of experience Low level of investment needed	**Medium level of experience** Medium level of investment needed	**Low level of experience** High level of investment needed
Product design, formulation development	< 250,000	350,000—750,000	350,000—750,000
Quality-assured API (see below)	< 50,000	Dossier development: 200,000—450,000	200,000—450,000
Specifications and quality control methods			
Excipients and packaging materials			
Stability testing			
Batch information (biobatch, production batch)			
Bioequivalence of generic oral solid finished product with a stringently assessed comparator[¥]	0—50,000	100,000—300,000	300,000—600,000
Capital investment for GMP-compliant production (including testing capacity during production) corresponding to expected market size	0—500,000	500,000—1,500,000	3,000,000+[§]

[§] Can be up to tens of million USD for a new facility

Manufacturers who are considering submitting a product to WHO for evaluation should also review:

- their level of in-house expertise and capacity and whether external assistance or subcontracted services will be needed for preparing an application
- the registration requirements and post-registration commitments in the markets in which product distribution is sought
- whether any means exist for rationalizing dossier development or accelerating registration.

** Source: BioBridge Strategies, based on personal interviews with manufacturers. Note that actual values could be outside these ranges, depending on the specific case and the type of product. For example, an abbreviated process is in place for already stringently assessed products, with recognition of SRA outcomes.*

[¥] Or safety and efficacy for originator products. In most cases, these will already have been assessed by an SRA, with few exceptions (notably in the case of artemisinin-based antimalarials).

GOOD-QUALITY APIS — BUILDING BLOCKS FOR QUALITY-ASSURED MEDICINES

Good-quality APIs are the building blocks of good-quality medicines. In their absence, commercialization of good-quality medicines is slowed and patients' access to safe and effective treatment is impeded. But good-quality APIs can be difficult to source. WHO therefore prequalifies APIs used in manufacturer of medicines for treating HIV, TB and malaria, influenza, neglected tropical diseases, diarrhoea and for reproductive health. (An API can be submitted to WHO for evaluation even if no associated application for evaluation of an FPP has been submitted.)

For FPP manufacturers, clear identification of APIs that have been evaluated and confirmed as being manufactured in compliance with WHO GMP standards, and for which quality regulatory documentation is maintained, saves them time and money in locating and registering their sources of API. Moreover, the time to prequalification for an FPP is likely to be shorter if it is manufactured with a prequalified API. This is because some evaluation will already have been performed, and the results found to be satisfactory.

- WHO list of prequalified APIs
- Information on WHO prequalification of APIs

MARKET PERSPECTIVES: WHERE TO FIND INFORMATION

Before deciding to invest in seeking prequalification of an FPP, manufacturers should consider the market situation and expected returns for that product, exploring questions such as:

What are current treatment recommendations?

Standard treatment guidelines for eligible medicines are referenced in the individual EOIs. These give information on indications, dosage and recommended alternatives. As such, they describe needed products. They may also indicate the anticipated future direction of treatment regimens and thus of the products that will be needed to deliver them. For instance, for antiretrovirals (ARVs), WHO is looking to simplify and optimize HIV treatment regimens for best cost-effectiveness.

- WHO: Treatment 2.0 at a Glance
- Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV infection: Recommendations for a Public Health Approach

How many competitors are in the market and in the pipeline?

For certain medicines on WHO EOIs, a large number of FPPs have already been prequalified. For example, in November 2013, eight manufacturers were already offering prequalified nevirapine 200 mg tablets — with one additional submission under assessment for prequalification — and a further five manufacturers were offering SRA-approved products. However, for some products, demand is significant. In which case, the number of prequalified versions required may be higher than the 3 to 5 that are usually deemed sufficient by procurers for the purpose of ensuring sustainable supply at an affordable price.

- WHO list of all APIs and FPPs invited for evaluation, and number prequalified or currently under assessment per product
- Global Fund lists of ARVs, anti-TB products and antimalarial products which give information about products that are subject to the Global Fund quality assurance policy, listed in national and/or WHO standard treatment guidelines, and classified according to the various options (A, B, and ERP-reviewed), as defined in the Global Fund quality assurance policy

What volumes have been procured, and at what prices?

Historical pricing information can give an indication about the potential for market entry and future market trends. For example, prices for many 1st-line ARVs have decreased steadily since 2006, and some products are offered by a large number of suppliers. Market entry could therefore be difficult. Conversely, given the recently-issued Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV infection some products are in high and increasing demand. These include the ARV efavirenz + emtricitabine + tenofovir (600 mg + 200 mg + 300 mg tablet). Information on prices is available from a number of sources, including:

- WHO AMDS Global Price Reporting Mechanism (medicines for treating HIV/AIDS)
- Global Fund Price and Quality Reporting (PQR) tool (medicines for treating HIV/AIDS, TB and malaria) (see link at bottom of page, Transaction Summary)
- MSF. Untangling the Web of Antiretroviral Price Reductions. 16th edition.
- MSF. TB drugs Under the Microscope. 2nd edition

Current pricing information is available online for some products:

- UNICEF product catalogue with indicative prices (excludes anti-TB medicines)
- Global Drug Facility product catalogue

What is the expected market outlook?

Most of the market information on donor-funded markets relates to products for treating HIV, malaria and TB, since this is where donors have made their largest investments, although information relating to reproductive health medicines can also be found.

- UNITAID medicines landscape and technical reports
- Reproductive Health Interchange: harmonized data on contraceptive orders and shipments for over 140 countries

STAYING INFORMED ABOUT MARKET DEVELOPMENTS

Procurement opportunities

Many donors and procurement agents publish restricted tenders using the lists of prequalified and ERP-reviewed products. They can be contacted about their anticipated needs for future procurement. Relevant links are as follows:

- GDF suppliers; GDF procurement notices (anti-TB products)
- UNFPA (reproductive health products)
- Global Fund procurement support services (ARVs, artemisinin-based combination therapies and rapid diagnostic tests)
- UNICEF Supply Division
- IDA Foundation
- MSF Supply
- Principal recipients of Global Fund grants

INFORMATION MEETINGS FOR MANUFACTURERS

UN agencies and donors regularly organize manufacturers' meetings to exchange information and plan for future procurement and market development.

Details of meetings can be found here:

- UNFPA/UNICEF/WHO meeting with manufacturers
- UNICEF medicines supplier meetings
- WHO/UNAIDS annual consultation on ARV forecasting

PUTTING IT ALL TOGETHER — TWO EXAMPLES

Medicine	Tenofovir (TDF)-based triple fixed-dose combinations (FDCs) for adults: TDF + emtricitabine + efavirenz (TEE), TDF + lamivudine + efavirenz (TLE)	Injectable kanamycin (Km)
Indication	TDF-based regimens are the preferred option in 2013 WHO 1st-line HIV standard treatment guidelines (STG); treatment to start at CD4 <350 or earlier.	Injectable component of a five-drug multi-drug resistant anti-TB regimen. Alternatives, more expensive: amikacin (Am), capreomycin (Cm)
Demand	Large increase expected for TDF-based ARVs: ▲ Shifts from other regimens: 1 million patients on stavudine 2—3.8 million patients on zidovudine ▲ Earlier treatment initiation will increase the demand further	Increase expected for MDR-TB medicines: ▲ More patients will be diagnosed due to new technology △ UNITAID is engaging with high-burden, middle-income countries to align their procurement with international standards ▽ MDR-TB regimens may evolve — e.g. shorter duration would decrease demand
Invited for prequalification	TEE 600 + 200 + 300 mg TLE 600 + 300 + 300 mg	Kanamycin, powder for injection 500 mg vial and 1g vial
Invited for ERP review	No	Yes
Stringently assessed products on the market*	TEE: 5 (3 prequalified + 2 USA-approved) TLE: 3 (1 prequalified + 2 USA-approved)	Prequalified: none SRA-approved: three (France, Japan, USA)
Products under assessment for PQ	TEE: 4 TLE: 2	2
Global Fund orders:§ Buyers 2012	Top 5 grant recipients in 33 countries: Malawi; Zimbabwe; Zambia; Kenya; Lesotho	Top 5 grant recipients in 20 countries: Indonesia; Philippines; Uzbekistan; Ukraine; Mongolia
Suppliers 2012	TEE: 2 WHO-prequalified products TLE: 1 WHO-prequalified product	2 (A: limited production capacity, B: supply interruption in 2010)
Value (million USD) 2010 | 2011 | 2012	TEE: 4.8 | 13.3 | 7.0 TLE: 2.2 | 11.0 | 45.2	Manufacturer A: 2.7 | 4.4 | 1.5 Manufacturer B: 0.0 | 0.1 | 0.3 In 2012, Km accounted for 40% of injectable anti-MDR-TB doses reported in PQR
Prices (USD)	Median 2010 | 2011 | 2012, per 30 tablets: TEE: 19.92 | 16.20 | 14.99 /30 tablets TLE: 17.08 | 14.25 | 11.99 /30 tablets	2012, per 1 g dose: Manufacturer A: USD 2.60 Manufacturer B: USD 0.80
Challenges	API shortages expected, e.g. for TDF. Demand will more than double by 2015.¥ Only one source of prequalified TDF API, but 5 under assessment.	Challenging API production: fermentation process, sterility. Demanding requirements for sterile finished product; but bioequivalence study not required.

* *The data referring to prequalified products and products under assessment by WHO relate to November 2013.*

§ *As reported in PQR as at August 2012. Due to reporting time lag, 2012 data are not complete.*

¥ *WHO. Antiretroviral Medicines in Low- and Middle-income Countries: Forecasts of Global and Regional Demand for 2012–2015.*

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