ARV prequalification update - 2011

- Product dossiers
- BCS based biowaivers
- Joint assessments
- Key Programme targets
- New generic guideline
- Prequalification of APIs
- Variations
- **Specific issue: Zidolam-N (Deus Mubangizi)**
<table>
<thead>
<tr>
<th>Product (INNs)</th>
<th>Strength</th>
<th>Unit</th>
<th>Dosage Form</th>
<th>Quality part</th>
<th>Efficacy part</th>
</tr>
</thead>
<tbody>
<tr>
<td>abacavir</td>
<td>20</td>
<td>mg/ml</td>
<td>solution, oral</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>abacavir</td>
<td>20</td>
<td>mg/ml</td>
<td>solution, oral</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>abacavir</td>
<td>60</td>
<td>mg</td>
<td>tablet</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>abacavir + lamivudine</td>
<td>60/30</td>
<td>mg</td>
<td>tablet</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>abacavir + lamivudine + zidovudine</td>
<td>60/30/60</td>
<td>mg</td>
<td>tablet</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>aminosalicylate sodium</td>
<td>60</td>
<td>%</td>
<td>granule</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>amodiaquine + artesunate</td>
<td>153.1/50</td>
<td>mg</td>
<td>tablet</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>amodiaquine + artesunate</td>
<td>306.2/100</td>
<td>mg</td>
<td>tablet</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>amodiaquine + artesunate</td>
<td>50/153</td>
<td>mg</td>
<td>tablet</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>amodiaquine + artesunate</td>
<td>50/153</td>
<td>mg</td>
<td>tablet</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
## Product dossiers accepted for assessment: 2005 – 2011 (as at 27 October 2011)

<table>
<thead>
<tr>
<th></th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
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<tbody>
<tr>
<td>HIV</td>
<td>67</td>
<td>42</td>
<td>25</td>
<td>42</td>
<td>24</td>
<td>21*</td>
<td>26</td>
</tr>
<tr>
<td>TB</td>
<td>17</td>
<td>9</td>
<td>17</td>
<td>12</td>
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<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Malaria</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Repr Health</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>4</td>
<td>7</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Influenza</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>NTD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total Accptd**  87  56  59  68  53  35  37

**Total Submitted**  90  92  83  51  57

* Includes 2 products (Water for Injection) not included in any of the EoIs

(...) dossiers accepted for assessment
### ARVs prequalified in 2011 (as of 28 Oct)

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>INN</th>
<th>Formulation and strength</th>
<th>Applicant</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>[Tenofovir disoproxil fumarate + Lamivudine] + Nevirapine</td>
<td>Tablets (co-packaged) [300mg + 300mg] + 200mg</td>
<td>Matrix Laboratories Ltd</td>
</tr>
<tr>
<td>IV</td>
<td>Didanosine</td>
<td>Delayed release capsules 125mg</td>
<td>Matrix Laboratories Ltd</td>
</tr>
<tr>
<td>IV</td>
<td>Didanosine</td>
<td>Delayed release capsules 200mg</td>
<td>Matrix Laboratories Ltd</td>
</tr>
<tr>
<td>IV</td>
<td>Didanosine</td>
<td>Delayed release capsules 250mg</td>
<td>Matrix Laboratories Ltd</td>
</tr>
<tr>
<td>IV</td>
<td>Didanosine</td>
<td>Delayed release capsules 400mg</td>
<td>Matrix Laboratories Ltd</td>
</tr>
<tr>
<td>IV</td>
<td>Emtricitabine</td>
<td>Capsules 200mg</td>
<td>Cipla Ltd</td>
</tr>
<tr>
<td>IV</td>
<td>Emtricitabine + Tenofovir disoproxil fumarate</td>
<td>Tablets 200mg + 300mg</td>
<td>Cipla Ltd</td>
</tr>
<tr>
<td>IV</td>
<td>Lamivudine + Stavudine</td>
<td>Dispersible tablets 30mg + 6mg</td>
<td>Cipla Ltd</td>
</tr>
<tr>
<td>IV</td>
<td>Lamivudine + Stavudine</td>
<td>Dispersible tablets 60mg + 12mg</td>
<td>Cipla Ltd</td>
</tr>
<tr>
<td>IV</td>
<td>Lamivudine + Tenofovir disoproxil fumarate</td>
<td>Tablets 300mg + 300mg</td>
<td>Hetero Labs Limited</td>
</tr>
<tr>
<td>IV</td>
<td>Lamivudine + Tenofovir disoproxil fumarate</td>
<td>Tablets 300mg + 300mg</td>
<td>Cipla Ltd</td>
</tr>
<tr>
<td>IV</td>
<td>Lamivudine + Zidovudine</td>
<td>Tablets 150mg + 300mg</td>
<td>Macleods Pharmaceuticals Ltd</td>
</tr>
<tr>
<td>IV</td>
<td>Lamivudine + Zidovudine</td>
<td>Dispersible tablets 30mg + 60mg</td>
<td>Ranbaxy Laboratories Ltd</td>
</tr>
<tr>
<td>IV</td>
<td>Lamivudine + Zidovudine</td>
<td>Tablets 150mg + 300mg</td>
<td>Universal Corporation Ltd</td>
</tr>
<tr>
<td>IV</td>
<td>Nevirapine</td>
<td>Tablets 200mg</td>
<td>Macleods Pharmaceuticals Ltd</td>
</tr>
<tr>
<td>IV</td>
<td>Stavudine</td>
<td>Capsules 30mg</td>
<td>Macleods Pharmaceuticals Ltd</td>
</tr>
</tbody>
</table>
BCS based biowaivers

- Currently eligible; stavudine, lamivudine and zidovudine
- Review of current HIV/AIDS EOI in terms of APIs potentially eligible for BCS based biowaiver
- Emtricitabine (BCS class I) and abacavir (BCS class III) eligible. Other APIs – insufficient data or do not meet requirements for class I or III
- BCS based biowaiver guidance doc's on PQP website to be updated shortly
Joint assessments

- 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) – both products jointly approved (HA488 in Aug 2010, TB217 in Jan 2011) and registered in Uganda, Tanzania and Kenya – Company experience: 
  "...The registration was fulfilled in much lesser time than is our experience with the registrations of formulations with these MOHs. We welcome this initiative taken by WHO and would be glad to participate in any further joint assessments that WHO would conduct with the EAC MOHs."
- New joint assessment Jan 2012 (MA dossiers) – Ethiopia, Tanzania, Kenya, Ghana, Nigeria, Cameroon
- Positives – capacity building, harmonization, prequalification and facilitation of national registration, no duplication of effort, incentive for the manufacturer
Key programme targets (indicators as at 30 June 2011)

- Initial screening of dossiers - median < 30 days (12 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 < 277 days (386 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)

- Total time to prequalify - median < 547 days (595 days)

- Receipt of variation to assessment – median < 90 days (30 days)
New generic quality guideline - two documents

Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP):

1. Preparation of product dossiers (PDS) in Common Technical Document (CTD) Format;

   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

- 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

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)
Prequalification of APIs (as of 19 Oct 2011)

Intended to identify quality API suppliers.
   – In order to facilitate the manufacture of quality FPPs.
   – To aid national authorities in regulating APIs.

Since initiation of the pilot project in October 2010:

- 26 applications have been received, including 4 applications for ARV APIs (emtricitabine, nevirapine, lamivudine and tenofovir).
- 5 APIs have been prequalified (only MA so far).
Prequalification of APIs

- The 1\textsuperscript{st} EOI was a pilot sample of APIs. The 2\textsuperscript{nd} EOI (March 2011) covers APIs present in the current FPP EOI. This includes the following ARVs.

- Abacavir
- Atazanavir
- Darunavir
- Didanosine
- Efavirenz
- Emtricitabine
- Etravirine
- Lamivudine
- Lopinavir
- Nevirapine
- Raltegravir
- Ritonavir
- Stavudine
- Tenofovir
- Zidovudine
Prequalification of APIs

- API prequalification requires assessment of the APIMF and an assessment of the GMP at the manufacturing sites (inspection by WHO or SRA).

- To avoid duplication of effort, the API PQ process recognises the GMP inspections and quality assessments conducted by other SRAs.

- 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).
Variations - update

- Update of variation requirements to be in line with the new Generic guideline (in terms of reduced stability requirements and CTD format) - clarification to this effect published on PQP website on 21 Feb 2011

- Many variations accepted after only one round of review (70% in the 1st half year of 2011) - applicants more experienced + clarification of procedure.

- WHOPAR Part 8 - variations
Information and Guidelines

Expression of Interest (EOI) Lists

- Invitations for Expression of Interest (EOI)
  - How to submit an EOI

General information related to prequalification of medicines

- General procedure [pdf]
- How to participate in the Prequalification
- Where to send the Product Dossier, as well as APIMF documentation and Site Master File
- Dates of Copenhagen assessment sessions
- Confidentiality
- Meetings with PQP Assessors
  - Meeting Request Form

Prequalification guidelines related to medicinal products

- Prequalification guidelines

Variations (changes) to prequalified medicines

- An introduction to the variation procedure
  - TRS943, Annex 6 - guidance on variations to a prequalified product
- Types of variations
- How to submit a variation
  - Variation application form
- Where to submit the variation application
- Grouping of variations
- Updated stability requirements for variations
- Information regarding API-related changes
- Clarification of minor variation 5c
Statistics

![Bar Chart: Response vs New Variation]

- **2008**: 200
- **2009**: 300 (100 Response, 200 New Variation)
- **2010**: 500 (300 Response, 200 New Variation)
- **2011 (1-9)**: 600 (200 Response, 400 New Variation)
Variation assessment times

The time taken to assess a variation has been reduced

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Before May 2010</th>
<th>From May 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notification</td>
<td>90 days</td>
<td>30 days or less</td>
</tr>
<tr>
<td>Minor &amp; major</td>
<td>No timeline</td>
<td>60 days or less</td>
</tr>
</tbody>
</table>
Revision of the variation guidance

- A revision of the current guidance (TRS943, annex 6) has been initiated in light of:
  - The new EU variation guideline (Jan 2010)
  - The new PQP generic guideline (Nov 2010)
  - Lessons learned from current guidance.
  - New approaches to variations, such as "do and tell"

- Draft for manufacturer consultation is expected in xxxx 2011.
Prequalification of Medicines Programme

Further information:  http://who.int/prequal/
10th HIV EOI (not yet updated)

- 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
Training and capacity building
(Jan-Sept 2011)

- 25 advocacy meetings, training workshops or conferences in support of good quality submissions to PQP and qualified regulatory assessments, organized or supported by PQP (for manufacturers/regulators).

- Quality of APIs promoted in co-operation with EDQM and other partners in major manufacturing countries (India, China).

- TA provided to manufacturers of priority medicines and to QCLs.

- Projects organized to strengthen GMP implementation in China and boost national inspection and quality control capacity.

- Individual training provided to regulatory assessors and inspectors from developing countries by involving them in PQP activities.
### 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, HSA (2009)
- Singapore, TÜV (2009)
- Canada, K.A.B.S. Laboratorie (2010)
- Ukraine, CLQCM (2010)
- Ukraine, LPA (2010)
- Peru, CNCC (2010)
- Uruguay, CCCM (2010)
- Bolivia CONCAMYT (2010)
- TFDA, Tanzania (2011)
- SGS, India (2011)
- SGS, Belgium (2011)
- Proxy, Netherlands (2011)
- INFARMED, Portugal (2011)
- FUNED, Brazil (2011)
Prequalified / interested laboratories (2)
October 2011

National QCLs
Other QCLs

QCLs interested
QCLs prequalified

AFRO
AMRO
EMRO
EURO
SEARO
WPRO
Capacity building

- Provided to national quality control laboratories

- Technical assistance
  - 4 in 2011
  - Focus on implementation of quality system

- Training
  - Seminar on quality management system in QCL (November 2010)
    - South Africa, 46 participants from 27 countries (AFRO, AMRO, EMRO, EURO, WPRO)
  - Training in dissolution and water determination (organized with AFSSAPS and EDQM in September 2011)
    - Senegal, 20 participants from 10 countries (AFRO, EMRO)
  - Training for microbiological laboratories (prepared for November 2011)
    - Jordan, 34 participants from 27 countries (AFRO, AMRO, EMRO, EURO, WPRO)

- Participation in External Quality Assessment Scheme for National Drug Quality Control Laboratories
Quality survey of antimalarials in Africa

- Cooperation with NDRAs in Cameroon, Ethiopia, Ghana, Kenya, Nigeria, Tanzania
- ACTs and sulfadoxine-pyrimethamine
- 935 samples collected at all distribution levels including informal market and screened by Minilab
- 306 tested in laboratory according to Ph.Int., USP or laboratory method

Total failure = 28.5%

- Failure for PQed products 4%
- Failure for non PQed products 40%

![Failure rate chart](chart.png)
Quality survey of anti-TB medicines in NIS

- Cooperation with NDRAs in Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine, Uzbekistan
- Rifampicin, Isoniazid, Rifampicin/Isoniazid, Ofloxacin, Kanamycin
- 291 samples collected at hospitals, dispensaries, pharmacies and tested according to Ph.Int. or USP
  
  Total failure = 11.3%

- None of 38 samples of WHO-prequalified products failed