WHO assistance for medicines manufacturers towards achieving PQ

Joint UNICEF, UNFPA and WHO meeting with manufacturers and suppliers

2-5 December 2019, UN City, Copenhagen, Denmark

Rutendo Kuwana
Technical Officer, WHO
Regulatory Systems Strengthening Team
Technical Assistance and Laboratories Group
Objectives

Explain and explore guidance on assistance to initiating and participation in PQ. Hopefully answer the following:

- What is the motivation for prequalification?
- What are the benefits of prequalification?
- Where to find information to inform your decision to participate in prequalification?
- What information is available?
- How to use the information sources.
- Explore what help you may need.
- Who can help you and how?
What prequalify

The Business Case

Access to more than $1,031bn donor-funded procurement markets - excluding government procurements and private markets in LMIC.

Opportunity for capacity building to enter wider market including the better regulated.

Bragging rights?
What’s in it for WHO and partners?

Accelerated access to quality assured products.

Raising overall standards of manufacturing and facilitating local production in some countries.

Contribution to lives saved.

Increased competition leading to savings due to lowering of prices while quality is assured.
Where to start first – the due diligence
Part 1: the market and propriety

As well as submitting an API or FPP for evaluation for prequalification, applicants may consider submission of FPPs for assessment by the Expert Review Panel (ERP). WHO-prequalified or products approved by a stringent regulatory authority are not available on the market for all needed medicines. Procurers may therefore find themselves in the position of having to urgently procure products about which little is known in terms of quality risk. ERP was created to help procurers assess such risk. The results of ERP assessments enable procurers — such as the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria and UNFPA (United Nations Population Fund) — to make an informed decision regarding time-limited procurement of the products assessed. ERP assessment is therefore another route to markets.

Links to all this information can be found below.

- MARKET AND MARKET-RELATED REPORTS
- PRODUCT AND PRICE INFORMATION BY ORGANIZATION
- BIDDING OPPORTUNITIES
- PATENTS AND LICENCES DATABASE

https://extranet.who.int/prequal/content/market-information
### The Market and prices

**MARKET AND MARKET-RELATED REPORTS**

- Disease Narrative for HIV and Areas for Intervention, updated April 2016 (UNITAID)
- Disease Narrative for HIV/HCV Co-infection, updated November 2015 (UNITAID)
- Disease Narrative for Tuberculosis, updated March 2016 (UNITAID)
- Global Contraceptive Commodity Gap Analysis 2018
- Hepatitis C Medicines Technology and Market Landscape: Update, September 2017 (UNITAID)
- HIV mid-year market memo, 2018, 20 June 2018 (Clinton Health Access Initiative)
- Strategies to Secure Access to Generic Hepatitis C Medicines, May 2015 (Médecins Sans Frontières (MSF))
- Untangling the Web of Antiretroviral Price Reductions (18th edition) July 2016 (MSF)
- UNFPA procurement statistics for 2016

**PRODUCT AND PRICE INFORMATION BY ORGANIZATION**

- Global Drug Facility catalogue
- Global Fund to Fight AIDS, Tuberculosis and Malaria
- Licensing and patent information for antiretrovirals: Medicines Patent Pool database
- Médecins Sans Frontières
- Reproductive Health Interchange
- UNFPA product catalogue
- UNICEF supply catalogue
- WHO database on procurement of HIV and hepatitis products
Which products are of PQ interest?

Expressions of Interest – API, FPP, QCLs
So what’s invited, what’s prequalified and what's in the pipeline? Recommended Gaps to Target

**KEY RESOURCES**

- Documents A-Z
- Prequalified Lists
- Prequalification Pipeline
  - Summary: FPPs & APIs invited/prequalified/under assessment
  - FPPs under assessment
  - FPPs and APIs Eligible for Prequalification ("EOIs")
- Key Performance Indicators
- Procedures & Fees for WHO

**Summary: FPPs & APIs Invited for Prequalification/Prequalified/Under Assessment**

This summary:

- brings together information on all the finished pharmaceutical products (FPPs) and active pharmaceutical ingredients (APIs) currently invited for prequalification (contained in the Invitations to Manufacturers to Submit an Expression of Interest for Product Evaluation)
- indicates the number (if any) of prequalified FPPs or APIs for each FPP or API currently invited for prequalification
- indicates the number (if any) of applications under assessment for FPP or API currently invited for prequalification.

All the FPPs listed are needed for international and/or national procurement. WHO invites manufacturers of these products to submit them for WHO prequalification.

For some FPPs, demand is significant. In such instances, the number of prequalified FPPs required may be higher than the three to five prequalified FPPs that are usually considered sufficient for the purpose of ensuring sustainable supply at an affordable price.

https://extranet.who.int/prequal/content/prequalification-pipeline
# FPPs (& APIs) Invited for Prequalification/Prequalified/Under Assessment

## Medicines for Treating HIV Infection and Related Diseases

<table>
<thead>
<tr>
<th>1. Antiretrovirals as single-ingredient formulations for use in adults and adolescents</th>
<th>Number of Individual FPPs prequalified</th>
<th>Number of Individual FPPs under assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1. Nucleoside/nucleotide reverse transcriptase inhibitors</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Abacavir, tablet 300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir, tablet 600 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2. Non-nucleoside reverse transcriptase inhibitors</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Efavirenz, tablet 400 mg</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Efavirenz, tablet 600 mg</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1.3. Protease Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir, capsule 150 mg</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Atazanavir, capsule 300 mg</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>2. Darunavir, tablet 600 mg</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Darunavir, tablet 800 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.6. Ritonavir, tablet (heat-stable) 100 mg</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1.4. Integrase Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.8. Dolutegravir, tablet 50 mg (preferably scored and dispersible)</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>2.9. Raltegravir, tablet 400 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Antiretrovirals as single-ingredient formulations for use in children</td>
<td>Number of Individual FPPs prequalified</td>
<td>Number of Individual FPPs under assessment</td>
</tr>
<tr>
<td>2.1. Solid dosage formulations of:</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Abacavir, tablet 60 mg (scored and dispersible)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz, scored tablet 100 mg (scored and preferably dispersible)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Efavirenz, scored tablet 200 mg (scored and preferably dispersible)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Anti-retrovirals as fixed-dose combinations (FDC) for adults and adolescents</td>
<td>Number of Individual FPPs prequalified</td>
<td>Number of Individual FPPs under assessment</td>
</tr>
<tr>
<td>3.1 Nucleoside/nucleotide reverse transcriptase inhibitors</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Emtricitabine + tenofovir, tablet 200 mg + 300 mg</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Lamivudine + tenofovir, tablet 300 mg + 300 mg</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Lamivudine + zidovudine, tablet 150 mg + 300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Anti-retrovirals as co-packaged formulations for adults and adolescents</td>
<td>Number of Individual FPPs prequalified</td>
<td>Number of Individual FPPs under assessment</td>
</tr>
<tr>
<td>4.1 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine + Abacavir, tablet 30 mg + 60 mg scored and preferably dispersible</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lamivudine + Abacavir, tablet 60 mg + 120 mg scored and dispersible</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lamivudine + Zidovudine, tablet 30 mg + 60 mg scored and preferably dispersible</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

https://extranet.who.int/prequal/content/summary-fpps-apis-invited-prequalificationprequalifiedunder-assessment
Assessment Status

FPPs Under Assessment

This section of the website provides information on the status of FPP dossiers that are currently under assessment (i.e. not yet prequalified).

It includes:
- only those dossiers that have been screened and accepted for assessment
- several FPPs with the same international proprietary name (INN), strength, unit and dosage form, that have are produced and have been submitted for evaluation by different manufacturers.

It does not include:
- prequalified FPPs; once an FPP has been prequalified it is included in the WHO List of Prequalified Medicinal Products.

<table>
<thead>
<tr>
<th>Product (INNs)</th>
<th>Strength</th>
<th>Dosage Form</th>
<th>Quality Status</th>
<th>Efficacy Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir (sulfate)/Lamivudine</td>
<td>600mg/300mg</td>
<td>Tablet, Film-coated</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Alnendazole</td>
<td>400mg</td>
<td>Tablet</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Amodiaquine (hydrochloride)/Artesunate</td>
<td>135mg/50mg</td>
<td>Tablet</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Amodiaquine (hydrochloride)/Artesunate</td>
<td>135mg/50mg</td>
<td>Tablet</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Amodiaquine (hydrochloride)/Artesunate</td>
<td>270mg/100mg</td>
<td>Tablet</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

https://extranet.who.int/prequal/content/dossier-status
The pipeline issues

- Few or no applications
- Dossiers or Sites not progressing in PQ assessment or inspection
- Maintenance or Continuous Improvement

Pre, in-process and post submission challenges
Available assistance - General

- Advice on selection of products for prequalification
- Advice on corrective actions and plans post inspection
- Clarification of requests for additional information during assessment.
- Preliminary review of data (API or FPP) intended to be submitted as part of application for PQ
- Training on specific topics identified during assessment or inspection (in collaboration with PQ)

NB – current policy is no 1-on-1 technical assistance, unless for special circumstances
Available assistance – special circumstances

• Support on product development.
• Quality management system audit.
• Development of corrective actions and plans post inspection.
• Review of data (API or FPP) intended to be submitted as part of application or additional data requested for PQ.
• Development or review of BE protocol.
• Audit of a BE study already conducted by a CRO pre WHO PQT submission.
• Advice on design of premises (API and FPP).
• Pre-submission GMP audit or gap analyses (API, FPP, CRO).
What are some of special circumstances?

Product of priority to PQ (global shortage, poorly represented in the pipeline or PQ list, products not progressing in pipeline).

Normally identified by WHO treatment groups, development partners and donors.

Specific funds available to support TA.

Manufacturer prepared to meet TA costs but does not have access to expertise.

Any other circumstances on a case by case basis.
The process

Support to Manufacturers, CROs and QCLs

Any active pharmaceutical ingredient (API), finished pharmaceutical product (FPP) or medicines quality control laboratory (QCL) for which prequalification is sought must meet international pharmaceutical standards. Recognizing that this can be difficult for manufacturers and QCLs, WHO makes available technical advice and technical assistance to help them understand and work out how to meet prequalification requirements, and, in the case of specific deficiencies how to overcome them.

Technical advice

Technical advice can be sought at any time by an applicant or manufacturer of APIs or FPPs that is invited for evaluation for prequalification. Advice can be provided as a written response or in a one-to-one meeting.

Technical assistance

WHO provides technical assistance to help recipients achieve compliance with international regulatory norms and standards, so that they can attain WHO prequalification for priority products or services and/or supply quality-assured products called for the UN Commission on Lifesaving Commodities for Women and Children (UNCoLSC).

https://extranet.who.int/prequal/content/support-manufacturers-cros-and-qcls-0
1on1 Technical Assistance activities: 2006 – 2018 for medicines and QCLs

Total of 248 Technical Assistance Activities from 2006-2018

Technical Assistance provided to Rx manufacturers for prequalification, National medicines QCL, Clinical Research Organisations for BE studies, Regulators
More stats ....

TAs by type since 2005

- 14% CRO
- 9% API manufacturers
- 7% FPP Manufacturers
- 70% Dossier Preparation

Time to PQ dossier submission

- Target time to PQ submission - 24 months
TA providers

Focus on Low to Middle Income Country (LMIC) manufacturers - represent more than 40% of all manufacturers

Trusted 3rd Parties contracted or recommended by WHO

Internal or External Pool of experts
Questions

• How much is charged?
  May be free in special circumstances. Recipients may be requested to pay some costs especially for external experts and 3rd parties

• Does WHO have the expertise?
  Not always

• How many times can TA be provided?
  Depends on recipient commitment and progress

• Does it include capital investments?
  No

• Can WHO facilitate or assist in building business case for PQ?
  Good question
Need more information?

Rutendo Kuwana (Mr)
Technical Officer
Regulatory Systems Strengthening
Regulation of Medicines and Other Health Technologies
Access to Medicines, Vaccines and Pharmaceuticals
World Health Organization
Geneva, Switzerland
Email: Kuwanaru@who.int
Office: +41 (0)22 791 3409