The WHO Prequalification of Medicines Programme

CPTR 2013 Workshop, Washington 1-3 Oct 2013

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WHO
The Prequalification of Medicines Programme (PQP) - Introduction

- Objectives/Scope of PQP
- Prequalification of Finished Pharmaceutical Products (FPPs)
  - Dossier assessments
  - Inspections
- Prequalification of Active Pharmaceutical Ingredients (APIs)
- Prequalification of Quality Control Laboratories (QCLs)
- Capacity building (incl technical assistance)
- Benefits to manufacturers and regulators of PQP’s activities
- New initiatives to facilitate national registration of prequalified products
The Prequalification of Medicines Programme - Introduction

- A United Nations Programme managed by WHO
- Started in March 2001 as a Pilot Project: Focus on HIV/AIDS
- Partners included WHO, UNICEF, UNFPA, UNAIDS and supported by World Bank
- Quickly expanded to include Tuberculosis, Malaria, Reproductive Health, Influenza and others
- Funded by donors – mainly UNITAID and Bill and Melinda Gates Foundation
PQ Programme objectives

- Contribute to the United Nations priority goal of addressing widespread diseases in countries with limited access to quality medicines

- In cooperation with National Regulatory Agencies and partner organizations, make quality priority medicines available for the benefit of those in need
Scope of prequalification

- Limited to priority medicines (and APIs) as published in Invitations for Expression of Interest (EOI)* on PQP website
- Medicines eligible for prequalification determined by WHO disease oriented programmes ("perceived medical need")
- Mostly generics
- Only products are prequalified!

*TB: 11th EOI (June 2012)
Therapeutic areas

- HIV/AIDS
- Malaria
- Tuberculosis
- Reproductive Health
- Influenza
- Acute diarrhoea in children (zinc)
- Neglected Tropical Diseases (NTDs)

Potentially other categories of products, if there is the need
Key outputs

- Published list of prequalified medicinal products (FPPs)
  - Used principally by UN agencies, including UNAIDS and UNICEF, and any other agency or organization involved in bulk purchasing of medicines, to guide their procurement decisions

- Published list of prequalified APIs
  - Can be used by FPP manufacturers to assure the quality of APIs
  - Can be used by NMRAs who wish to verify the standard of APIs that have been used to manufacture nationally registered medicines

- Published list of prequalified QC laboratories
  - The list may be used by any organization to ensure that testing for quality monitoring is done to an acceptable standard
Why prequalify medicines?

- Quality needs to be built into the product, it cannot be tested in.
- Provide quality products for UN procurement, but also other partners (GF, NGOs and country procurement).
- Lack of well established drug regulatory systems (50% have varying capacity and level of development, 30% minimal or limited regulation)
- Increasing demand for generics, several players, substandard products on the market
- Lack of quality assured medicines can have serious consequences – ineffective treatment, drug resistance, side effects etc
PQP vs national approval procedures

- Only certain therapeutic areas/products are invited
- Voluntary - no direct legal implications
- Not a national marketing authorisation (but some countries may use it for this purpose). WHO is not a supra-national reg authority.
- Fees introduced on 1 Sept 2013 (new dossiers, major variations)
- Assessments and inspections done by multinational teams
- Assessment and inspection outcomes are publicly available (WHOPARs and WHOPIRs)
- Technical assistance and regulatory support possible
Prequalification process

Expression of Interest

Product dossier SMF

Assessment

Additional information and data

Acceptable

Inspections

Corrective actions

Compliance

Prequalification

Maintenance and monitoring
Prequalification of FPPs

- Assessment of Quality and Efficacy/Safety (BE, BCS-based biowaivers)
- Inspection of manufacturing sites (FPP, API) and CROs
- Monitoring of the products after prequalification (variations, requalification, inspections, random QC sampling, investigation of complaints)
Dossier assessment

- **Assessors**
  - In-house and external (90%), mostly from SRAs (subject to availability). Personal capacity. Total assessor pool 50+.

- **Assessment sessions every 2 months in Copenhagen for 5 days**
  - Dossiers are assessed by at least 2 assessors (Q and BE separate), each report is reviewed by a more senior assessor; ≈35 assessors/session.
  - Assessors from developing countries constitute ≈ 40%
  - Capacity building
  - A unique opportunity for assessors from all over the world to work together
  - Frequent manufacturer meetings and TCs

- **In-between assessment sessions (WHO HQ)**
Dossier assessment

- WHO, ICH and specific PQP guidelines and the International Pharmacopoeia and other pharmacopoeias are applied
  - Developed in collaboration with international experts
  - Adopted by WHO Expert Committee, with international representation

- Maintenance (variations to prequalified products, as well as requalification) done in house and during assessment sessions

- CTD format
## Product dossiers submitted and accepted for assessment 2005 – 2013 (as of 30 August 2013)

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>HIV</td>
<td>67</td>
<td>42</td>
<td>40</td>
<td>52</td>
<td>31</td>
<td>21</td>
<td>33</td>
<td>42</td>
<td>32</td>
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<tr>
<td>TB</td>
<td>17</td>
<td>9</td>
<td>20</td>
<td>17</td>
<td>18</td>
<td>16</td>
<td>21</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Malaria</td>
<td>3</td>
<td>5</td>
<td>11</td>
<td>17</td>
<td>12</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Rep Health</td>
<td>0</td>
<td>0</td>
<td>19</td>
<td>5</td>
<td>10</td>
<td>7</td>
<td>3</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Influenza</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>NTD</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>87</strong></td>
<td><strong>56</strong></td>
<td><strong>90</strong></td>
<td><strong>92</strong></td>
<td><strong>83</strong></td>
<td><strong>51</strong></td>
<td><strong>68</strong></td>
<td><strong>82</strong></td>
<td><strong>82</strong></td>
</tr>
</tbody>
</table>

**Accepted** (submitted same year)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>59</td>
<td>63</td>
<td>39</td>
<td>35</td>
<td>44</td>
<td>62</td>
<td>72</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Accepted** (submitted prev year)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>5</td>
<td>14</td>
<td>18</td>
<td>4</td>
<td>11</td>
<td>9</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

* No screening. All applications included in assessment
# Products under assessment (on website)

<table>
<thead>
<tr>
<th>Product (INNs)</th>
<th>Strength</th>
<th>Unit</th>
<th>Dosage Form</th>
<th>Quality part</th>
<th>Efficacy/Safety part</th>
</tr>
</thead>
<tbody>
<tr>
<td>abacavir</td>
<td>20 mg/ml</td>
<td>solution, oral</td>
<td></td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>abacavir</td>
<td>20 mg/ml</td>
<td>solution, oral</td>
<td></td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>abacavir</td>
<td>60 mg</td>
<td>tablet</td>
<td></td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>abacavir + lamivudine</td>
<td>60/30 mg</td>
<td>tablet</td>
<td></td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>abacavir + lamivudine + zidovudine</td>
<td>60/30/60 mg</td>
<td>tablet</td>
<td></td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>aminosalicylate sodium</td>
<td>60 %</td>
<td>granule</td>
<td></td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>amodiaquine + artesunate</td>
<td>153.1/50 mg</td>
<td>tablet</td>
<td></td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>amodiaquine + artesunate</td>
<td>306.2/100 mg</td>
<td>tablet</td>
<td></td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>amodiaquine + artesunate</td>
<td>50/153 mg</td>
<td>tablet</td>
<td></td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>amodiaquine + artesunate</td>
<td>50/153 mg</td>
<td>tablet</td>
<td></td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>
TB dossiers - Status as of 19 Sept 2013

- FPPs prequalified (total=359, TB=70) – see PQP website

- FPPs in PQP pipeline (= under assessment) (total=150, TB=44)
  - 31 of 44 (=70%) are 2nd line TB products (cycloserine, prothionamide, capreomycin, kanamycin, streptomycin, levofloxacin, moxifloxacin, and amikacin)
# 1st line single ingredient TB products (19 Sept 2013)

<table>
<thead>
<tr>
<th>Drug Description</th>
<th>Individual FPPs PQ’d</th>
<th>Individual FPPs under assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol (E), tablet/capsule 200 mg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ethambutol (E), tablet/capsule 275 mg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pyrazinamide (Z), tablet/capsule 250 mg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rifampicin, capsule 150 mg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rifampicin, capsule 300 mg</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Streptomycin, powder for injection 1g (vial)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Streptomycin, powder for injection 0.75 g (vial)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
### 1st line FDC TB products

<table>
<thead>
<tr>
<th>Product Description</th>
<th>Individual FPPs prequalified</th>
<th>Individual FPPs under assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid/Rifampicin, coated tablet/capsule 150 mg + 150 mg</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Isoniazid/Rifampicin, coated tablet/capsule 150 mg + 300 mg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Isoniazid/Pyrazinamide/Rifampicin, coated tablet/capsule 150mg + 500mg + 150mg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Isoniazid/pyrazinamide/Rifampicin, film coated tablet/capsule 75mg + 400mg + 150mg</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
## 2nd line single ingredient TB products

<table>
<thead>
<tr>
<th>Product Description</th>
<th>Individual FPPs prequalified</th>
<th>Individual FPPs under assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin, solution injection 500 mg/2 ml vial, amp</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Amikacin, powder for injection 1g vial, amp</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Kanamycin, powder for injection 1g, vial</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Kanamycin, powder for injection 500 mg, vial</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Levofloxacin, tablet 750 mg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ofloxacin, tablet/capsule 400 mg</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Prothionamide, tablet/capsule 250 mg</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Para-aminosalicylic acid (PAS) sachets, 4 g granules</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PAS sodium 100 g jar granules; powder for oral solution sachets</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PAS sodium 4 g sachets granules; powder for oral solution sachets</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PAS sodium 9.2 g sachets granules; powder for oral solution sachets</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Terizidone, tablet/capsule 250 mg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Terizidone, tablet/capsule 300 mg</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
### Pediatric TB products – oral solid dosage forms
(preferably dispersible or crushable tablet)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Individual FPPs prequalified</th>
<th>Individual FPPs under assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin/Isoniazid/Pyrazinamide 75/50/150 mg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rifampicin/Isoniazid 75/50 mg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ethambutol, 100 mg</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ethambutol, 50 mg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Isoniazid, 50 mg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pyrazinamide, 150 mg</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Prequalification of SRA approved products (innovator or generic)

- Assessment and inspections by a stringent regulatory authority (SRA) are recognised

- SRAs are 1) ICH member, 2) ICH observer or 3) RA associated with an ICH member through a legally binding, mutual recognition agreement.

- Abbreviated process for prequalifying medicines approved by an SRA (no duplication)

- Variations handled by the SRA

- Also limited to defined priority medicines (EOIs)
Alternative pathways for inclusion in the list

- USA FDA tentative approvals (PEPFAR)
  - HIV/AIDS products only (n=97)

- EU Article 58 (n=3; two ARVs, one MA product)

- Canadian access to medicines regime (CAMR) (n=1, ARV)

- Included in WHO prequalified medicines list as special category
Inspections (GMP)

- The evaluation of a medicine for prequalification includes inspection of FPP and API manufacturing sites, and CROs, i.e. no dossier, no inspection.

- Inspections conducted by an SRA are taken into account when planning inspections.

- WHO reserves the right to inspect all manufacturers and clinical sites listed in a product dossier - to assess compliance with WHO GMP, GCP and GLP.

- The need for inspections of API sites and CROs are decided on a case by case risk basis.
Inspections

- Inspections are conducted during the assessment process, on an on-going basis and in special circumstances
- Frequency is determined on a risk basis
- Inspections are normally announced 1-2 months in advance
- Under special circumstances, very short notice is given
Types of inspections

- Initial inspection
- Routine inspection
  - Frequency determined on risk basis
- Special inspection
  - may be conducted at any time, e.g. for complaint follow-up
- Follow-up inspection
  - if necessary to close out deficiencies from the last inspection
- Data verification inspections may also be done
Inspections

- Inspections are conducted by a team
  - A WHO inspector leads the team
  - An inspector from another Regulatory Authority (usually a PIC/S member) assists (co-inspector)
  - The Regulatory Authority of the country of manufacture is invited (and encouraged) to accompany the team as observer (host country).
  - Inspectors from developing countries may be included in the team as observers for training purposes (potential recipient)
Benefits of PQP team inspections

- A unique opportunity for inspectors to work together, discuss requirements, interpretations and procedures
- Contributes to consistency and harmonisation
- Capacity building opportunity for developing country inspectors
Number of inspections performed

- FPP
- API
- CRO
- QCL

Year: 2005 to 2012
Products prequalified 2007- end Aug 2013

[Bar chart showing the number of products prequalified for each year from 2007 to 2013, categorized by disease: NTD, Diarrhea, Influenza, RH, Malaria, TB, and HIV.]
Prequalified medicines at 31 August 2013

- Prequalified generics and innovators as of August 31 2013: 359 products

- Total listed as of August 31 2013 (including those listed based on USFDA-PEPFAR/EMA Article 58/HC approvals): 460 products

Countries that have submitted and had products prequalified:  Belgium (5); Canada (16), China (11); France (16); Germany (8); Greece (3); Hungary (1); Iceland (2); India (214); Japan (1), Kenya (1); Republic of Korea (1); Latvia (1); Netherlands (8); Pakistan (1); Romania (7); Russia (1), South Africa (9); Spain (7); Switzerland (17); United Kingdom (31); USA (3); Zimbabwe (2).

Countries of manufacture of prequalified products: Australia; Belgium; Canada; China; Finland; France; Germany; Hungary; India; Korea, Latvia, Morocco; Netherlands; Pakistan; Romania, Russia, South Africa; Spain; Switzerland; Uganda; United Kingdom, USA; Zimbabwe.
PQP - Transparency

- Product pipeline (FPPs) on PQP website

- WHOPARs and WHOPIIRs (where found to be compliant) are published on the PQP website in response to a World Health Assembly resolution (2004)

- Notices of Concern or Notices of Suspension may be issued and published if there are serious non-compliances requiring urgent attention
The API prequalification started as a pilot project in October 2010.

API Prequalification seeks to verify and publicise quality sources of APIs by:

- Assessment of API data (APIMF).
- Evaluation of the GMP at the manufacturing sites (critical).
- Publishing of API and manufacturer details (PQP website).

List of PQ APIs:

http://www.who.int/prequal/info_applicants/API_PQ-List.htm
API prequalification:

1. To facilitate the identification of API sources by FPP manufacturers and support the availability of quality medicines.

2. A resource for NMRAs who do not have the means to undertake API assessment themselves.

http://www.who.int/prequal/info_applicants/API_info_applicants.htm
## Prequalification of APIs

Invited APIs reflect those APIs used in invited FPPs.

A 5th EOI (July 2013) includes the following TB APIs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Capreomycin</td>
<td>Cycloserine</td>
<td>Ethambutol</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Isoniazid</td>
<td>Kanamycin</td>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Ofloxacin</td>
<td>PAS</td>
<td>PAS Sodium</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>Pyrazinamide</td>
<td>Rifampicin</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>Terizidone</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*World Health Organization*
Prequalification of APIs (19 Sept 2013)

- APIs prequalified (total=47, TB=13)
  - Ethambutol, pyrazinamide (3), isoniazide, rifampicin (5), prothionamide, ethionamide, cycloserine

- APIs in PQP pipeline (total=50, TB=8)
  - Amikacin, capreomycin (2), ethambutol, isoniazide, levofloxacin, moxifloxacin, rifampicin
Progress has exceeded expectations, due in part to the willingness of manufacturers previously involved with PQP to participate.

### Prequalification of APIs

<table>
<thead>
<tr>
<th></th>
<th>1 Jan 2011</th>
<th>1 Jan 2012</th>
<th>1 Jan 2013</th>
<th>Presently</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative number of applications received</td>
<td>2 (0)</td>
<td>36 (5)</td>
<td>74 (20)</td>
<td>100 (22)</td>
</tr>
<tr>
<td>Cumulative number of APIs Prequalified</td>
<td>0 (0)</td>
<td>8 (2)</td>
<td>28 (6)</td>
<td>47 (13)</td>
</tr>
</tbody>
</table>

( ) – TB related APIs
Prequalification of APIs

Challenges for TB APIs:

Few manufacturers:

- Many invited TB APIs are older chemicals having low commercial value limiting FPP manufacturer interest world-wide.

A large proportion of APIs are derived from fermentation:

- Production is a relatively complex procedure.

- Quality standards, and in particular GMP standards, present a challenge to many potential manufacturers.
Prequalification of QCLs

- Established in 2004 (WHO, Unicef, UNAIDS, UNFPA, UNITAID, supported by World Bank) - for QC laboratories in Africa only

- 3rd EOI published in September 2007
  - Without regional limitation

- Scope - chemical and microbiological testing (including LAL test) of medicines (vaccines, biologicals or toxicological tests not included)

- Voluntary
  - Any laboratory (private or governmental) can participate
  - Free of charge

- Priority to
  - National QC laboratories and laboratories providing testing services to the government
  - QC laboratories in areas where UN agencies identify the need for quality testing
Prequalified/interested QCLs
(June 2013)

Prequalified QCLs:
- South Africa, RIIP+CENQAM (2005)
- Algeria, LNCPP (2005)
- South Africa, Adcock Ingram (2007)
- Morocco, LNCM (2008)
- Kenya, NQCL (2008)
- India, Vimta Labs (2008)
- France, CHMP (2008)
- Vietnam, NIDQC (2008)
- Kenya, MEDS (2009)
- Singapore, TÜV (2009)
- Canada, K.A.B.S. Laboratories (2010)
- Ukraine, CLQCM (2010)
- Ukraine, LPA (2010)
- Peru, CNCC (2010)
- Uruguay, CCCM (2010)
- Bolivia CONCAMYT (2010)
- Tanzania, TFDA (2011)
- India, SGS (2011)
- Belgium, SGS (2011)
- Netherlands, Proxy (2011)
- Portugal, INFARMED (2011)
- Brazil, FUNED (2011)
- Russia, FSBI-SCEEMP (2012)
- Belarus, RCAL (2012)
- Thailand, BDN (2012)
- NIFDC, China (2012)
- Laboratorios Basi, Portugal (2013)
Capacity building

- **Seminars and workshops**
  - General – PQP procedures and WHO requirements
  - Annual PQP assessment training
  - Problem or product specific; HIV/AIDS, TB, antimalarial or RH products
  - Pharmaceutical development/paediatric dosage forms
  - Training of NRA staff and manufacturers frequently combined
  - International experts frequently involved
  - Support is given to training organized by others
  - Focus on "training of trainers"

- **Within the assessment/inspection process, advisory meetings, review of protocols**

- “Inclusive” (assessments, inspections), 3-month rotational post at WHO HQ (n=20; Zimbabwe, Uganda, Tanzania, Ethiopia, Kenya, Ukraine, Zambia, Botswana, Ghana, DR Congo, China)

- **Technical assistance to eligible manufacturers**
Training workshops and meetings organized, co-organized or supported by PQP

- More than 120 trainings have been delivered.
Trainings
More than 1550 participants

Participants in workshops and meetings organized or co-organized by PQP
Technical assistance

- Provision of expert consultants to
  - Manufacturers
  - Quality control laboratories

- Assistance focuses on
  - GMP, GCP or GLP compliance
  - Data development and compilation of dossier

- Technical assistance is separated from the assessments and inspections
Conditions for provision of technical assistance

Manufacturers:

- Participation in the Prequalification of Medicines Programme
- Capable and willing to improve
- Located in a developing country

Products:

- Inclusion in the EOIs
- High public health value
- Poorly represented in the prequalified list.
More than 110 technical assistance missions have been organized and delivered.
New activities in WHO to facilitate access to quality medicines

- African Medicines Registration Harmonization Initiative (AMRHI) – pilot in East Africa (EAC) – WHO providing technical support (assessments/registration, GMP, IMS, QMS)

- Joint assessment WHO PQP-EAC (Kenya, Tanzania, incl Zanzibar, Uganda, Rwanda and Burundi)
  - Prequalification and national registration as close as possible in time (successful pilot in 2010 with times to national registration reduced by 50% in EAC countries). New joint assessment ongoing as of July 2013. Recent session in Sept, next one in Nov.

- Collaborative registration procedure (accelerated registration pilot project; started June 2012; 7 products - 6 ARVs, one RH - registered in 4 countries as of 9 Aug 2013 - Zimbabwe, Namibia, Kenya and Uganda) – For 6 ARVs, NMRA decision is pending.

- Joint inspection (in EAC since 2010)
Benefits of PQP to regulators and manufacturers in the regions?

- **Regulators**
  - Capacity building/training – improved technical knowledge and skills
  - Practice and experience from various collaborative ventures
  - Offers a lot of practical tools and guidelines
  - Helps to build more credible regulatory systems
  - Saves resources

- **Manufacturers**
  - Access to international funds (participation in tenders)
  - Facilitated registration in some recipient countries
  - Capacity building (within the process)
  - Possibility for technical assistance
  - Recognition as a WHO listed company (better image, more trust from procurement and regulators)
Key achievements

• Contribution to increased access to quality medicines, for example:
  – in 2012, 8 million people living with HIV and in need of treatment were receiving treatment, around 6.5 million of whom were taking WHO-prequalified antiretrovirals (ARVs);
  – and sales of WHO-prequalified artemisinin-based combination antimalarials exceeded 180 million individual treatment courses in 2010)


PREQUALIFICATION PROGRAMME
A United Nations Programme managed by WHO

Vision
Good quality medicines for everyone.

Mission
In close cooperation with national regulatory agencies and partner organizations, the Prequalification Programme aims to make quality priority medicines available for the benefit of those in need.

This is achieved through its evaluation and inspection activities, and by building national capacity for sustainable manufacturing and monitoring of quality medicines.

Strategy

- Apply unified standards of acceptable quality, safety and efficacy.
- Comprehensively evaluate the quality, safety and efficacy of medicinal products, based on information submitted by the manufacturers, and inspection of the corresponding manufacturing and clinical sites.
- Prequalify sources of active pharmaceutical ingredients by comprehensively evaluating the quality of the API based on information submitted by the manufacturers, and inspection of the corresponding manufacturing sites.
- Prequalify quality control laboratories of pharmaceuticals.
- Build the capacity of staff from national regulatory authorities, quality control laboratories, and from manufacturers or other private companies, to ensure medicines quality.

Key output
The list of prequalified medicinal products used for HIV/AIDS, malaria, tuberculosis and for reproductive health is available on the website.
Further information:  http://www.who.int/prequal/

Email:  prequal@who.int
BACK-UP SLIDES
Risk-based approach in:
Conclusion following an inspection

- **When there are "other" observations only:**
  - considered to be operating at an **acceptable level of compliance with WHO GMP**.
  - The manufacturer is expected to provide CAPAs.
  - CAPAs are evaluated and followed up during the **next routine inspection**.

- **When there are "other" and a few "major" observations:**
  - **compliance** with WHO GMP is made **after the CAPAs have been assessed**.
  - CAPAs for majors to include documented evidence of completion.
  - CAPAs paper evaluated ± an on-site follow up inspection.

- **When there are "critical" or several "major" observations:**
  - considered to be operating at an **unacceptable level of compliance with WHO GMP guidelines**.
  - Another inspection will most likely be required
Risk-based approach in: Definition and classification of deficiencies

- Deficiencies are descriptions of non-compliance with GMP requirements.

- A distinction is made between deficiencies as a result of: -
  - a defective system or,
  - failure to comply with the system.

- Deficiencies may be classified as:
  - Critical Observation – potential risk harm to the user
  - Major Observation – major deviation from GMP/GCP
  - Minor or Other Observation – departure from good practice
Update on timelines and statistics

- **First inspection**: 6 months from dossier acceptance for assessment or from site confirms it is ready.
- **Routine inspection**: ± 3 months from due date.
- **Notification**: 1 – 2 months before inspection.
- **Onsite days**: 3 – 5 days.
- **Report**: 30 days from last date of inspection.
- **CAPAs**: 30 days from receipt of report (max 2 rounds, comprehensive, on CDs and not hard copies)
- **Closing of inspection**: 6 months from inspection.
- **Follow-up inspection**: 6 months from inspection
Analysis of inspection of observations

Total number of Observations

Average number of observations

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>FPP</th>
<th>API</th>
<th>CRO</th>
<th>QCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Observations</td>
<td>2885</td>
<td>1440</td>
<td>1218</td>
<td>329</td>
<td>198</td>
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<tr>
<td>Critical Observations</td>
<td>82</td>
<td>15</td>
<td>34</td>
<td>23</td>
<td>10</td>
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<tr>
<td>Major Observations</td>
<td>727</td>
<td>246</td>
<td>304</td>
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<td>43</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>FPP</th>
<th>API</th>
<th>CRO</th>
<th>QCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average all observations</td>
<td>15.6</td>
<td>19.2</td>
<td>18.7</td>
<td>10.6</td>
<td>14.1</td>
</tr>
<tr>
<td>Average critical</td>
<td>0.4</td>
<td>0.2</td>
<td>0.5</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Average Major</td>
<td>3.9</td>
<td>3.8</td>
<td>4.7</td>
<td>3.0</td>
<td>3.1</td>
</tr>
</tbody>
</table>
A WHO inspection may be avoided or the frequency reduced if, e.g.:

- The scope of inspection by the SRA was relevant
- The inspection is recent – less than 2 years ago
- The report did not identify areas of concern needing follow-up
- The inspection report and response is available to WHO
- There is not a need for specific data evaluation/verification unless need for follow-up of a specific request from WHO assessors
- There isn't a need for investigation of a serious complaint
Prequalification Programme: Use of Inspection reports from other NMRAs

 Inspectorates whose reports are recognized:
  - PICS member inspectorates
  - EU (EDQM + EMA)
  - USFDA – new member of PICS

 What GMP evidence to submit:
  - SMF – Up-to-date
  - Inspection report - conducted NMT 2 years
    - + CAPAs to deficiencies + final conclusion
  - Product Quality Review – not more than 1 year old

 Review of the report:
  - Scope covered the specific FPP, API or BE study
  - Is comprehensive and supports the final outcome.

 PQP reserves the right to inspect the manufacturer – as long as product is active in WHO-PQP.

 on-going GMP compliance will be confirmed by WHO-PQ
WHO-PQ Inspections
Summary and Conclusions

- API, FPP and CRO/BE Inspections are an important part of the WHO-PQP evaluation and continuous monitoring process.

- International norms, standards and guidelines are used in inspection activities to ensure wide applicability.

- Collaborative and Risk management principles are applied to ensure efficient use of available resources.

- Information put in public domain - available for use by NMRAs: WHOPIRs and NOCs

- Inspection results show that there are still a lot of poor manufacturing practices out there. Collaborative effort and skills are needed to ensure access to medicines of assured quality. Results show that WHO-PQP has made tremendous contribution in this respect.

- The support of NRAs in providing co-inspectors and observers is appreciated. This is good for:
  - Tapping into international skills
  - Ensuring transparency
  - Facilitating ownership
  - Contributing to capacity building
Prequalification Programme: International norms, standards and guidelines used in inspection activities to ensure wide applicability

Other guidelines e.g. ICH, ISO

http://www.who.int/prequal/assessment_inspect/info_inspection.htm#2
Prequalification Programme: International norms, standards and guidelines used in inspection activities to ensure wide applicability


Prequalification Programme: norms, standards and guidelines used...

  

  

  
  http://www.who.int/entity/medicines/areas/quality_safety/quality_assurance/GMPWatePharmaceuticalUseTRS970Annex2.pdf
WHO GMP for **HVAC systems**. WHO, Geneva, 2011 (TRS, No. 961, Annex 5)


http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf


Prequalification Programme: norms, standards and guidelines used...

  http://whqlibdoc.who.int/trs/WHO_TRS_957_eng.pdf#page=95


- Other guidelines e.g. ICH, ISO
[http://whqlibdoc.who.int/trs/WHO_TRS_957_eng.pdf#page=144](http://whqlibdoc.who.int/trs/WHO_TRS_957_eng.pdf#page=144)

Other guidelines listed under FPP:
- GMP: main principles
- Hazardous Substances
- Sterile pharmaceutical products
- Validation
- Water for pharmaceutical use
- HVAC systems
- Sampling of pharmaceutical products and related materials
- Hazard analysis and critical control point (HACCP)
- Pharmaceutical Quality Control Laboratories
- Pharmaceutical microbiology laboratories
- Chemical reference substances
- Transfer of technology
Prequalification Programme: International norms, standards and guidelines used in inspection activities to ensure wide applicability

- HANDBOOK FOR GOOD CLINICAL RESEARCH PRACTICE (GCP) Guidance for implementation


Other guidelines e.g. ICH
WHO GMP Guidelines

- Contained in a compendium of guidelines and related materials – Volume 2, 2nd updated edition
- Adopted by WHO Expert Committee (international representation)
- Available on the WHO Prequalification webpage
- Manufacturers must comply with the main principles as well as other relevant guidelines in Technical Reports
Prequalification of QCLs - Steps of the procedure I

1. Expression of interest
   – Currently free of charge
   – WHO reserves the right to charge fee on a cost-recovery basis

2. Submission of laboratory information
   – Guidelines for preparing LIF available (WHO TRS, No. 961, 2011, Annex 13)
   – Quality Manual can be submitted (amended as necessary)

3. Evaluation of submitted laboratory information
   – Assessment of the laboratory's potential to successfully pass an inspection
     • If ready ⇒ WHO organizes an inspection
     • Gaps ⇒ For a national QCL, WHO may organize a pre-audit/technical assistance
4. Site inspection

- **Compliance with WHO recommended standards**
  - WHO Good practices for pharmaceutical quality control laboratories (GPCL)
  - WHO Good practices for pharmaceutical microbiology laboratories
  - WHO Good manufacturing practices – parts relevant to QCLs

- **Audit report from another authority (e.g. EDQM)**
  - Compliance with WHO standards is evaluated and WHO inspection may not be necessary
  - ISO accreditation considered but not simply recognized as it does not cover GMP aspects

- **Report communicated to the laboratory**
  - If corrective actions to be taken by the laboratory, WHO decides after their evaluation

5. If compliant, laboratory is included in the published list and WHOPIR is published
6. Monitoring after prequalification

- Re-inspections at a frequency based on risk assessment
  - At least once every 3 years

- Evaluation of results from participation in proficiency testing
  - WHO External Quality Assurance Scheme, AFSSAPS network of Francophone African countries

- Brief report requested to be submitted annually
  - Summary of services provided to UN agencies, number of analysed samples, methods used, complaints received
  - Changes with significant impact on the laboratory (key personnel, facility, equipment) and update LIF

- WHO may suspend or withdraw a laboratory from the list when there is evidence of noncompliance
Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP):


*published in TRS 961, Annex 15 (2011)*

2. *Quality part*

*adopted in 46th EC meeting, 13 October 2011*
New quality guideline
- objectives

The two documents will assist applicants and WHO by;

- Harmonizing with international approaches (format and contents)
- Facilitating the compilation and assessment of product dossiers

Adopting CTD format:

- allows for a single dossier to be submitted to multiple agencies, and
- allows for a common “language” between regulators and manufacturers, increasing the efficiency of the assessment process.
Key changes 1

- CTD format adopted
- Updating of requirements
- Elaboration of how to meet quality requirements, including full elaboration on the four options for submitting API data:
  - Prequalified API
  - CEP
  - APIMF
  - full API data provided in the dossier
Key changes II

Reductions in requirements:

- fewer batches required to establish the FPP shelf-life

- process validation report for pilot batches no longer required (replaced by content uniformity demonstration for the biolot)

- reduced process validation/pharmaceutical development requirements for “established” generics

- uniformity requirements are now in line with PhInt (i.e. 5% and 5 mg as the threshold for content versus mass uniformity, for both single component and FDC products)
Variations – update I

In May 2013, the new variation Guideline was implemented:

- Guidance on Variations to a Prequalified Product
- Procedural Guidance on submitting variations to a Prequalified Product
- Variation application forms
Variations – update II

- “Do and tell"
- Provide detailed instruction to classify and document changes
- PQP focus on the changes where the level of risk is considered to be high
- Reduced workload for both the applicant and PQP for filling and reviewing changes to prequalified products
Variations – update III

As per the new guideline, the changes are classified into the following categories:

- **Notifications**: have minimal or no adverse effects on the overall quality, efficacy and safety of the FPP.
  - IN (Immediate notification): do and tell immediately
  - AN (Annual notification): do and tell within 12 months following implementation

- **Minor variations**: may have minor effects on the overall quality, efficacy and safety of the FPP.
  - can be implemented if no objection letter has been issued within 60 days of acknowledgment of receipt of the application;

- **Major variations**: could have major effects on the overall quality, efficacy and safety of the FPP.
  - Prior acceptance by WHO-PQP is required before the changes can be implemented
  - 90 days
## Variations – update IV

### Variation submissions from May to August 2013:

<table>
<thead>
<tr>
<th>Variation application</th>
<th>Vmaj</th>
<th>Vmin</th>
<th>IN</th>
<th>AN</th>
<th>rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>64</td>
<td>26</td>
<td>15</td>
<td>12</td>
<td>3</td>
</tr>
</tbody>
</table>

| Review time Range (median) | 13-38 (28) | 2-38 (20) | Receipt acknowledged within 7 days |

- Review time
  - Range (median): 13-38 (28) days, 2-38 (20) days
  - Receipt acknowledged within 7 days

- Variation application: 64
  - Vmaj: 26
  - Vmin: 15
  - IN: 12
  - AN: 8
  - Rejection: 3
The Procedure for prequalification of pharmaceutical products requires holders of WHO-prequalified products to submit a quality review after five years from the date of prequalification of the product, or when requested to do so by PQP (whichever date is earlier)
Why Requalify?

- Verify that the product meets acceptable norms and standards
- Follow up on commitments made at prequalification
- Confirm that the manufacturer is still in control of product quality – consistency of quality and manufacturing process
- No unsolicited or unapproved changes/variations
Requalification - Requirements I

- Cover letter attesting that information is "true and correct"
- Completed PQIF based on current PQP requirements.
- Current copies of SmPC and Patient Information Leaflet
- Sample(s) of the product in all pack types and sizes, as prequalified.
- Summary of key product information – comparing key information at prequalification and for requalification (see guide*)
- Copies of current API and FPP specs and methods – signed, dated, ref #, version, effective date and change history
- List of variations (major and Minor) since prequalification (pending, approved and unapproved by PQP) (See guide*)
- Electronic copies of dossiers should be submitted on CD/DVD and the PQIF should be in WinWord format.

A Product Quality Review report may be submitted as supporting data. It may however be requested during assessment.

Additional paper documents may be submitted as supporting information.
Product Quality Review Report (1)

- Should be based on data and information derived from all batches manufactured over the period of the last 12 months of the five year period. *(Note: If the number of all consecutive batches is less than 10 over the period of the last 12 months, then the review period should be extended to the last three years).*

- A table of reviewed batches with batch numbers, manufacturing dates and batch size. Any differences from the prequalified batch size clarified.

- Review of starting materials (active pharmaceutical ingredients and excipients).

- Review of primary packing materials used in the FPP, including reference to those from new sources.

- A tabulation of batch analysis data (including in-process test results and finished product quality control results) together with statistical and trend analysis where appropriate (excluding failed batches)

NB "Review" implies summary of data and analysis/discussion thereof AND a conclusion
Product Quality Review Report (2)

- A list of validated analytical + manufacturing procedures incl. revalidation dates; and

Review of

- All OOS and related investigations
- All deviations
- Variations - including those already submitted/granted/refused by PQP
- Any other changes not listed above
- Results of the stability-monitoring program + trend analysis
- Validation and stability commitments, where applicable
- All quality-related returns, complaints and recalls
- Adequacy of any corrective actions
Major achievements in 2012

- Record number of FPPs (48) including significant number of anti-TB (19) and anti-Malaria (10) products were prequalified in 2012
  - Several first time anti-malarial products including dispersible Artemether/Lumefantrine, Artesunate +SP, and Artesunate/Mefloquine tablets
  - First Zn product

- Significant numbers of APIs (20) - 4 HIV, 4 TB and 12 MA - were also prequalified

- Revised variation guide adopted by WHO Expert Committee (implemented 1 May 2013)

- Collaborative procedure for accelerated registration of prequalified products in countries - adopted and implementation started
**Key programme targets**

- Initial screening of dossiers - median < 20 days *(8 days)*

- Dossier assessment from acceptance of the dossier, not including stop-clock time - median < 270 days *(210 days)*

- Target stop-clock time (manufacturers time) - median < 450 days *(314 days)*

- Initial inspection - median < 180 days from acceptance of dossier *(105-204 days)*

- Issue inspection report - median < 30 days from on-site inspection *(21 days)*

- Receipt of any variation to assessment – median < 60 days *(28 days)*
## Time to prequalification (prequalified first half of 2013)

<table>
<thead>
<tr>
<th></th>
<th>Days to PQ</th>
<th>Assessment Days (WHO time)</th>
<th>Stop Clock Days (Manufacturer time)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic submissions (full dossier)-16 products</strong></td>
<td></td>
<td></td>
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<tr>
<td>Median Days</td>
<td>610</td>
<td>210</td>
<td>314</td>
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<tr>
<td>Range</td>
<td>369 - 1821</td>
<td>121 - 459</td>
<td>193 - 1451</td>
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<tr>
<td><strong>SRA + Innovator-22 products</strong></td>
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<tr>
<td>Median Days</td>
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</tr>
<tr>
<td>Range</td>
<td>36 - 389</td>
<td>4 - 58</td>
<td>0 - 246</td>
</tr>
</tbody>
</table>
Access to quality medicines - comparison of failure rates of prequalified and non-prequalified products

Quality survey of antimalarials in 6 African countries (2008/9)

AL: artemether/lumefantrine

AA: artesunate/amodiaquine

PQ total Non-PQ total AL PQ AL non-PQ A&A co-p PQ A&A co-p non-PQ
TB APIs (BCS class)

- Ethambutol (III), isoniazid (III), levofloxacin (I), moxifloxacin (as hydrochloride) (I), ofloxacin (I), pyrazinamide (III)

- Prequalifications based on BCS-based biowaivers:
  - 5 TB (ofloxacin 3, levofloxacin2),
  - 9 ARVs
  (May 2008-20 Sept 2013)
## Main characteristics of the prequalified medicinal product

1. **Product WHO Reference number**
2. **INN of active ingredient(s)**
3. **Dosage form and strength**
4. **Trade name(s) of the product (if applicable)**
5. **Name of applicant and official address**
6. **Name of manufacturer of finished product, physical address of manufacturing site(s) (and unit, if applicable)**
7. **Finished product specifications (ref N° and/or version; ref to pharmacopoeia)**
8. **Finished product batch size (approved)**
9. **Name of API manufacturer, physical address of manufacturing site(s) (and unit, if applicable)**
10. **API specifications (ref N° and/or version; ref to pharmacopoeia)**
10.1. **Retest period of the API(s)**
11. **Product description (as in finished product specifications, i.e. coated, scored, etc)**
12. **Pack size(s), primary and secondary packaging material(s)**
13. **Storage conditions**
14. **Shelf-life**
Generic dossier deficiencies

Deficiencies in generic product dossiers as submitted to the WHO Prequalification of Medicines Programme

Wondiyfraw Z Worku¹, John Gordon², Matthias MS Stahl¹ and Lembit Rägo¹

Abstract
This study was undertaken to determine the type and extent of deficiencies in generic product dossiers in the therapeutic areas of HIV/AIDS, tuberculosis, malaria and reproductive health, as submitted to the WHO Prequalification of Medicines Programme. There were considerably more quality-related deficiencies in tuberculosis, malaria and reproductive health dossiers compared to HIV dossiers, especially in the category specification of active pharmaceutical ingredients, development pharmaceutics, manufacturing method and finished pharmaceutical product specifications. The deficiencies related to the efficacy/safety portion of the dossiers displayed a trend similar to that observed in the quality portion in that the most critical deficiencies such as an incorrect study design, the use of an unacceptable comparator or the failure to include a study occurred considerably more frequently in the tuberculosis, malaria and reproductive health dossiers than in the HIV dossiers. The frequency of dossier-related deficiencies as determined on screening and assessment of the dossiers seemed to be inversely related to the number of product dossiers that had been prequalified by the end of 2010. The results of this study stress the need for continued capacity building of local generic manufacturers, further development of pharmacopeial monographs by WHO (PhInt) and other pharmacopeial commissions, not least to promote development of generic products, as well as development of new guidelines (WHO guidelines for development of generic and paediatric products and a technology transfer guidance document are currently being finalized). To our knowledge, this is the first comprehensive review of the quality and efficacy/safety portions of generic product dossiers, originating from pharmaceutical companies in emerging markets, and comparison of dossier deficiencies across four critically important therapeutic areas.
Dossier deficiencies - quality

Figure 2. Deficiencies observed in generic product dossiers on the assessment of the quality (chemistry–pharmaceutical) part of the dossier, presented as the mean number of quality deficiencies per dossier and therapeutic area, by each of the 10 main categories.

Deficiencies are related to incomplete or incorrect information provided for the identified category.

HIV: human immunodeficiency virus; TB: tuberculosis; RH: reproductive health; API: active pharmaceutical ingredient; and FPP: finished pharmaceutical product.
Figure 3. Deficiencies observed on the assessment of the efficacy/safety [i.e. BE/biowaiver] part of the dossier, presented as percentage of the total number of dossiers surveyed that contained each identified deficiency, per therapeutic area and by each of the four main categories.

Unless otherwise specified, deficiencies are related to incomplete or incorrect information provided for the identified category. HIV: human immunodeficiency virus; TB: tuberculosis; RH: reproductive health; BE: bioequivalence; PK/stat: pharmacokinetic/statistical; and WHO: World Health Organization.
A WHO Public Assessment Report (WHOPAR) provide summaries of the assessment of the product data and information:

- Part 1 – Abstract
- Part 2a – All accepted presentations
- Part 2b - Visual appearance of the product
- Part 3 – Product Information Leaflet
- Part 4 – Summary of Product Characteristics
- Part 5 – Label
- Part 6 – Discussion
- Part 7 – Steps before Prequalification
- Part 8 – Steps following Prequalification

Excludes confidential/proprietary information
WHOPIR

- The WHO Public Inspection Report (WHOPIR) is a summary of the inspection report of:
  - a manufacturing site for API;
  - a manufacturing site for FPP;
  - an organization such as a Contract Research Organization (CRO) where a BE study or other clinical study has been performed (CROs);
  - a QC laboratory

- Gives a summary of the observations and findings made during the inspection, but excludes confidential/proprietary information.
Time to PQ by submission order
(118 generic products prequalified between 2009-2012; 12 applicants)