Technical Specifications Series and other PQ IVD guidance

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PQT/IVD

December 2024

World Health Organization

WHO PQ Technical Specifications Series (TSS)

- Each TSS document is tailored to a specific pathogen/type of assay
  - Requirements that address needs of Member States in LMIC
  - Requirements that relate to general performance characteristics
- Summarize minimum performance requirements for WHO prequalification, to establish:
  - Performance validation criteria
  - Appropriate reference methods and reference materials
- Clarify requirements:
  - Manufacturers
  - Assessors

Technical Specification Series (TSS) (I)

- TSS-1: Human Immunodeficiency Virus (**HIV**) rapid diagnostic tests for professional and/or self-testing.
- TSS-2: In vitro diagnostic medical devices (IVDs) to identify Glucose-6-phosphate dehydrogenase (**G6PD**) activity.
- TSS-3: **Malaria** rapid diagnostic tests.
- TSS-4: In vitro diagnostic medical devices (IVDs) used for the detection of high-risk Human Papillomavirus (**HPV**) types in cervical cancer screening.
- TSS-5: Rapid diagnostic tests used for surveillance and detection of an outbreak of **cholera**.
- TSS-6: **Syphilis** rapid diagnostic tests.
- TSS-8: Immunoassays to detect **hepatitis C** antibody and/or antigen.
- TSS-9: Immunoassays to detect **HIV** antibody and/or antigen
- TSS-10: In Vitro Diagnostic (IVDs) medical devices used for the qualitative and quantitative detection of **Hepatitis C** RNA
- TSS-11: In Vitro Diagnostic (IVDs) medical devices used for the quantitative detection of **HIV-1** nucleic acid
- TSS-12: In Vitro Diagnostic (IVDs) medical devices used for the qualitative detection of **HIV-1 and HIV-2** nucleic acid
- TSS-13: Rapid diagnostic tests to detect **Hepatitis B** virus surface antigen
- TSS-14: Immunoassays to detect **Hepatitis B** virus surface antigen
- TSS-15: In vitro diagnostic medical devices used for the quantitative detection of **Hepatitis B** virus nucleic acid
- TSS-16: **Hepatitis C** rapid diagnostic tests for professional use and/or self-testing (replaces TSS-7)
- TSS-17: In vitro diagnostic (IVD) medical devices used for the qualitative detection of **Mycobacterium tuberculosis** complex (MTBC DNA) and mutations associated with drug-resistant tuberculosis (DR-TB)

Technical Specification Series (TSS) (II)

- TSS-18: Haemoglobin A1c point of care analysers for professional use
- TSS-19: In-vitro diagnostic medical devices for monitoring of blood glucose in capillary blood
- TSS-20: In vitro diagnostic medical devices used for the qualitative detection of **SARS-CoV-2** nucleic acid
- TSS-21: **SARS-CoV-2** antigen rapid diagnostic tests for professional use and self-testing
- TSS-23: Immunoassays to detect **mycobacterial** lipoarabinomannan (LAM) antigen

In development

- TSS-22: **Haemoglobin** point of care analysers
- TSS-3: **Malaria** rapid diagnostic tests (update – HRP2/3 deletion)
- TSS-24: In vitro diagnostic medical devices used for the qualitative detection of **Neisseria gonorrhoeae**, **Chlamydia trachomatis** and **Trichomonas vaginalis** nucleic acid
- TSS-25: Rapid diagnostic tests to detect **Neisseria gonorrhoeae** antigen
- TSS-26: Rapid diagnostic tests to detect **Chlamydia trachomatis** antigen
- TSS-27: **Syphilis** rapid diagnostic tests for professional use and/or self-testing

https://extranet.who.int/pqweb/vitro-diagnostics/technical-specifications-series

Technical guidance series documents (TGS)

https://extranet.who.int/prequal/vitro-diagnostics/technical-guidance-series

- Stability
- Principles of performance studies
- Test method validation
- IFU
- Quality assurance and quality control panels
- Risk management
- Quality control

- Each TGS provides detailed guidance on a specific aspect related to IVD performance/safety/quality
- Covers broad principles related to validation and verification of the performance of an IVD
- TGS provides detailed guidance with examples relevant for PQ assessment
- Reflect our current thinking and not a requirement

TGS & TSS documents

- Developed in alignment with relevant international and national standards, literature and best practise (e.g., CLSI, IMDRF, FDA, ISO ..) as applicable
  - Deviations might be due to additional requirements to demonstrate
  - Suitability of the IVD in resource limited settings
  - Lessons learned
  - Scientific evidence/experience/disease programme
- Benchmark for both manufacturers and assessors (standardization …)
- Communicate to manufacturers what is required
  - Aiming to strike balance between needs, alignment and practicability
  - Avoid inefficiency, time, resources (assessing inadequate studies, repeating work)

TSS requirements that might differ from requirements of other stringent regulatory assessments….

PQ require manufacturers to demonstrate suitability of the IVD in resource limited settings:

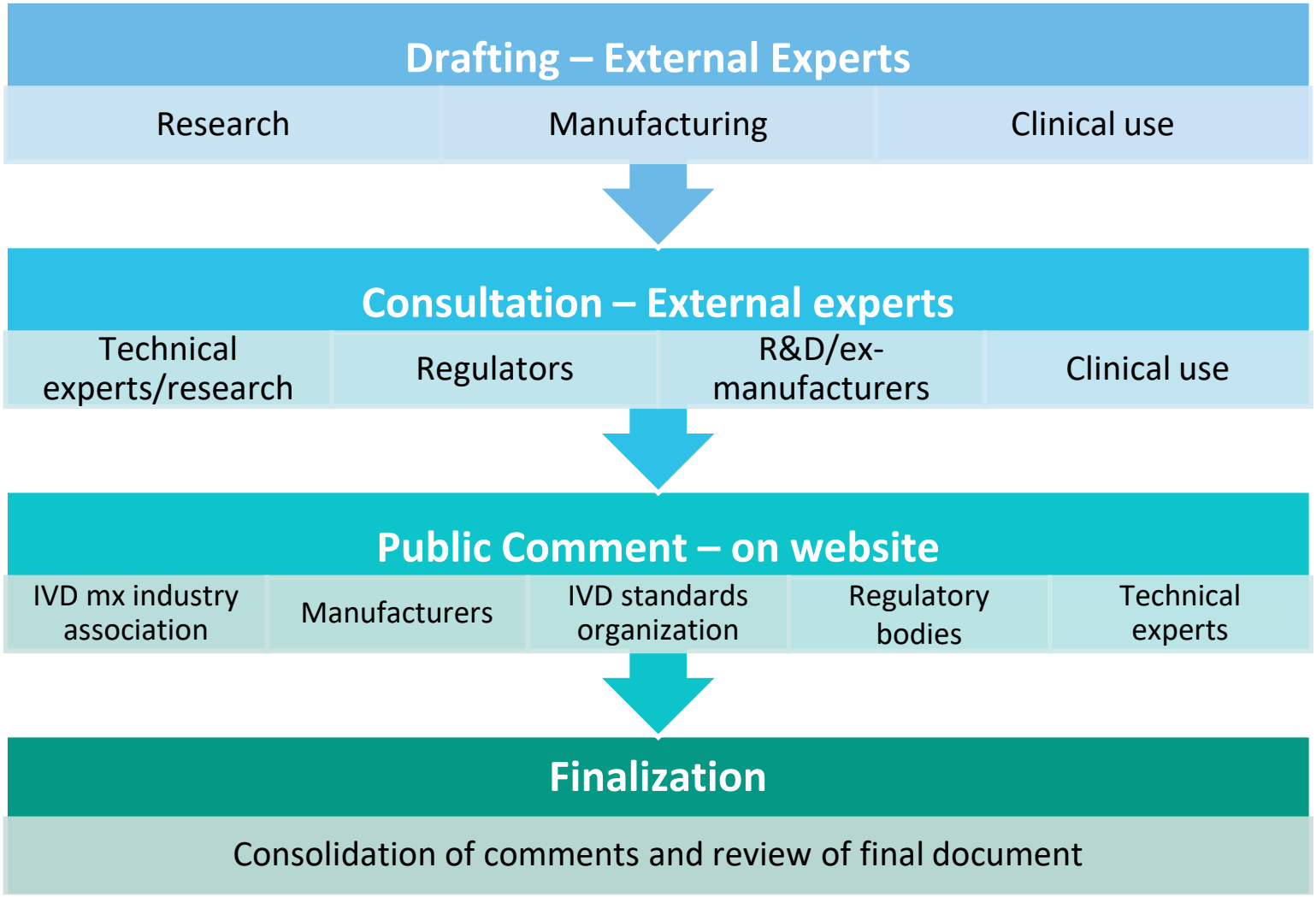
- specimen validation studies/specimen equivalence studies (capillary blood vs venous blood)
- stability claim (transportation..)
- analytical specificity (cross reactivity, interfering substance)
- clinical studies (geographical location, genotypes, comorbidity, testing environment, intended users)
- studies required for self testing claims

Photos courtesy of Lia Lewis Ximenez

Guidance development process

Preventing perceived conflict of interest when engaging stakeholders in the drafting process

Allow opportunity for input and feedback from broad range of stakeholders



TSS - Overall Structure

Introductory sections A - D

- Introduction
- Other WHO guidance documents
- Performance principles for WHO PQ
  - Intended use
  - Diversity of specimen types, users and testing environments
  - Applicability of supporting evidence to the IVD under review (locked down design of IVD, IFU, lots, reference standard)
- Table of Requirements
  - Part1/ToC Chapter 3: Analytical performance & other evidence
  - Part2/ToC Chapter 4: Clinical evidence
  - Part3/Usability Study - For IVDs intended for SELF-TESTING
- Source documents

IMDRF – IVD Medical Device Market Authorization Table of Contents (IVD MA ToC)

Dossiers must follow ToC format/numbering:
TSS 6 – TSS 17: ToC format
TSS 18 ff: ToC format & numbering

Verbal forms used in TSS documents

- "shall" indicates that the manufacturer is required to comply with the technical specifications.
- "should" indicates that the manufacturer is recommended to comply with the technical specifications, but it is not a requirement.
- "may" indicates that the technical specifications are suggested methods to undertake the testing, but not requirements.

Part 1/ ToC Chapter 3 - Analytical performance & other evidence I

Specimen Stability Collection, processing, transport, storage of all specimen type(s) claimed in the IFU	**Analytical Specificity** ▪ Potentially interfering substances (endogenous, exogenous) ▪ Cross-reactivity ▪ Microbial interference
Validation of Specimens ▪ Demonstration of equivalence ▪ Demonstration of equivalence between specimen collection methods	**High Dose Hook Effect**
Metrological traceability of calibrators and control material values	**Measuring Range of the Assay**
Accuracy of Measurement ▪ Trueness ▪ Precision (repeatability, reproducibility)	**Validation of Assay Cut-off**
Analytical Sensitivity ▪ Limit of detection ▪ Limit of quantitation	**Validation of Assay Procedure** ▪ Whole system failure ▪ Carry over contamination

Part 1/ ToC Chapter 3 - Analytical performance & other evidence II

Software	**Usability/human factors** ▪ Flex studies ▪ Qualification of Usability
Cleaning and Disinfection Validation	**IVD Stability** ▪ Shelf life ▪ In-use stability ▪ Transport/Shipping stability

Part 2/ ToC Chapter 4 - Clinical evidence

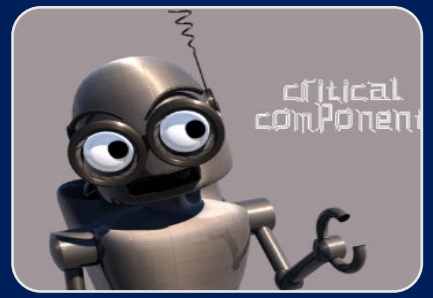
Diagnostic Sensitivity	
Diagnostic Specificity	

Part 3/ ToC Chapter 3 & 4 - Usability Studies (Self-tests)

Label Comprehension Study
Result Interpretation Study
Observed untrained User Study

Applicability of supporting evidence to the IVD under review

For WHO prequalification, design lock-down is the date that final documentation, including quality control and quality assurance specifications, is signed off and the finalized method is stated in the IFU.



Where more than one lot is required, each lot shall comprise different production (or manufacturing, purification, etc.) runs of critical reagents, representative of routine manufacture.

The true clinical status (e.g., presence or absence of active infection) status shall be determined using a suitable reference method. For WHO purposes this should be a test that currently is at a developed stage of technical capability based on the relevant consolidated findings of science, technology and experience (commonly referred to as state of the art). Justification for the choice of method/testing algorithm, shall be provided.

Other PQ Guidance documents

https://extranet.who.int/prequal/vitrodiagnostics/prequalification-guidance

- A risk-based approach for the assessment of in vitro diagnostics (IVDs) (PQDx_152 v1, 13 May 2014)
- Risk-based classification of diagnostics for WHO prequalification) (PQDx_172 v1, 13 May 2014)
- Eligibility criteria for WHO prequalification of in vitro diagnostics (PQDx_298 v7, 10 July 2023)
- Overview of WHO prequalification of in vitro diagnostics assessment (version 9, 04 January 2021)
- Prequalification assessment and change assessment target deadlines (PQDx_300 v1, 21 July 2017)
- Abridged prequalification assessment (PQDx_173, November 2023)
- Instructions for the completion of the pre-submission form for application for prequalification of an in vitro diagnostic (PQDx_017 v6, 01 November 2021)
- Instructions for compilation of a product dossier – IMDRF ToC (PQDx_18 v5, 2023)
- Information for manufacturers on the inspection of manufacturing sites (Assessment of the quality management system) (PQDx_014 V4, 08 September 2017)
- Prequalification fees: WHO prequalification of in vitro diagnostics (PQDx_299 v2, 01 August 2018)

Expert Review Panel for Diagnostics

Process, expectations and useful tips

Dr Fatima Gruszka
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December 2024

World Health Organization

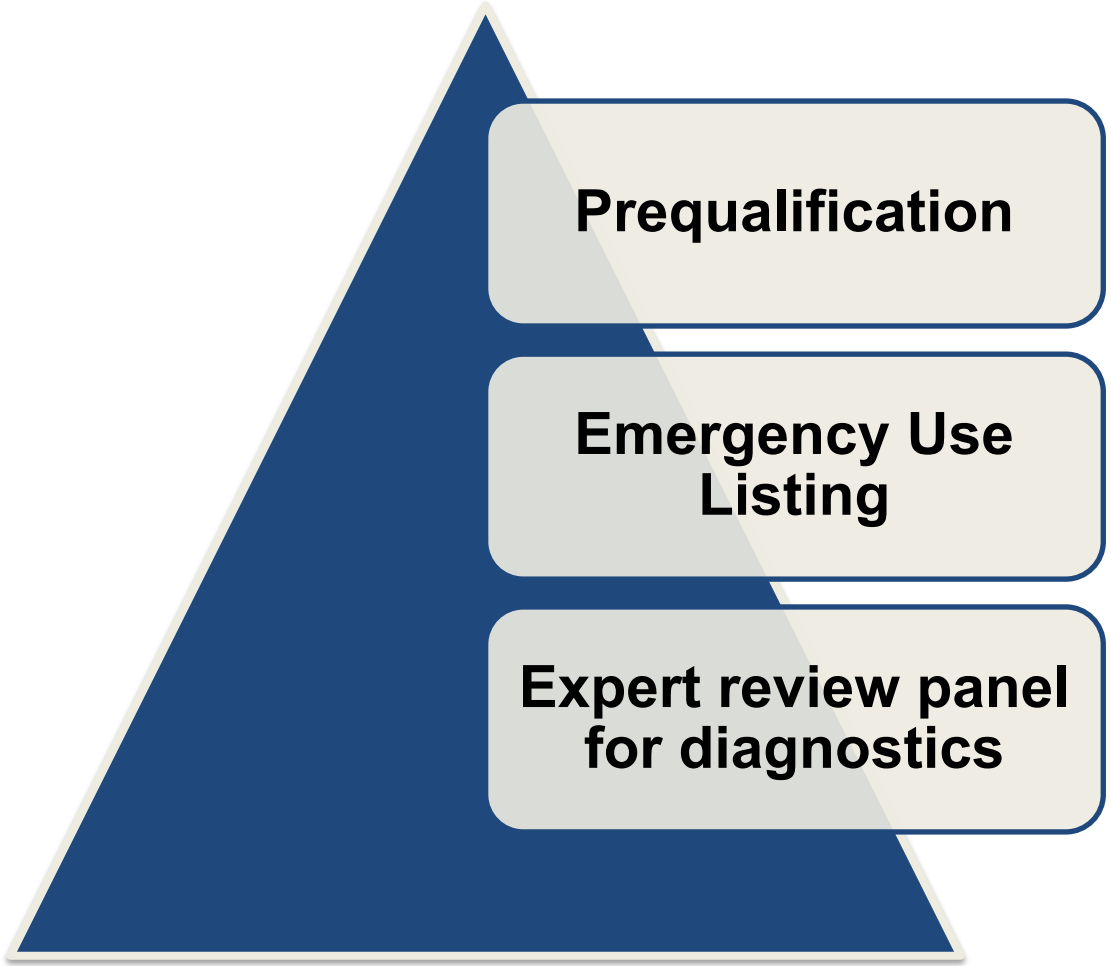
Content

1. What is ERPD
2. ERPD review steps
3. Pillars to QA and safe IVDs
4. Overview of ERPD questionnaire and what we expect you to submit
5. Risk categorization
6. Dengue example
7. Q and A

Expected outcomes

1. Gain more insight into ERPD process, timelines
2. Understand the expectations when preparing for ERPD submission, basis for the assessment
3. Feedback on our experience of the review process
4. For us, hopefully more complete applications.

Options for making recommendations for IVDs



A comprehensive assessment of individual IVDs through a standardized procedure which may include dossier review, performance evaluation, and inspection of manufacturing sites.

A risk-based procedure for assessing and listing IVD for use during a PHEIC with the aim of expediting the availability of these products

ERPD is an independent advisory group of technical assessors coordinated by WHO, responsible for evaluating IVD by assessing their quality, safety, performance

Comparison of assessment pathways

	Prequalification (PQ)	ERPD	EUL
Timing	Open call for applications within eligibility criteria	Defined in each ERPD EOI	Defined in the EUL EOI (PHEIC-driven)
Responsibility for receiving applications	WHO PQ	•Global Fund/UNITAID or •Procurement agency or •WHO technical programme	WHO PQ
Assessment fees	PQ fees payable	No fees payable	No fees payable
Responsible for the technical review	WHO PQ	WHO PQ	WHO PQ
Assessment components	•Product dossier •Site inspection •Performance evaluation •Labelling review	Completed ERPD questionnaire and documented evidence	Documented evidence defined in the EUL EOI

Comparison of assessment pathways

	Prequalification (PQ)	ERPD	EUL
Requirements	Defined in PQ documents, including PQ Technical Specifications (TSS)	Risk-based approach	Essential data requirements outlined in the EUL instruction document
Outcome	Products that meet requirements added to WHO Prequalification List	A risk category for procurement will be assigned	Products that meet requirements added to WHO Emergency Use List
Publication of assessment outcomes	For PQ-listed products only	Managed by the agency/programme responsible for EOI/eligibility	For listed products and products which failed EUL listing

Disease areas eligible in EOIs

TB/MDR TB

Syphilis

HIV

HBV/HCV

Malaria

Filariasis

Leishmaniasis

Meningococcal

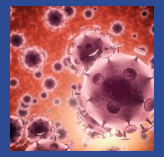
Dengue

Since 2023




Expert Review Panel for Diagnostics

Purpose

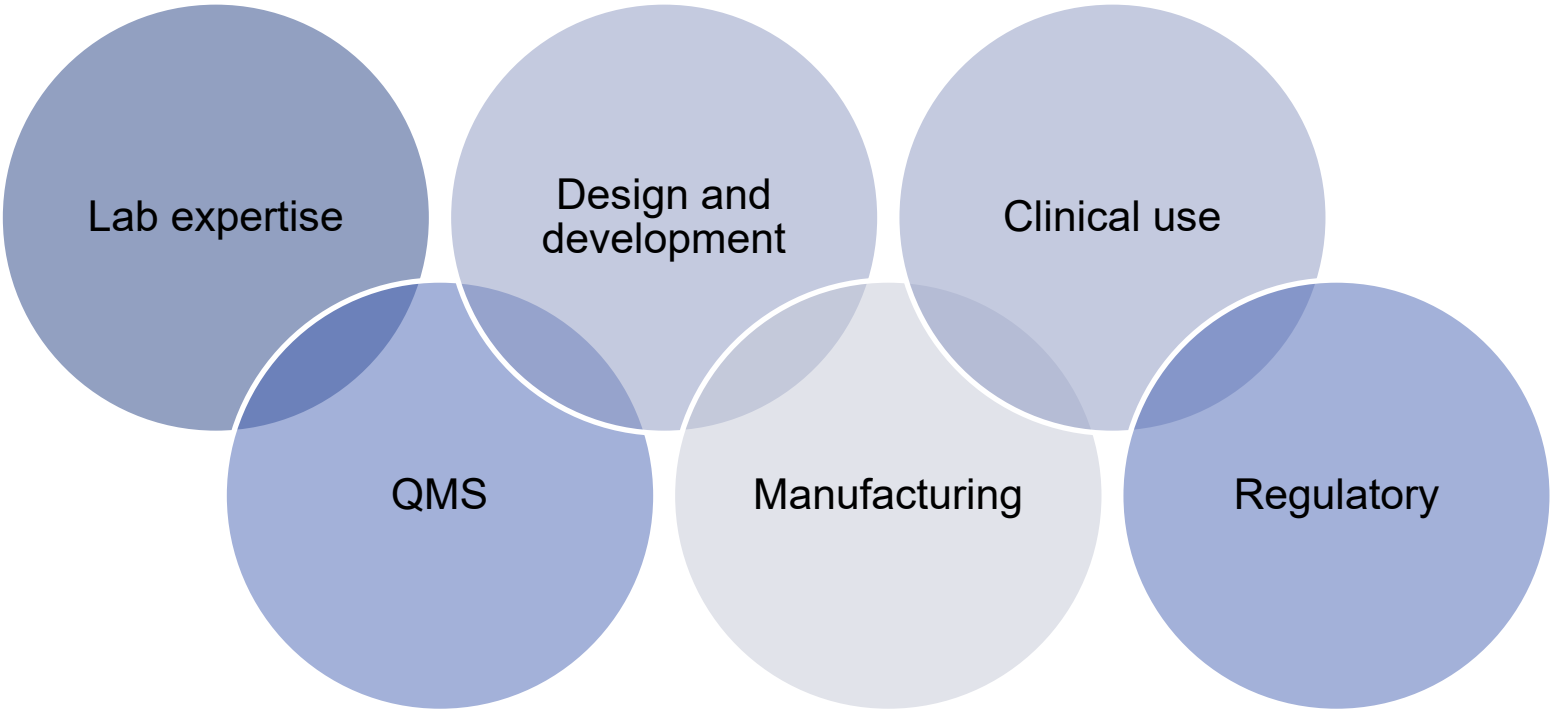


ERPD mechanism aims to ease access to innovative or neglected diseases diagnostics when no other quality assured IVD is available

ERPD is risk/benefit assessment process based on a desk review of available data on the product

ERPD is a bridge to WHO PQ or SRA assessment

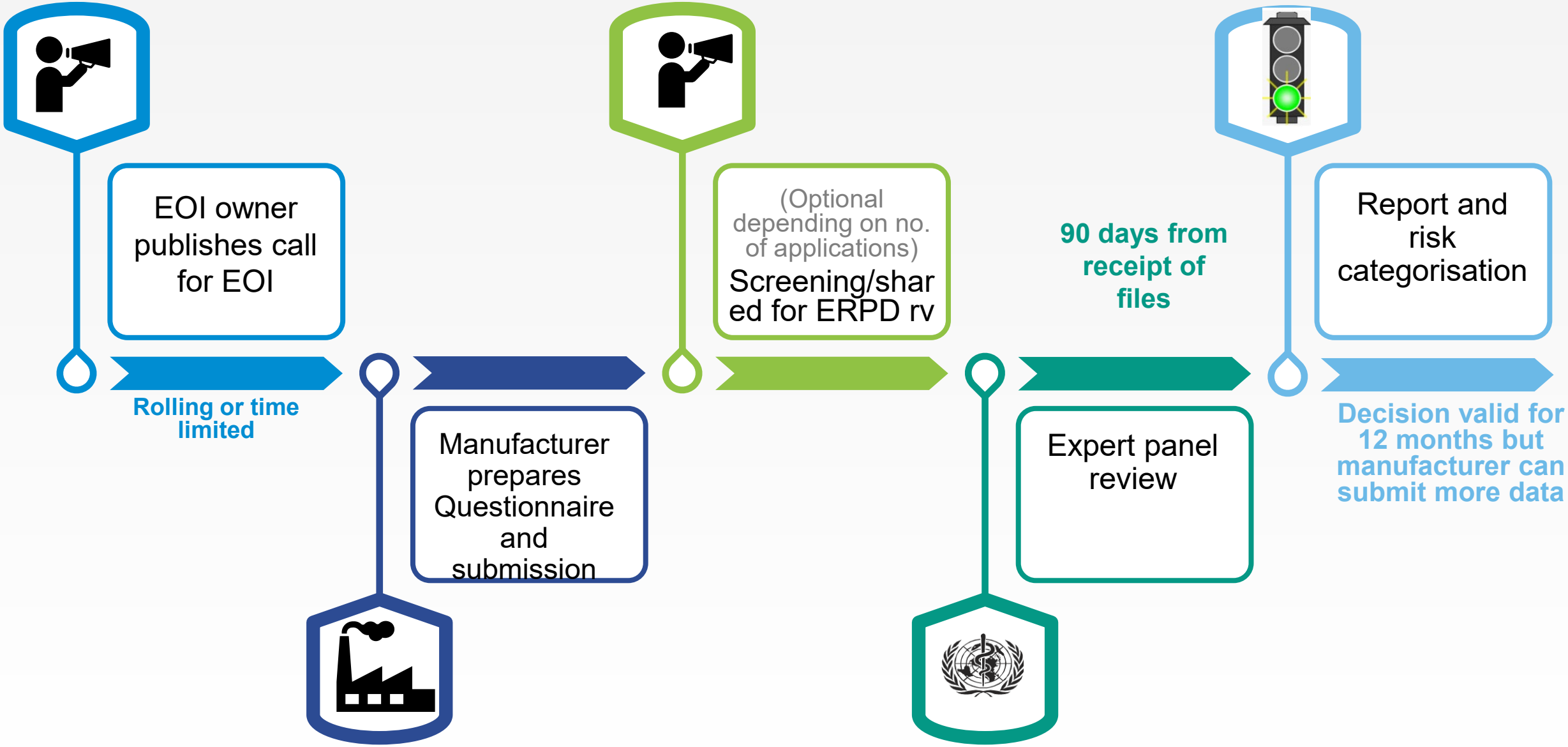
Expert Review Panel for Diagnostics (ERPD)



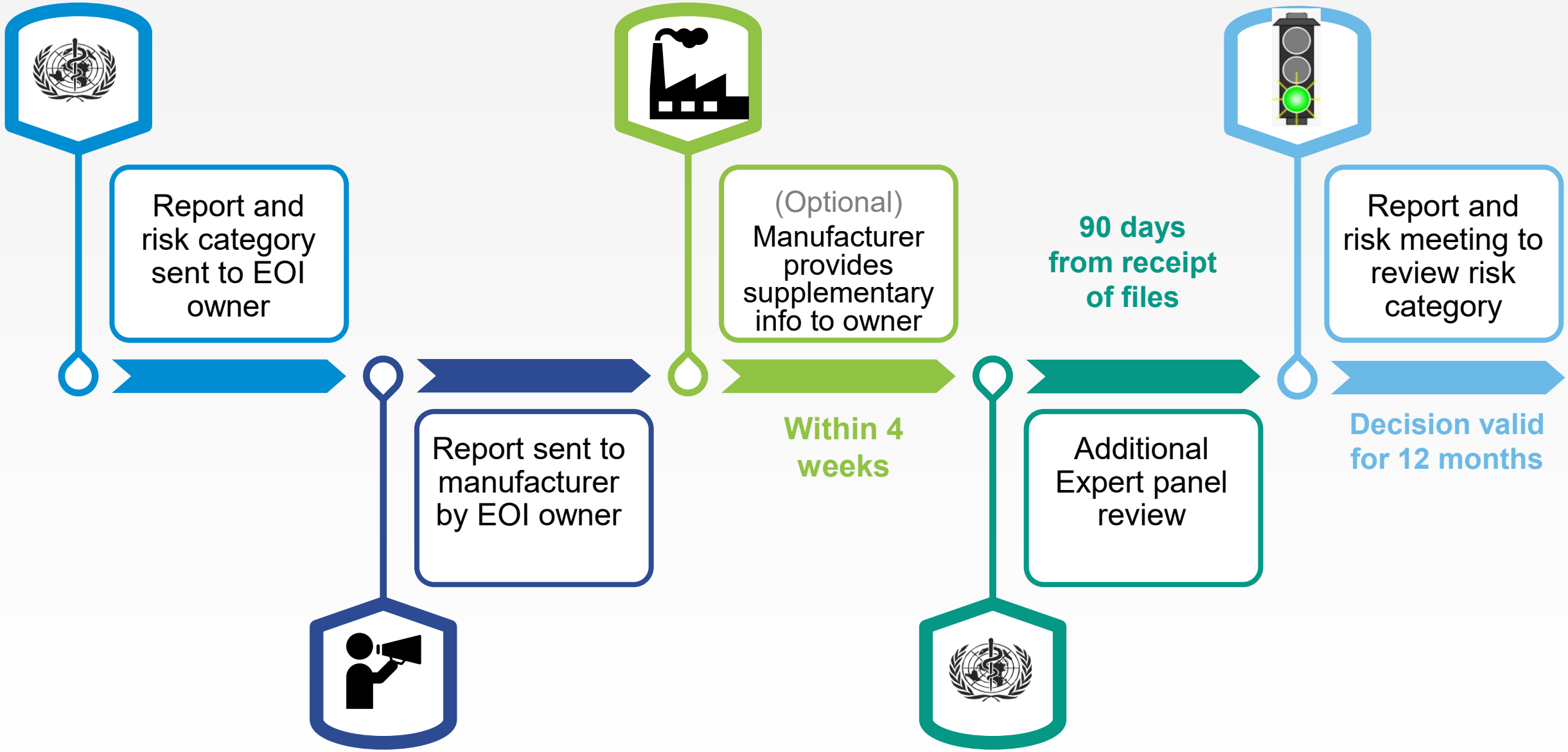
ERPD Members have technical expertise in the field of IVD performance, quality and safety, have scientific knowledge and experience of diagnostic procedures




Steps for ERPD assessment



Steps for ERPD assessment



Expert Review Panel for Diagnostics

How to demonstrate that your product meets its claims and quality objectives ?

Expert Review Panel for Diagnostics
Five pillars to

Expert Review Panel for Diagnostics

Is meeting WHO TSS and TGS a requirement ?

Gap assessment and B/R assessment by the Expert panel

TGS
http://extranet.who.int/prequal/vitro-diagnostics/technical-guidance-series
TSS
http://extranet.who.int/prequal/vitro-diagnostics/technical-specifications-series

ERPD Questionnaire

Diagnostic Product Questionnaire

Product Evaluation by the Expert Review Panel for Diagnostic Products

World Health Organization

Diagnostic Product Questionnaire

Product Evaluation by the

Expert Review Panel for Diagnostic Products

Expert Review Panel for Diagnostics

Questionnaire application

- Product version and description
- Design, Manufacturing & QC information
- Product performance specifications, associated analytical and clinical validations studies
- Labelling
- QMS major procedures
- Customer support and PMS




How to Complete the Form

1. Submit searchable PDF
2. Document control, date and signed documents. Authorized personnel.
3. Explain if N/A

Rationale on the Product and Submission

Purpose: Assist WHO Experts in capturing necessary information about a product for ERPD evaluation

Accurate and complete submission is crucial

Justification for the product's suitability: Compliance with specifications outlined in the Invitation to Manufacturer




Manufacturer Information

Legal Manufacturer details

Rebranders are authorized to submit to ERPD

All information on the OEM supplier and control should be provided




Product Information

Product name, code, catalog number

Instructions for use (IFU) and user manual in English

Transport, storage, and operating temperatures




Product Intended Use

- Disease category to be diagnosed
- Intended population
- Analyte(s) detected
- Specimen type(s) (e.g., serum, plasma, whole blood)




Assay Format

- Immunochromatographic, immunofiltration, EIA, NAT, etc.
- Manual, RDT, semi-automated, etc.
- Methodology (qualitative or quantitative)




Product Operation

Sample collection and transport materials

Assay controls and accessories required

Product usage (Trained healthcare workers, POC, Self-test)




Performance Characteristics

- Preanalytical performance (Sample storage and stability of analytes)
- Analytical performance studies (protocols and reports)
- Clinical performance studies (manufacturer and independent)




Product Stability Studies

Transport, shelf-life, and in-use stability

Details of any studies conducted on other design versions

Regulatory and Commercial Status

- Regulatory status of the product
- Commercial agreements and rebranding
- List of regulatory approvals

Quality Management System

Is a QMS in place for design, development, and production?

ISO 13485 certification details

Other similar standards compliance




Risk Management

Risk analysis conducted?

ISO 14971 Standard?/ Other guidelines followed?

Risk file : Annexes for risk report, management plan, and control procedures




Customer needs	Marketing needs	State-of-the-art	Disease-related risks	Comorbidities risks associated with the device
Regulatory needs	Format requirements	Type of sample	Shipping	Manufacturing issues
Limited capacities of supply	Analytical performance	Reproducibility	Repeatability	Cross reaction
Interference	Stability issues	Clinical performance	component with their specific risks (supply, control, performance,	with their specific risks (supply, control, performance,
Quality control, sampling, definition of lot, etc.	Reference material issues, availability, nature, stability	False positive	False negative	Release, Etc.

Risk Management

- Foreseeable failure
- Foreseeable risks
- Foreseeable problem under normal conditions of use
- Implemented mitigation means
- Planned actions and level of implementation
- Overall risk assessment




Sites of Product Manufacture

Product design manufacturing flowchart

Lot release procedure

Manufacturing capability and capacity




Key Suppliers

List of key suppliers and subcontractors

Details of components/products/services supplied

Annexes for supplier evaluation and quality control procedures




Manufacturer Declaration

Data support for claims

List of annexes required

Justification if not provided




Annex Details

- Hazardous classification (MSDS)
- Instructions for use (IFU)
- Labeling and packaging




Expert Review Panel for Diagnostics

Safe and affordable products

quality assured IVD, compliant with WHO policies

Risk Category criteria

	RC 1	RC 2	RC 3	RC 4
QMS Compliance	QMS compliant site.	QMS compliant site.	Generally QMS compliant, but some minor non-conformities that are being addressed.	Not sufficient evidence that the site is QMS compliant.
Risk Management & Control of Manufacturing	Adequate risk management and appropriate control of manufacturing processes.	Adequate risk management and appropriate control of manufacturing processes.	Limited risk management and/or control of manufacturing processes.	Evidence of risk management and control of manufacturing processes is inadequate.
Evidence of Analytical Performance	Adequate evidence.	Adequate evidence for most key aspects. Additional studies ongoing.	Analytical methods not sufficiently validated/limited performance data and/or comparator/reference method not acceptable.	Inadequate study design and insufficient evidence to substantiate analytical performance.

Risk Category criteria

	RC 1	RC 2	RC 3	RC 4
Evidence of Clinical Performance	Adequate evidence, including data in the intended use settings and with all relevant specimen types.	Well controlled, but limited, clinical performance data in intended use settings. Additional studies ongoing.	Clinical methods not sufficiently validated (i.e.: limited data available and/or inappropriate reference method).	Inadequate study design and insufficient evidence to substantiate clinical performance.
Stability studies	Submitted study data support claimed shelf life on at least 3 production lots and minimum of 6-12 months for shelf life.	Acceptable accelerated stability data on 3 lots; real time studies in progress with 6 months data.	Submitted stability data on 1 or 2 lots and the potential for stability issues.	Current stability data are not satisfactory and do not allow assignment of shelf life.
Labelling, including IFU	Consistent with international standards (IMDRF, ISO)	Consistent with international standards. Minor improvements identified.	Partially compliant with international standards. Need for improvements identified.	Labelling and IFU are not satisfactory.
Customer support & PMS	Test suitable for LMIC, customer support network.	Most aspects suitable for LMIC, customer support network.	Operational aspects adequate, poor customer support.	Operational aspects incompatible with LMIC.

Decision and Extension Request

RISK CATEGORY 1 & 2:

NO OBJECTION TO TIME-LIMITED PROCUREMENT

RISK CATEGORY 3:

OBJECTION TO PROCUREMENT

MAY BE CONSIDERED WHEN THERE ARE NO ALTERNATIVES, AND PROVIDED THE BENEFIT OUTWEIGHS THE RISK OF PROCURING A PRODUCT WHICH IS NOT FULLY QUALITY ASSURED

RISK CATEGORY 4:

OBJECTION TO PROCUREMENT

RISK CATEGORY ASSIGNMENT IS FOR A TIME-LIMITED PERIOD

EXTENSION MAY BE CONSIDERED WITH NEW RISK CATEGORY ASSIGNMENT



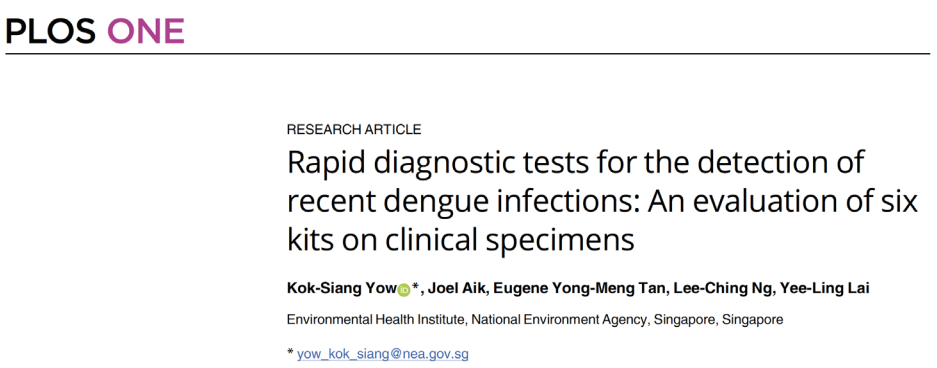

ERPD – Dengue

World Health Organization

ERPD - Dengue

Dengue IVDs are not yet prequalified – several evaluations published in literature

To address this gap NTD, WHE and PQ jointly established an Expert Review Panel for Diagnostics (ERPD)


PLOS ONE

RESEARCH ARTICLE

Rapid diagnostic tests for the detection of recent dengue infections: An evaluation of six kits on clinical specimens

Kok-Siang Yow*, Joel Aik, Eugene Yong-Meng Tan, Lee-Ching Ng, Yee-Ling Lai

Environmental Health Institute, National Environment Agency, Singapore, Singapore

* yow_kok_siang@nea.gov.sg

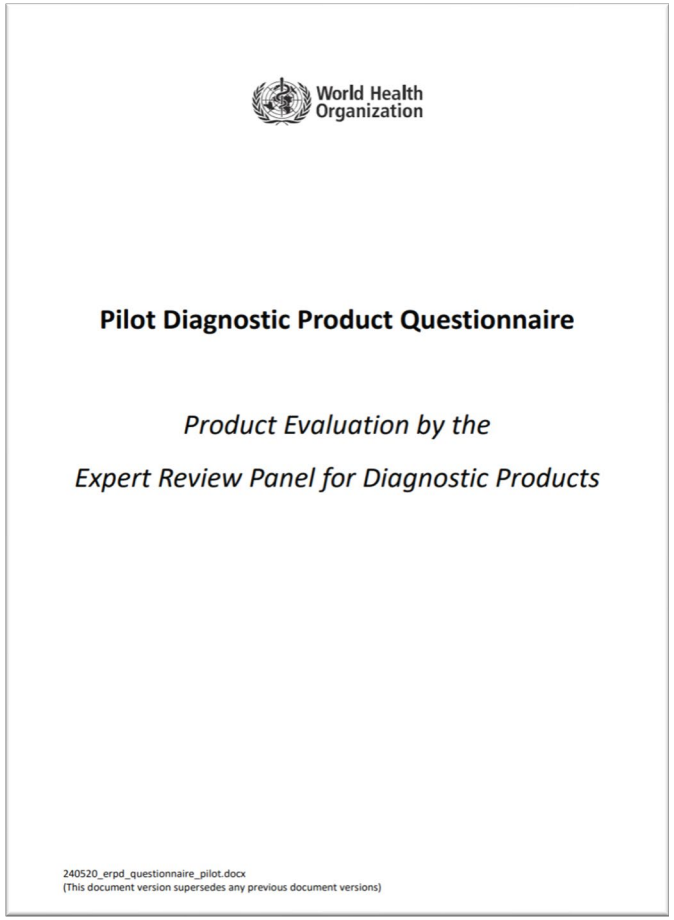
Test Methodologies included in ERPD:

- Rapid Diagnostic Test (RDTs)
- Nucleic Acid Amplification tests
- Enzyme Immunoassay - ELISA




Invitation to Manufacturers - Dengue

- Invitation to manufacturers (ItM) call published on 24 May 2024 and closed on 7 July 2024
- Manufacturers submit an expression of interest (EOI) for the product to be evaluated and fill a diagnostic product questionnaire.
- Questionnaire: 11 sections and 24 pages



World Health Organization

Pilot Diagnostic Product Questionnaire

Product Evaluation by the

Expert Review Panel for Diagnostic Products

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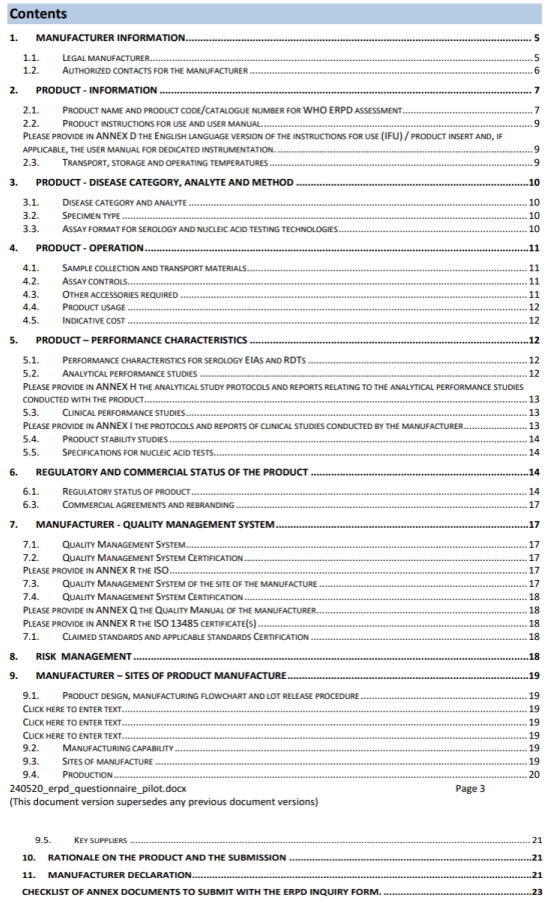
(This document version supersedes any previous document versions)



Contents




Essential Criteria

1. Technical criteria

- **Antigen and antibody detecting point of care rapid diagnostic tests (RDTs)**: rapid test (≤30 mins) for diagnosis of acute dengue infection, must include **detection of antigen (NS1) and antibodies (IgM) (+/- IgG) of all serotypes**, though they need not differentiate the serotypes, intended for point-of-care testing.
- **NAAT tests**: For diagnosis of acute dengue infection, dengue specific[2] and could be pan specific and/or serotype specific (multiplex), for point-of-care testing, near-patient testing or lab-based testing.
- **Enzyme immunoassay tests**: Immunoassay e.g. ELISA, must include detection of antigen (NS1) or antibody (IgM) of all serotypes, though they need not differentiate the serotypes. Must allow concurrent testing of multiple samples and intended for lab-based testing.

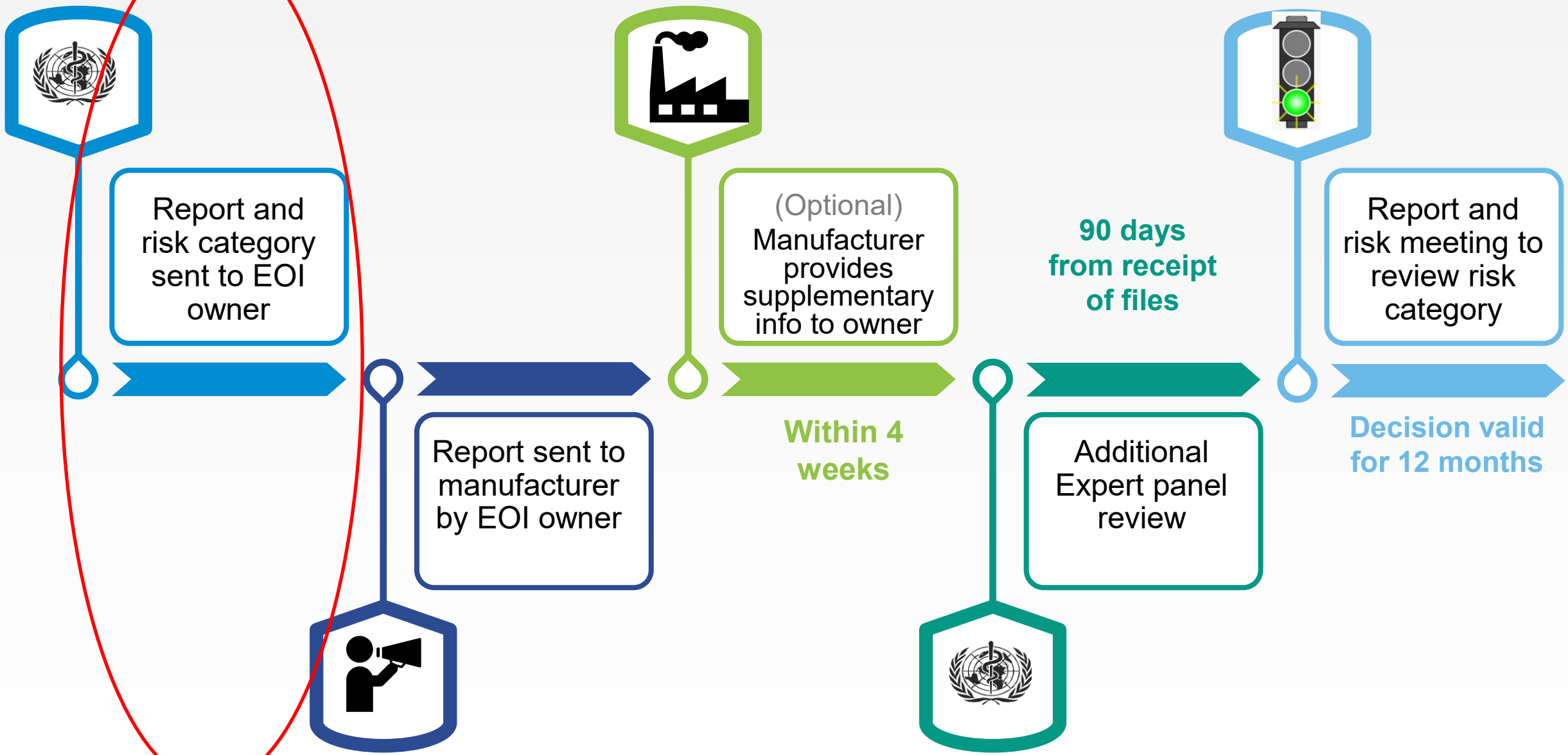
2. Quality assurance criteria

- Provide evidence that are designed and manufactured under a relevant quality management system, compliant with **ISO 13485** or equivalent standard
- Must be original equipment manufacturers (OEM)
- Company must have necessary registrations to enable sale and export out of the home country. Chinese companies - NMPA
- Manufacturer should provide evidence of ability to support design, manufacturing, distribution, sales and post-market activities such as customer support, response to regulatory vigilance activities, in and for all WHO Member States
- Application is limited to manufacturers who commit to submit their product to PQ (when eligible), SRA approval or registration in accordance with the product classification.

Preferred criteria –to be used for short listing products

- Sample types include **whole blood, serum or plasma.**
- Kits contain all reagents **essential** to perform the assay (i.e. not just primers and probes for NAAT)
- **Internal controls included**
- For NAAT – **thermocycler interoperability**
- **Shelf life ≥ 12 months**
- **Cold chain not required for shipping**
- **Storage temperature ≥-20°C (for NAAT, ELISA) and ≥ 4°C for RDTs**
- Supplier has consumables bundling capacity to minimize supply chain burden
- **Registration** – (non-stringent category)
  - US-FDA, TGA (Australia), PMDA (Japan), HSA (Singapore), MFDS (Korea) or ANVISA (Brazil)
  - if CE-IVD (self-certified/declared) must also include registration with ≥ 1 authority listed in 1 or have a WHO prequalified test for another infectious disease in the same test type group.
- The intended population criteria and performance data should include a well characterized population in an **at risk region, in acute phase of illness (initial 5-6 days), ideally including all age groups and other flaviviruses**
- For performance evaluation include analysis against **recent and currently globally circulating dengue viruses; in the case of NAAT at least in silico analysis (cross-reactivity and inclusivity analysis)**

Steps for ERPD assessment

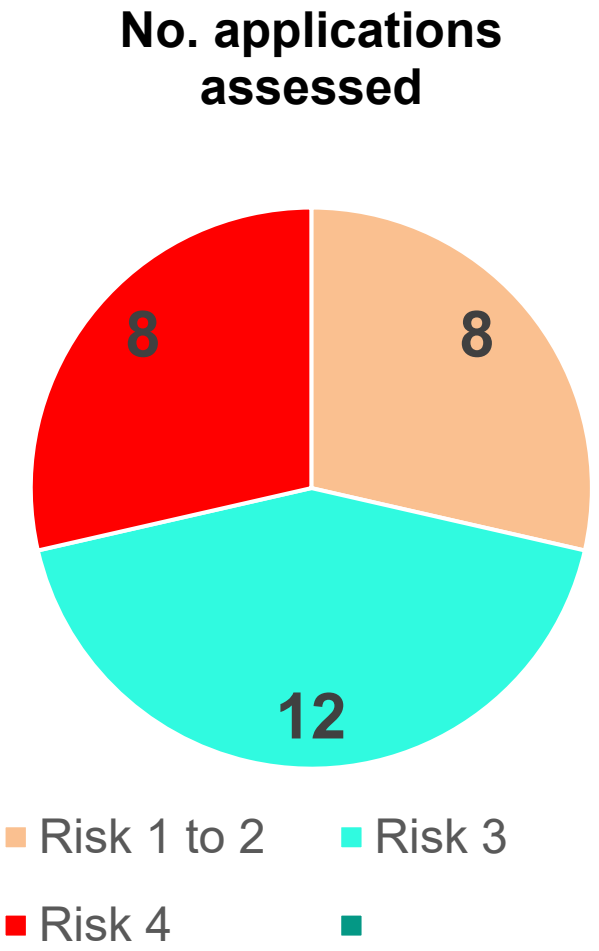


ERPD 2024

36 ERPD application received in 2024
- **28** assigned risk category
- **8** under assessment

- The majority applications (22/36) were initial reviews, and 14 resubmissions/extension requests

Main partner for ERPD review is **Global Fund** (rolling submissions) and since end 2023, a new time-limited pilot ERPD for **NTDs/VPDs (GAVI, WHE, NTD**)






THANK YOU!

Questions?