Prequalification of Medicines Programme

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ARV prequalification update - 2010

- General
  - Prequalified products
  - Revised HIV EOI
  - Joint WHO/EAC assessment
  - Key Programme targets
  - New initiatives

- Specific
  - New generic guidelines
  - Prequalification of APIs
  - New variation procedure
### Product dossiers accepted for assessment:
**2005 – 2010 (as at 29 Nov 2010)**

<table>
<thead>
<tr>
<th></th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>67</td>
<td>42</td>
<td>25</td>
<td>42</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>TB</td>
<td>17</td>
<td>9</td>
<td>17</td>
<td>12</td>
<td>11</td>
<td>8</td>
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<tr>
<td>Malaria</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>9</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Repr Health</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>4</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Influenza</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total Acc</strong></td>
<td><strong>87</strong></td>
<td><strong>56</strong></td>
<td><strong>59</strong></td>
<td><strong>68</strong></td>
<td><strong>53</strong></td>
<td><strong>31</strong></td>
</tr>
<tr>
<td><strong>Total Submitted</strong></td>
<td>90</td>
<td>92</td>
<td>83</td>
<td>47</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Dossier status on the web

This image shows a table from the World Health Organization's website, detailing the dossier status of various medical products. The table includes columns for Product (INNs), Strength, Unit, Dosage Form, Quality part, and Efficacy/Safety part. The status symbols indicate assessment in progress, additional data to be provided by the manufacturer, and dossier part acceptable.

<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>
<tr>
<td>Category</td>
<td>Number</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARVs</td>
<td>17 (21; 2009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive Health</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prequalified ARVs to date</td>
<td>159</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## ARVs prequalified in 2010

<table>
<thead>
<tr>
<th>INN</th>
<th>Formulation and strength</th>
<th>Applicant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir (as sulfate)</td>
<td>Dispersible tablets</td>
<td>Cipla Ltd</td>
</tr>
<tr>
<td>Atazanavir (as sulfate)</td>
<td>Capsules</td>
<td>Matrix Laboratories Ltd</td>
</tr>
<tr>
<td>Atazanavir (as sulfate)</td>
<td>Capsules</td>
<td>Matrix Laboratories Ltd</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Capsules</td>
<td>Matrix Laboratories Ltd</td>
</tr>
<tr>
<td>Emtricitabine + Tenofovir disoproxil fumarate</td>
<td>Tablets</td>
<td>Matrix Laboratories Ltd</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Tablets</td>
<td>Cipla Ltd</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Tablets</td>
<td>Cipla Ltd</td>
</tr>
<tr>
<td>Lamivudine + Zidovudine</td>
<td>Tablets</td>
<td>Varichem Pharmaceuticals (Pvt) Ltd</td>
</tr>
<tr>
<td>Lamivudine + Zidovudine</td>
<td>Tablets</td>
<td>Micro Labs Limited</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Tablets</td>
<td>Abbott GmbH and Co. KG</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Powder for oral solution</td>
<td>Cipla Ltd</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate + Efavirenz + Emtricitabine</td>
<td>Tablets</td>
<td>Matrix Laboratories Ltd</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate + Efavirenz + Lamivudine</td>
<td>Tablets</td>
<td>Matrix Laboratories Ltd</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate + Lamivudine</td>
<td>Tablets</td>
<td>Matrix Laboratories Ltd</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Tablets</td>
<td>Hetero Drugs Limited</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Tablets</td>
<td>Matrix Laboratories Ltd</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Tablets</td>
<td>Micro Labs Limited</td>
</tr>
</tbody>
</table>
Revised HIV EOI – 10th

- Published on PQP website on 4 Nov 2010

- New inclusions, for example:
  - Etravirine (NNRTI), darunavir (PI), raltegravir (II) adults/adolescents
  - Scored formulations for children (eg. darunavir, efavirenz, nevirapine)
  - Lopinavir/ritonavir sachet/granules for children
  - Co-packaged formulations for adults/adolescents (RTI + NNRTI, RTI + PI)

- Note some exclusions (adults/adolescents and children)

- An EOI is complete in itself (a new EOI replaces any previous versions)

- No deadline for submission

- EOI decided by WHO clinical (based on inclusion in WHO TG and/or EML)

- EOI revision at any point in time
Joint WHO/EAC assessments – a pilot

- Joint WHO/EAC assessment of two dossiers started in March 2010
- Abacavir disp tabl 60 mg and amikacin inj
- 4 sessions (March, May, July, Nov) – abacavir disp tabl (HA488) jointly approved in Aug and now registered in Uganda and Tanzania.
- Amikacin close to approval
- Positives – capacity building, harmonization, prequalification and facilitation of national registration, no duplication of effort, incentive for the manufacturer
Key programme targets

- Initial screening of dossiers - median < 30 days
- Dossier assessment from acceptance of the dossier, not including stop-clock time - median < 270 days
- Target stop-clock time (manufacturers time) - median < 277 days
- Initial inspection - median <180 days from acceptance of dossier
- Issue inspection report - median < 30 days from on-site inspection
- Total time to prequalify - median < 547 days
New initiatives

- Initiatives to better understand PQ from a manufacturers point of view
  - July 2010: A survey designed to increase understanding of manufacturers' perceptions of PQP completed
  - Ongoing: A project to understand and quantify the value of WHO prequalification and PQP activities to manufacturers
New generic quality guideline
- background

Policy/approaches to assessment change continually over time due to harmonization efforts, scientific advances, development of approaches

- e.g. process validation, pharmaceutical development approaches have changed dramatically over the past 10 years
New generic quality guideline - two documents

**Preparation guideline:** 10.375: Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): *Preparation of product dossiers (PDS) in Common Technical Document (CTD) Format;*

**Quality guideline:** 10.373: Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): *Quality part*
The two documents are intended to assist applicants and WHO by:

- Harmonizing with international approaches (format and contents)
- Facilitating the preparation and assessment procedures for product dossiers

Single dossier to be submitted to multiple agencies
Guideline development process

- Consultation process with PQP senior assessors and manufacturers (June-July)
- External consultation process (EC circulation)
- Posting on PQP website (manufacturers, others)
- Presentation to 45th EC on Specifications for Pharmaceutical Preparations

Currently: guidelines provisionally accepted for pilot use in PQP. Published on PQP website – comments still invited!
Key changes from the previous guideline

- CTD format adopted
- Updating of requirements
- Elaboration of how to meet quality requirements, including full elaboration on the three ways to submit API data:
  - CEP
  - APIMF
  - full API data provided in the dossier
Key changes from the previous guideline

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
Active Pharmaceutical Ingredient (API) information

There are two schemes for facilitating the evaluation of API manufacturing information within PQP;

- **APIMF procedure** - to support prequalification of a Finished Pharmaceutical Product (FPP).

- **API Prequalification (NEW)** - to support the prequalification of quality APIs.
The APIMF procedure

- It is solely used to support the evaluation of FPP prequalification applications and has been active since March 2008.

- An APIMF contains information on the control and preparation of the API.

- It is popular with API manufacturers because:
  - It allows the submission of confidential information by the API manufacturer to WHO without disclosure to the FPP applicant.
  - One APIMF may be used to support multiple FPP applications without the need for repeated evaluations.
  - It is applicable to both pharmacopoeial and non-pharmacopoeial APIs.
The APIMF procedure (2)

- 135 APIMFs now involved in the PQ programme.
- 54 of the 135 APIMFs are ARV-related, covering 13 different APIs.
- 23 of these 52 APIMFs have now been accepted.
- 15 of the 22 APIMFs were accepted in the past 12 months.
Prequalification of APIs

- A new initiative in the Prequalification of Medicines Programme that commenced 21 October 2010.

- It is intended to identify quality active pharmaceutical ingredient suppliers.
  - In order to facilitate the manufacture of needed quality finished pharmaceutical products.
  - To aid national authorities to regulate APIs.
Prequalification of APIs (2)

- The 1st invitation for Expressions of Interest (EOI) is a pilot sample of APIs, but this will be extended in the next invitation.

- The EOI currently includes the following ARV-related APIs:

  Abacavir  Lopinavir
  Atazanavir  Nelfinavir
  Ciprofloxacin  Nevirapine
  Didanosine  Ritonavir
  Efavirenz  Stavudine
  Emtricitabine  Tenofovir
  Lamivudine  Zidovudine
API prequalification requires both the assessment of the APIMF and an assessment of the GMP at the manufacturing sites (WHO/SRA).

Successful API suppliers' details will be published in the WHO list of Prequalified APIs.

The API prequalification scheme is unique amongst other regulatory programmes in that API manufacturers with both acceptable quality (APIMF) and GMP will be identified publicly.

APIMFs previously accepted as part of FPP prequalification can undergo an abbreviated procedure (= no re-evaluation).
WHO List of prequalified APIs

- The assigned WHO application number.
- The INN name of the active pharmaceutical ingredient.
- The date of prequalification.
- The name of the applicant company.
- The sites of API manufacture.
- The APIMF version number.
- The API specification version number.
- The primary and secondary packaging components.
- The assigned re-test period.
- The recommended storage conditions.
Variations

Variation submission

<table>
<thead>
<tr>
<th>Year</th>
<th>New</th>
<th>Additional data</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>182</td>
<td>74</td>
</tr>
<tr>
<td>2009</td>
<td>254</td>
<td>131</td>
</tr>
<tr>
<td>2010 (1-11M)</td>
<td>411</td>
<td>118</td>
</tr>
</tbody>
</table>
## Timetables

<table>
<thead>
<tr>
<th></th>
<th>New EU</th>
<th>PQ (previous)</th>
<th>PQ (aim)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Notification</strong></td>
<td>Do and tell, may be rejected</td>
<td>90 days</td>
<td>30 days</td>
</tr>
<tr>
<td><strong>Minor</strong></td>
<td>7 days (verification) + 30 days</td>
<td>No timeline</td>
<td>60 days</td>
</tr>
<tr>
<td><strong>Major</strong></td>
<td>60 days</td>
<td>No timeline</td>
<td>60 days</td>
</tr>
</tbody>
</table>

Time for each round of assessment
New variation procedure

To improve PQP's handling of variation applications and to facilitate the assessment:

A Clarification regarding variation application was published on PQP website on 14 April 2010

Three items must be contained in a variation submission
New variation procedure

- **A covering letter:**
  - A statement that the information submitted is true and correct.
  - A statement that there are no changes other than those applied for in the submission.
  - In case a minor variation, a statement that all conditions are met (supportive documents if applicable).

- **A summary of the intended change** in comparison with the current state / with a justification

- **A variation dossier / supportive documents**

From May to July, Notifications were reviewed within 1 month of receipt.

Reduced time for other changes (within 2 Months or less)
Prequalification of Medicines Programme

Further information:  http://who.int/prequal/