

Prequalification of Medicines Programme

Matthias Stahl

Head of Assessments, Medicines Prequalification Programme



**World Health
Organization**

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)

	<u>2005</u>	<u>2006</u>	<u>2007</u>	<u>2008</u>	<u>2009</u>	<u>2010</u>
HIV	67	42	25	42	24	12
TB	17	9	17	12	11	8
Malaria	3	5	7	9	3	5
Repr Health	-	-	10	4	7	5
Influenza	-	-	-	1	7	0
Diarrhoea	-	-	-	-	1	1
Total Acc	87	56	59	68	53	31
<i>Total Submitted</i>			90	92	83	47

Dossier status on the web

New Page 1 - Microsoft Internet Explorer provided by WHO

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Information for applicants

Invitations for EOIs




List of Prequalified Medicines





















Status - Dossier assessments and Inspections

Quality Control Laboratories

Training material, workshops and meetings

Press and media

 assessment in progress
  additional data to be provided by the manufacturer
  dossier part acceptable

Product (INNs)	Strength	Unit	Dosage Form	Quality part	Efficacy/Safety part
abacavir	20 mg/ml	solution, oral			
abacavir	20 mg/ml	solution, oral			
abacavir	60 mg	tablet			
abacavir + lamivudine	60/30 mg	tablet			
abacavir + lamivudine + zidovudine	60/30/60 mg	tablet			
aminosalicylate sodium	60 %	granule			
amodiaquine + artesunate	153.1/50 mg	tablet			
amodiaquine + artesunate	306.2/100 mg	tablet			
amodiaquine + artesunate	50/153 mg	tablet			
amodiaquine + artesunate	50/153 mg	tablet			



Number of prequalified products in 2010

ARVs	17 (21; 2009)
TB	5
Malaria	1
Influenza	1
Reproductive Health	5
Prequalified ARVs to date	159

ARVs prequalified in 2010

INN	Formulation and strength	Applicant
Abacavir (as sulfate)	Dispersible tablets	Cipla Ltd
Atazanavir (as sulfate)	Capsules	Matrix Laboratories Ltd
Atazanavir (as sulfate)	Capsules	Matrix Laboratories Ltd
Emtricitabine	Capsules	Matrix Laboratories Ltd
Emtricitabine + Tenofovir disoproxil fumarate	Tablets	Matrix Laboratories Ltd
Lamivudine	Tablets	Cipla Ltd
Lamivudine	Tablets	Cipla Ltd
Lamivudine + Zidovudine	Tablets	Varichem Pharmaceuticals (Pvt) Ltd
Lamivudine + Zidovudine	Tablets	Micro Labs Limited
Ritonavir	Tablets	Abbott GmbH and Co. KG
Stavudine	Powder for oral solution	Cipla Ltd
Tenofovir disoproxil fumarate + Efavirenz + Emtricitabine	Tablets	Matrix Laboratories Ltd
Tenofovir disoproxil fumarate + Efavirenz + Lamivudine	Tablets	Matrix Laboratories Ltd
Tenofovir disoproxil fumarate + Lamivudine	Tablets	Matrix Laboratories Ltd
Zidovudine	Tablets	Hetero Drugs Limited
Zidovudine	Tablets	Matrix Laboratories Ltd
Zidovudine	Tablets	Micro Labs Limited



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***



New quality guideline - objectives

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

Atazanavir

Ciprofloxacin

Didanosine

Efavirenz

Emtricitabine

Lamivudine

Lopinavir

Nelfinavir

Nevirapine

Ritonavir

Stavudine

Tenofovir

Zidovudine



Prequalification of APIs (3)

- 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).



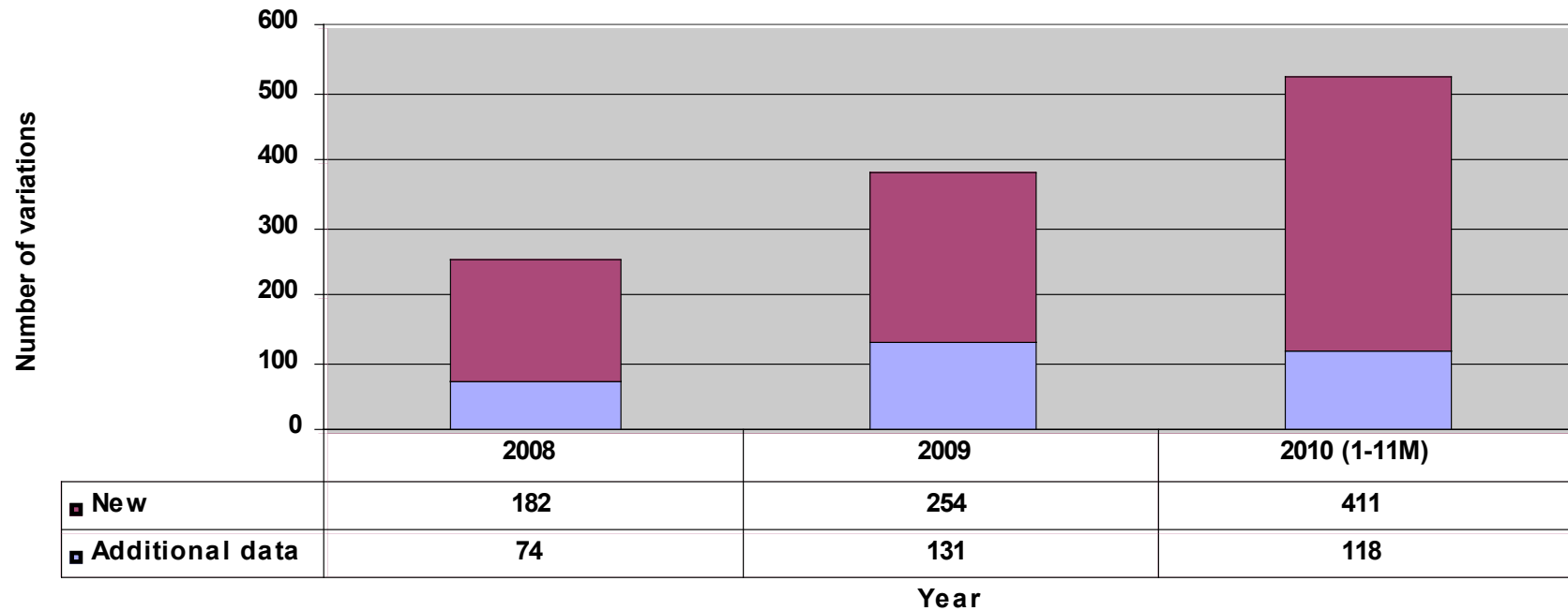
WHO List of prequalified APIs

- 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



Timetables

	New EU	PQ (previous)	PQ (aim)
Notification	Do and tell, may be rejected	90 days	30 days
Minor	7 days (verification) + 30 days	No timeline	60 days
Major	60 days	No timeline	60 days

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/>

