Expert Review Panel for Diagnostics

Terms of Reference

June 2014

Part 1: Background

At its 22nd Meeting in December 2010, the Global Fund Board approved a Quality Assurance Policy for Diagnostic Products ("QA Policy")[1]. The QA Policy came into effect on 1 March 2011. A revision to the QA Policy was approved in February 2014[2] . The QA Policy and its amendments aim to introduce globally harmonized quality standards for key diagnostic products, while expediting access to innovative diagnostic products meeting these standards. These aims were emphasized by the recommendations of the Global Fund's technical partners that met in April 2013 to review the QA Policy, as well as those of the Global Fund's Market Dynamics Advisory Group (MDAG) at its 3rd Meeting in March 2013.

The revised QA Policy provides the following product-specific quality standards for key product categories funded with Global Fund grant funds:

> "In *addition to the requirements of Section 7… Diagnostics Products for HIV Immunoassays, HIV Virological and CD4 technologies, tuberculosis Diagnostic Products and Malaria Rapid Diagnostic Tests shall meet any one of the following standards:*
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> *(i) shall be recommended by WHO for use in HIV, tuberculosis and malaria programs, as applicable, based on a technical review of quality and performance indicators (as applicable to the specific type of Diagnostic Product, as published by the Global Fund on its website from time to time)[3]; or*
>
> *(ii) shall be authorized for use by one of the Regulatory Authorities of the Founding Members of GHTF when stringently assessed (high risk classification). This option is only applicable to HIV Immunoassays Products and HIV Virological Technologies; or*
>
> *(iii) shall be acceptable for procurement using Grant Funds, as determined by the Global Fund[4], based on the advice of an Expert Review Panel. At its discretion, for Diagnostic*

[1] as set out in the Board Decision (GF/B22/DP10)

[2] http://www.theglobalfund.org/documents/psm/PSM_QADiagnostics_Policy_en/

[3] The Global Fund will from time to time indicate on its website the relevant link to the corresponding WHO websites.

[4] Notwithstanding a determination made by the Global Fund that a relevant product is acceptable or not-acceptable for procurement by a Recipient using Grant Funds, the Global Fund shall not be responsible or liable for any loss or damage arising out of or in connection with the manufacture, distribution, use or non-use of such product. The Global Fund may revoke or amend such determination in its sole discretion at any time.

Products for which there is a public health need and which are not yet compliant with Section 8 (i) and (ii), the Global Fund may request advice from the Expert Review Panel to determine the acceptability for procurement of such Diagnostic Products for use by Recipients, for a time-limited period as recommended by the ERP, pending full assessment by one of the processes listed in Section 8.

Manufacturers of Diagnostic Products referred to in this Section 8 are encouraged to submit their applications for full product review to the WHO Prequalification of Diagnostics Programme or for stringently regulated products types (those to which the option described under 8 ii is applicable, i.e. HIV Immunoassays Products and HIV Virological Technologies) to one of the Regulatory Authorities of the Founding Members of GHTF.

9. Upon the request of the Global Fund, the Expert Review Panel will advise the Global Fund on the potential risks and benefits associated with the use of a Diagnostic Product/ Technologies not meeting the criteria as per Section 8. Such determination of the Global Fund may not be disputed, challenged or appealed.

The Global Fund's technical partners at its April 2013 meeting confirmed the need to establish the Expert Review Panel for Diagnostics (ERPD) initially focusing on diagnostic products to be procured with grant funds. Once established with financial support of UNITAID and the Global Fund, the ERPD may be used by other organizations. This document sets out terms of reference for the ERPD for approval by the Global Fund and UNITAID.

This document serves to detail the purpose, scope of work, composition and division of functions.

Part 2: Purpose of the ERPD

The ERPD will be a panel of independent technical experts working under the oversight of WHO to advise the Global Fund and UNITAID (a co-funder of the ERPD through WHO and funder of Diagnostic products for eligible countries), on the potential risks and benefits associated with the use of diagnostic products that are not yet recommended by WHO and/or approved for use after a stringent assessment by a GHTF Founding Member.

The purpose of the ERPD is to review the potential risks/benefits associated with the use of finalized diagnostic technologies that are not yet WHO –prequalified or authorized by an SRA after stringent assessment. The ERPD will provide advice to The Global Fund and UNITAID on whether to allow respective grant funds to be used to procure such diagnostic technologies and recommend measures and/or conditions to be imposed to mitigate the risks (see Part 5 for details).

The Global Fund and UNITAID may also call upon the ERPD to provide follow-up advice on a product in case of any quality issues that warrant reconsideration of earlier ERPD advice, or in cases where earlier ERPD advice may no longer be applicable.

Once established and operational, the ERPD may be approached by selected organizations seeking advice on the risks/benefits of procurement and use of diagnostic products which are not yet meeting harmonized, globally accepted quality standards. The use of a single review mechanism by multiple stakeholders will promote harmonization of quality standards in procurement of needed diagnostic products, as well as rational use of scarce expertise and resources.

Part 3: Division of functions between The Global Fund Secretariat and the ERPD

The Global Fund Secretariat will be responsible for the following operational tasks:

i. publishing the ERPD Terms of Reference and plan of action of ERPD review;

ii. liaising with the ERPD Coordinator to request each ERPD ad-hoc review of selected diagnostic technologies (products), and to agree on a timeframe for delivery of the ERPD recommendations (normally no longer than 4 months after the receipt of the documentation sent by the manufacturers);

iii. inviting the manufacturers of the selected diagnostic technologies (products) concerned to submit an Expression of Interest (EoI) for ERPD review, including product information, data and audit reports as identified by the ERPD (see Part 6);

iv. deciding, based on the ERPD's advice, whether and under which conditions grant funds can be used (or continue to be used) to procure the product concerned;

v. notifying the manufacturers of the outcome of the ERPD's review and of the UNITAID and Global Fund's procurement decision, including any recommendations to mitigate quality risk if the decision is positive;

vi. maintaining on its website an up-to-date list of diagnostic products eligible for procurement with grant funds based on ERPD advice, together with the ERPD recommendations to mitigate quality risks associated with the use of the product;

vii. enforcing any recommendations made by the ERPD to mitigate the quality risk associated with the use of the product;

viii. promptly exchanging information with grant recipients and UNITAID on any quality issues related to ERPD-reviewed products, and on how to address these issues.

WHO will be responsible for:

i. appointing an ERPD Coordinator who will manage the ERPD membership and functioning;

ii. overseeing ERPD responsibilities (defined below);

iii. supporting the operationalization of the ERPD with co-funding from UNITAID and the Global Fund.

The ERPD coordinator, in consultation with Global Fund/ UNITAID and WHO will be responsible for:

i. managing the ERPD membership;

ii. convening ERPD members for a specific ad-hoc diagnostic product review requested by the Global Fund and/or UNITAID, with balanced expertise as acceptable to the Global Fund and/or UNITAID;

iii. requesting additional product data for review (see Part 6), in addition to those submitted by the manufacturer, from the relevant body, e.g. the WHO Prequalification Programme, regulatory authorities which are GHTF founding members, or any other organization that agrees to share pertinent information;

iv. delivering to the Global Fund and UNITAID the ERPD's report and recommendations, including validity period for the selected diagnostic technology reviewed, within the agreed timeline.

The ERPD members under WHO oversight will be responsible for:

i. defining a methodology for ERPD reviews, including procedures and confidentiality guidelines;

ii. determining useful product information to be reviewed for selected diagnostic technologies, as further described in Part 6 below;

iii. reviewing eligible diagnostic products at the request of the Global Fund and/or UNITAID; and

iv. providing a report on each ad-hoc review, including the background, method, findings, conclusions and recommendations of the review.

Part 4: ERP Membership

1. The ERPD shall consist of a pool of senior experts covering all relevant aspects including analyte specific issues to be assessed who may be called upon to participate in the review of diagnostic products. Out of that pool, a minimum of three experts will be selected by the ERPD Coordinator to conduct a specific review of available assessment findings (this includes the ERPD questionnaire and inspection reports). The group of experts for each ad hoc review shall have balanced representation of expertise to advice on possible risks associated with the specific product.

2. ERPD membership shall be representative of a wide range of expertise in the field of in-vitro diagnostics medical devices. Each ERPD Member shall have extensive professional experience in at least one of the following technical areas: in-vitro diagnostics medical devices regulatory affairs; manufacturing of diagnostic products including; quality assurance/performance of diagnostic products; public health, i.e. use of diagnostic products in health programmes in low and middle income countries.

3. ERPD members shall serve in their personal capacities only (that is, they shall not represent their employers or another organization when serving as ERPD members).

4. ERPD members are covered by the requirements of the Global Fund's Policy on Ethics and Conflict of Interest for Global Fund Institutions ("Ethics Policy")/ WHO Policy. Accordingly, each member shall be required to complete and submit declaration of interest forms to the Global Fund's Ethics Official in accordance with the requirements set out in the Ethics Policy.

5. ERPD members are required to sign a confidentiality statement prepared in accordance with the ERPD's internal rules and procedures.[5]

Part 5: Scope of work of the ERPD

1. As requested by the Global Fund and UNITAID, the ERPD shall assess the quality of diagnostic technologies that meet the eligibility criteria set out in section 8 of the Quality Assurance Policy for Diagnostic Products and as described in the EoI for ERPD.

2. The eligibility criteria for diagnostic technologies (products) to be reviewed by the ERPD are the following:

   i. The technology either currently has a dossier already under review by WHO Prequalification or is undergoing a stringent regulatory approval process of one of the GHTF founding members;

OR

The technology has not yet been submitted to the WHO Prequalification or has not yet been approved by a stringent regulatory authority that is a GHTF founding member but

[5] Such guidelines shall be developed by the ERPD

does have a commitment from the manufacturer to sign a Letter of Agreement either to (1) enter the WHO Prequalification or (2) commence the regulatory approval process through one of the GHTF founding members after a successful ERPD review.

AND

ii. The product /technology is manufactured at a site that is compliant with the requirements: ISO 13485:2003 or an equivalent quality management system recognized by an appropriate body (e.g. recognized certification body by a stringent regulatory authority which is a founder member of GHTF or successfully assessed by WHO Prequalification);

AND

Any part of the diagnostic technology (product) for which section 5.ii above does not apply, must be manufactured at a site compliant with all applicable requirements of the ISO 9000 series.

3. For each such assessment, the ERPD shall review the diagnostic product questionnaire and related documents that have been sent to the ERPD Coordinator from the Global Fund. The ERPD assessment shall focus on the technical areas specified in Part 6 below.

4. The ERPD shall prepare and submit a report to the Global Fund and UNITAID, which outlines the key findings of its review and provides a recommendation on whether the Global Fund and UNITAID should allow the diagnostic technology to be procured with grant funds.

5. The ERP review process should be conducted in accordance with and in close collaboration with the WHO Prequalification and WHO disease programmes.

Part 6: Technical Areas of ERPD review and reporting scope

The ERPD will determine what product information it will review, considering the specificities of the selected diagnostic technologies (products), the agreed timelines for ERPD review and the context of the review (e.g. whether it is an initial ad-hoc review or a follow-up review prompted by specific quality issues reported from its use in the field).

The ERPD will conduct a review focussing on the following technical areas:

i. Product registration information, i.e. regulatory status of the diagnostic product,

ii. ISO 13485 certification or equivalent quality management system recognized by an appropriate body of the manufacturing site and outcomes of recent assessments (i.e. 1 or 2 most recent and valid audit reports);

iii. Risk management and control of manufacturing processes;

iv. Specifications and analytical and clinical performance studies data

v. Stability testing data (accelerated and/or real time studies)

vi. Product labelling information, including the Instruction for Use;

vii. Operational aspects suitability for use in low income countries;

viii. Customer support network.

The ERPD will review the product data submitted, and will deliver a report to the Global Fund and UNITAID, including:

i. a clear analysis of benefits associated with the use of the product (e.g. in terms of increase number of people knowing their serostatus, additional patients enabled to access treatment in a given population in a defined timeframe, additional patients benefiting from an adequate monitoring of their treatment);

ii. a clear description of the potential risks associated with the procurement and the use of the product; and

iii. recommendations on measures and/or conditions that should be imposed to mitigate the specific risks identified if grant funds are used to procure the products reviewed. Such measures and conditions could include for example:

- random independent pre-shipment product sampling and testing of shipped lots for reagent kits; or
- systematic randomized post-shipment sampling and testing of consignments; and
- quality monitoring measures at the site of use, i.e. quality control and/or external quality assessment; and
- limitation of product use to specific settings or specific intended use, with specific conditions when appropriate; and
- guarantees by the manufacturer to replace any defective product (equipment/reagent kits/) at no cost for the Global Fund and UNITAID within a specified timeframe.
- provision of training
- provision of post market surveillance system, with clear communication lines

Part 7: Validity of the ERPD advice

As specified in the QA policy, if the ERPD advices on the use of a diagnostic product, the ERPD's advice shall be valid for a period of no more than 12 months or until the diagnostic product is WHO-prequalified or SRA-authorized whichever is the earlier. However, the Global Fund may, at its sole discretion, request the ERPD to consider extending the ERPD recommendation period for up to an additional 12 months if the diagnostic product is not yet WHO-prequalified or SRA-authorized within the ERPD Recommendation Period. Such requests can only be considered/granted based on supporting evidence that the risks for using the product have been reduced and/or the benefits have increased. The time limitation of eligibility for procurement (for products that can be readily replaced by other brands) may vary from one diagnostic technology to another.

Part 8: Transparency

The ERPD Terms of Reference and the working rules for ERPD review will be made publicly available on the Global Fund, UNITAID and WHO websites. All products eligible for procurement with grant funds based on ERPD advice, as well as the additional QA requirements for the procurement of such products, will also be listed on the aforementioned websites. The number and names of all diagnostics that have been submitted for each EoI for ERPD review will be listed as well.

Part 9: Logistics

1. ERPD members may receive an honorarium for their services, as approved by the Global Fund/UNITAID and WHO, in addition to travel expenses and per diems.

2. The ERPD is supported by a formal contract which is signed between the Global Fund and WHO[6] to facilitate its activities, in particular with regards to the arrangements for the ERPD sessions as well as provision of the relevant documentation for review.

Part 10: Evaluation of the ERPD

1. No later than 12 to 18 months after the establishment of the ERPD, the Global Fund and UNITAID will evaluate the performance of the ERPD against the indicators that will be set forth in the agreement between the Global Fund and the WHO.

[6] WHO serves as the host organization for UNITAID and as such will directly factor any inputs agreed with UNITAID into the contract to be agreed on and signed between the Global Fund and WHO.