QUALITY ASSURANCE POLICY for DIAGNOSTICS

The Expert Review Panel mechanism

June 2014

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Background

- The Global Fund's Board approved the Quality Assurance (QA) Policy for Diagnostic Products in December 2010.
  - QA Policy was implemented in March 2011.
  - QA Policy is based on the recommendations of a group of experts on regulatory, technical, implementation issues related to diagnostics.
- After 3 years of implementation, the Secretariat reviewed the policy (February 2014) in light of **experience gained with implementation, advances in technologies, market developments, assessment of new products and partners' harmonization efforts.**

Global Fund QA Policy for Diagnostics

- Global Fund financing can only be used to procure diagnostics manufactured according to the applicable ISO or equivalent standards. These products must be monitored and used in compliance with national or WHO policies and guidance, appropriate for the intended use settings.
- *In addition, HIV and Malaria Immunoassays,* ***HIV molecular (VL & EID), CD4 and TB molecular technologies*** *must meet any one of the following criteria:*
  - ***Recommendation by WHO*** *for use in applicable treatment programs, based on technical and/or performance review*
  - ***Authorization by a stringent regulatory authority (SRA) who is a founding member of the Global Harmonization Task Force*** *when stringently assessed (not valid for CD4, malaria & TB); or*
  - ***Approved by the Global Fund through advice of an Expert Review Panel for Diagnostics (ERPD) .***

Expert Review Panel for Diagnostics (ERPD)

Background

- Mechanism integrated in the QA Policy for Diagnostics based on previous experience with ERP for medicines.
- Early 2013, UNITAID joined effort to establish an ERPD
- At its April 2013 meeting The Global Fund's technical partners **confirmed the need to establish ERPD**
- The Global FUND/UNITAID requested WHO to organize a ERPD rounds for selected diagnostic technologies

ERPD: Purpose

- To assess the potential risks/benefits associated with the procurement of diagnostic products that may have a high public health impact, but have not yet undergone a stringent assessment, either by WHO Prequalification or by a SRA.

- To advise the Global Fund/UNITAID in their decision on whether to allow grant funds to be used for the time-limited procurement of the diagnostics reviewed by the ERPD.

- **ERPD risk/benefit assessment does not replace WHO PQ/SRA assessment, but should be seen as a step towards a WHOPQ/full regulatory review.**

- ERPD mechanism should help expediting access to innovative diagnostic products, if the associated risks are deemed less than the potential benefits.

ERPD: Operationalization

- ERPD is hosted by WHO as requested by Global Fund's Board

  WHO's Essential Medicines and other Health Products Department (Regulation of Medicines and other Health Technologies Unit) leads the technical implementation.

- Terms of Reference (TORs) for ERPD have been developed under the oversight of The Global Fund and UNITAID with inputs from partners (MSF, OGAC, UNICEF, USAID, WHO).
- ERPD rounds are organized for selected diagnostic technologies according to agreed upon timelines:
  - Expression of Interest (EoI) for submission of product questionnaire is developed and published
  - Review of product questionnaires and preparation of reports performed in a 4 month timeline
  - Lessons learned serve to improve ERPD procedures

ERPD: Membership

An **independent technical body** :

- Established and administered with guidance from WHO

- Composed of external technical experts: representatives from a wide range of expertise in the field of *in-vitro* diagnostics medical devices:
  - *in-vitro* diagnostic medical device regulatory affairs,
  - manufacturing of diagnostic products including quality management systems,
  - quality assurance/performance of diagnostic products,
  - public health, use of diagnostic products in health programs in low income countries.

ERPD: Mechanism

- Submission of product documentation:
  - in response to a Global Fund/UNITAID invitation for EoI to submit a product questionnaire
  - submission of documentation is subject to eligibility criteria
- Assessment of product questionnaires submitted by manufacturers
- Transmission of advice to the Global Fund/UNITAID and other partners as to whether the benefits of procurement outweigh the potential risks.
- Definition of the validity period of the advice: to be determined by ERPD.

ERPD: Eligibility criteria

Regulatory status

• The product either has a dossier already under review for WHO Prequalification or is undergoing an SRA approval process,

OR

• There is a commitment from the manufacturer to submit a dossier to WHO Prequalification or to a SRA for stringent assessment,

AND

Quality Management System (QMS) status

• ISO 13485:2003 or an equivalent QMS documentation,

AND

• Any component of the diagnostic technology for which section above does not apply, must be manufactured at a site compliant with all applicable requirements of the ISO 9000 series.

Documentation to be submitted by manufacturers as per EoI requirements

1. A cover letter expressing interest to submit to ERPD for review,
2. A letter from the WHO Prequalification Programme or from a SRA confirming that the product is currently under review for the intended use,

OR

In the absence of such a confirmation letter, a letter of commitment from the manufacturer to submit product dossier either to WHO prequalification or to an SRA,

1. QMS documents substantiated by one or two most recent and valid inspection reports,
2. A completed questionnaire as per generic instructions outlined in the EoI.

ERPD: GF Secretariat responsibilities

The Global Fund QA Senior Officer :

- prepares and circulates the invitations for EoI in close collaboration with UNITAID and partners,
- manages the receipt of product questionnaires as sent by manufacturers,
- forwards complete questionnaires and associated documents to the ERPD Coordinator for review,
- notifies manufacturers of the outcome of the ERPD's review of their respective submissions,
- maintains on the website an up-to-date list of diagnostics submitted and/or eligible for procurement as per QA policy, based on ERPD advice.

ERPD: Coordinator's responsibilities

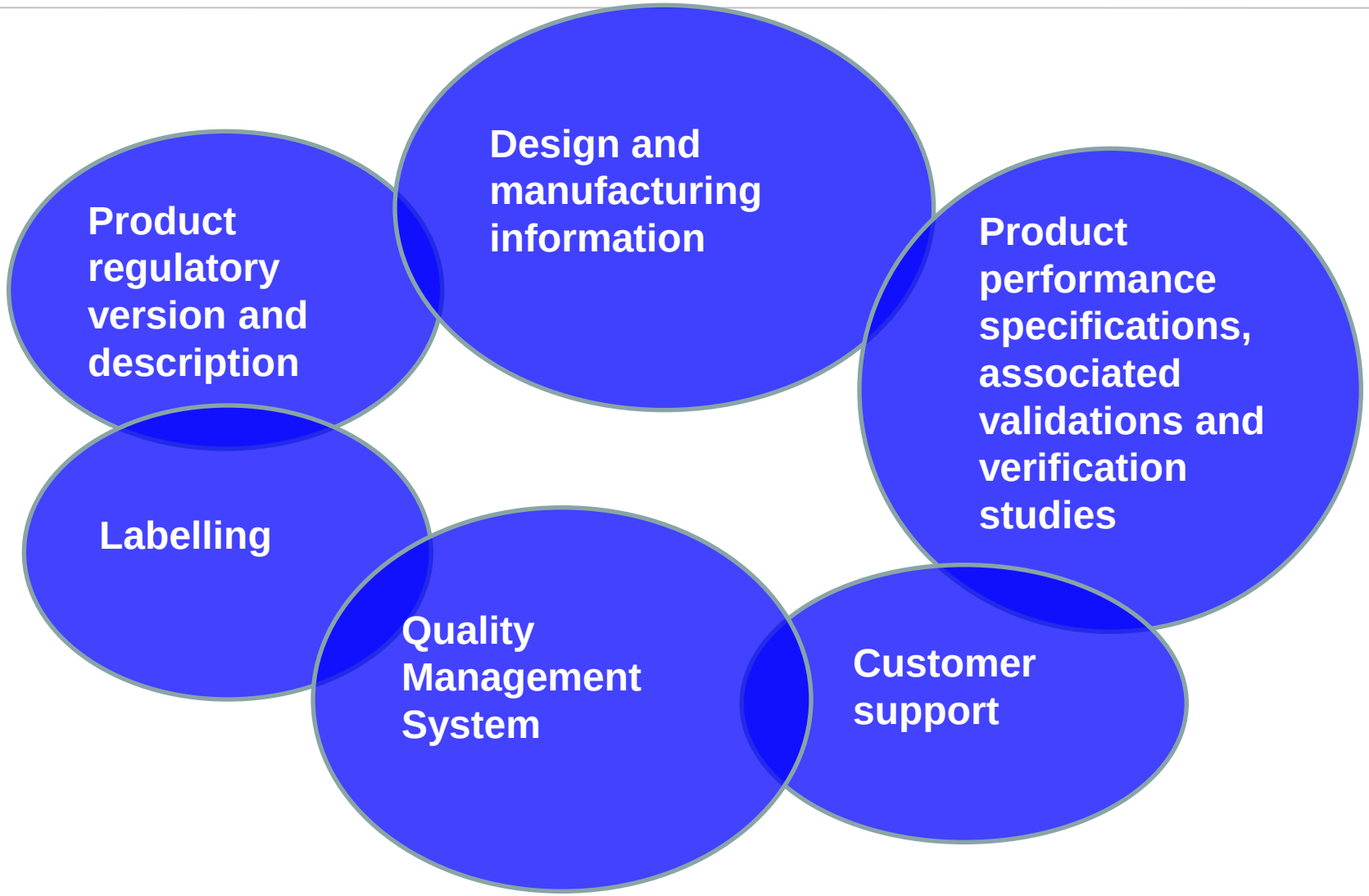
- manages the selection of ERPD members according to the TORs,
- ensures that ERPD members remain aware of most recent relevant WHO PQ and International Medical Device Regulators Forum (IMDRF) guidelines,
- arranges the timely review of the product questionnaires,
- based on the ERPD members' advice, reports the conclusion on the acceptability or non-acceptability for procurement of each product,
- provides advice on measures to mitigate identified risks,
- drafts the respective communications to the Global Fund/UNITAID and ensures timely delivery of the reports.

ERPD: Member's responsibilities

The selected ERPD members:

- Assess data provided in the submissions, draft the corresponding quality risk assessment reports, and allocate each product questionnaire to the appropriate risk category; the data for each product will be reviewed at least by two assessors,
- The assessors will present their findings at the ERPD meeting and provide advice on measures to mitigate identified risks,
- Advise the ERPD coordinator which products can be considered as acceptable for **time-limited procurement**.

Technical areas of ERPD review: see product questionnaire included in EoI



Assessment criteria for ERPD review

The following major product attributes will be used as a basis for assessment of the products:

a. QMS status of the manufacturing process

b. IVD risk management and control of the manufacturing processes

c. Performance specification, study design and evidence of performance: analytical and clinical study data

d. Stability data

e. Labelling, including Instructions For Use, suitability of the product for the intended use settings, customer support

Risk categories of ERPD reviewed products

Classification of products in 4 risk categories:

- Products classified in **risk categories 1 and 2** may be considered for time-limited procurement.
- Products classified in **risk category 3** may be considered for time- limited procurement only if there is no other option and if the risk of not diagnosing and/or making treatment decisions is higher than the risk of using the product.
- Products classified in **risk category 4** may not be considered for procurement under any circumstances.

Risk Category 1 Products

Risk Category	Characteristics **The product is described by ALL of the following:**	ERPD advice	Application of Global Fund QA Policy
1	The product is manufactured at SRA or WHO PQ Dx QMS compliant site(s) (ISO 13485:2003 or equivalent)	**Product may be considered, for time-limited procurement**	Procurement of such product with Global Fund resources acceptable for a time-limited period if no sufficient WHO PQ or SRA authorized products are available for use at all levels of Health Care System. **Product can be listed on the Global Fund list of eligible product for procurement with validity period , published on website**
	Adequate risk management and appropriate control of the manufacturing processes		
	Adequate evidence of analytical and clinical performance including data in the intended use settings and utilization of all relevant specimen types.		
	The submitted data support the claimed shelf life on at least 3 production lots, and a minimum of 6-12 months shelf-life can be assigned, as per ERPD product requirement		
	Labelling, including instructions for use in line with internationally accepted standards (IMDRF, ISO), operational aspects suitable for low income countries, reasonable customer support network		

Risk Category 2 Products

Risk Category	Characteristics The product is described by ALL of the following	ERPD advice	Application of Global Fund QA Policy
2	The product is manufactured at SRA or WHO PQ Dx QMS compliant site(s) (ISO 13485:2003 or equivalent)	**Product may be considered, for time-limited procurement**	Procurement of such product with Global Fund resources acceptable for a time-limited period if no sufficient WHO PQ or SRA authorized products are available for use at all levels of Health Care System. **Product can be listed on the Global Fund list of eligible product for procurement with validity period , published on website**
	Adequate risk management and appropriate control of the manufacturing processes		
	Adequate evidence of analytical performance, well controlled but limited clinical performance data in the intended use settings. Additional studies ongoing.		
	Submitted accelerated stability data on three lots, with acceptable variation. Real time studies in process, no main concerns, data support stability of at least 6 months		
	Labelling, including instructions for use in line with internationally accepted standards (IMDRF, ISO), operational aspects suitable for low income countries, reasonable customer support network		

Risk Category 3 Products

Risk Category	Characteristics The product is described by:	ERPD advice	Application of Global Fund QA Policy
3	The product is manufactured at SRA or WHO PQ Dx QMS compliant site(s) (ISO 13485:2003 or equivalent), except for some minor non conformities that are being addressed **and ANY of the following:**	**Product may be considered for procurement only if there is no other option and the risk of not diagnosing or monitoring efficacy of disease treatment is higher than the risk of using the product.**	Global Fund determines, in consultation with WHO and other relevant technical partners, if there is no other option, taking into account relevant factors such as country context. Time-limited procurement of such product with Global Fund resources may be permitted on an exceptional basis. To be considered on case by case basis. **Because of the exceptional nature of a category 3 product and the likely conditionality on its use, the product will not be listed on the Global Fund list of eligible products for procurement published on website.**
	Limited risk management and control of the manufacturing processes		
	Limited performance data available and/or the comparator reference method is not acceptable, thus analytical methods are not sufficiently validated		
	Submitted stability data on one or two batches and the potential for stability issues		
	Labelling, including the instructions for use in line with internationally accepted standards (IMDRF, ISO) and operational aspects of product are adequate but insufficient customer support networks in low income countries		

Risk Category 4 Products

Risk Category	Characteristics The product is described by ANY of the following:	ERPD advice	Application of Global Fund QA Policy
4	There is not sufficient evidence that the product is manufactured at SRA or WHO PQ Dx QMS compliant site(s) (ISO 13485:2003 or equivalent)	Product may not be considered for procurement under any circumstances	Procurement of such product may not be allowed with Global Fund resources Product not listed on the Global Fund list of eligible products for procurement published on website
	The risk management and control of manufacturing processes are inadequate		
	Inadequate study design and insufficient evidence to substantiate analytical and/or clinical performance		
	The current stability data are not satisfactory and do not allow any assignment of shelf life		
	Labelling, in particular instructions for use in line with internationally accepted standards (IMDRF, ISO) are inadequate or operational aspects of product incompatible with low income countries		

Next Steps – Q3/Q4 2014

- Lessons learned from pilot phase has resulted in improved documentation and ERPD management,
  - EoI
  - TORs finalized and published
  - Revised version of ERPD product questionnaire
- Manufacturers briefing sessions
  - Individual requests for teleconferences via e-mail Joelle.Daviaud@theglobalfund.org and Martine.Guillerm@theglobalfund.org
  - ERPD briefing sessions at the UN manufacturers meeting (Copenhagen, 23-25 September 2014) and the ASLM meeting (Cape Town, November 2014)
- Schedules for up-coming EoI for ERPD :
  - EoI for CD4/VL/EID/use of DBS (including POC testing platforms) published in June, submission of dossiers end of August, conclusions in November 2014
  - Following EoI on ad-hoc basis, in Q4 2014 if needed
- Up-date of Global Fund/UNITAID websites

Conclusion: ERPD as a single mechanism used by multiple stakeholders

The ERPD is designed to:

- Be a single expert review mechanism intended to be endorsed and used by multiple stakeholders and avoid unnecessary duplication,
- Promote harmonization of quality standards for the time-limited procurement of needed diagnostic products, prior to their full assessment by WHO or SRA,
- Promote the rational use of scarce expertise and resources

The ERPD sponsors (Global Fund/UNITAID) encourages stakeholders to seek advice from them on:

- Time-limited procurement of diagnostic products
- Identifying specific priority products to be reviewed by ERPD.