Introduction to the WHO Prequalification of in vitro diagnostics

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World Health Organization

The current landscape

Every year, hundreds of millions of US dollars' worth of IVDs and medicines are purchased by or through international financing or procurement mechanisms – such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), UNITAID and UNICEF – for distribution in resource-limited countries

The overall picture for HIV, HCV, HBV, TB and malaria is one of vast improvement. Yet if progress towards achieving international development goals is to be maintained, significant work must be carried out to **ensure accurate diagnosis and monitoring**, and to continue **scale up of treatment** with quality-assured medicines.

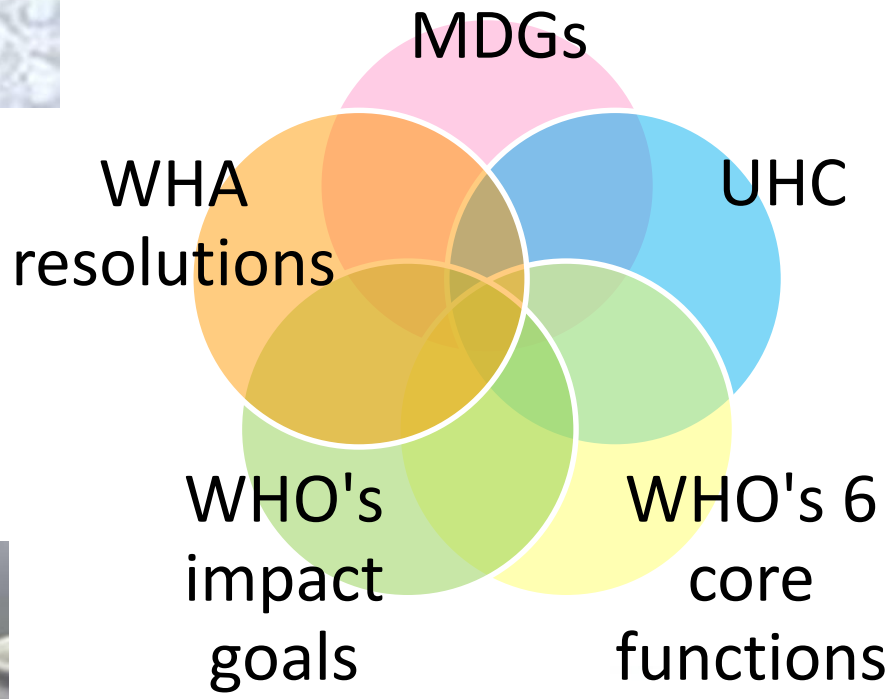
The current landscape cont'd

Health products and technologies save lives, reduce suffering and improve health, but only when they are of good quality, safe, effective, available, affordable, acceptable and properly used.

IVDs play a critical role in ensuring blood safety, surveillance, diagnosis and treatment initiation and monitoring.

- The world community and the health financing partnerships have shown an increasing awareness of IVDs' crucial role in scaling up of treatment programs for the major diseases in resource limited countries and their contribution in health systems strengthening.

WHO's work in IVDs area: background



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Millennium development goals

The United Nations Millennium Development Goals are eight goals that all 191 UN Member States have agreed to try to achieve by the year 2015.

4. to reduce child mortality;
5. to improve maternal health;
6. to combat HIV/AIDS, malaria, and other diseases;

Universal health coverage

Universal coverage is based on the WHO constitution of 1948 declaring health a fundamental human right and on the Health for All agenda set by the Alma-Ata declaration in 1978.

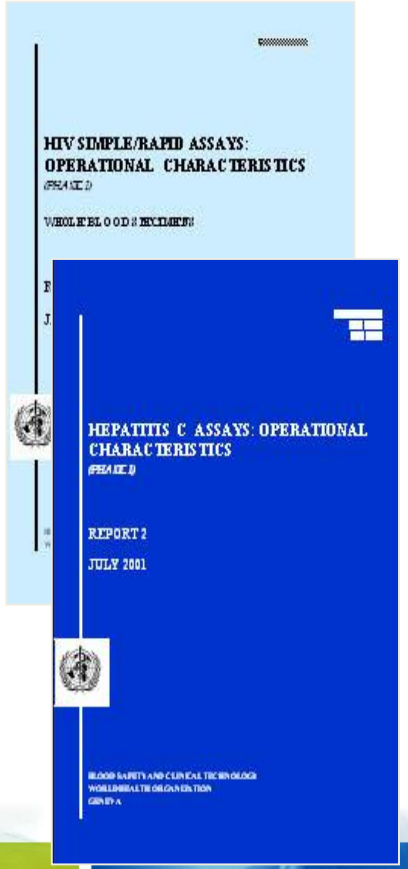
For a community or country to achieve universal health coverage, several factors must be in place, including:

Access to essential medicines and technologies to diagnose and treat medical problems.

IVDs activities within WHO

WHO has been assessing **IVDs performance and operational characteristics** since 1988

- HIV assays since 1988
- Hepatitis B assays since 2000
- Hepatitis C assays since 2000
- Syphilis assays since 2001
- Chagas assays since 2002
- Malaria assays since 2002
- CD4 technologies ad-hoc in 1996 & 2003



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IVDs global market trends

Outsourcing of production - moved to countries with less stringent diagnostics regulation

Re-branding of test kits (OEM) - same name but different production site, different quality standards

Easy to operate tests/methods facilitate near patient testing, hard-to-reach populations, non-lab environments

Increased availability of **funds for IVDs and laboratories**

WHO's response

Shift from test kit evaluations to **prequalification of IVDs**:

More **stringent** approach

Alignment with global standards for assuring quality of diagnostics

Through a rigorous process identify diagnostics that meet the quality standards

PQDx: aim, scope and impact

- The aim of PQDx is to promote and facilitate access to safe, appropriate and affordable IVDs of good quality
- Focus is placed on IVDs for priority diseases and their suitability for use in resource-limited settings
  - HIV, malaria, Hepatitis C and B, HCV, G6PD
- The findings of PQDx are used to provide independent technical information on safety, quality and performance of IVDs, principally to other UN agencies but also to WHO Member States and other interested organizations

The PQDx status, in conjunction with other procurement criteria, is used by UN agencies, WHO Member States and other interested organizations to guide their procurement of IVDs

PQDx components

PQDx undertakes a comprehensive assessment of individual IVDs through a standardized procedure aimed at determining if the product meets WHO prequalification requirements.

The prequalification assessment process includes three components:

- Review of a product dossier;
- Performance evaluation including operational characteristics; and
- Manufacturing site(s) inspection.

Reference documents

PQDx is aligned with best international practice for IVDs

- ISO (and EN) standards: QMS, risk mgt, stability, labelling, perf. evaluations, etc.
- GHTF/IMDRF guidance: STED, MDSAP, labelling, EPs, PMS
- CLSI guidance: stability, V&V,
- NRAs: FDA, EU

What does PQ do differently to GHTF/IMDRF

Requirements are based on the same set of standards – PQ is aligned with internationally accepted practice BUT

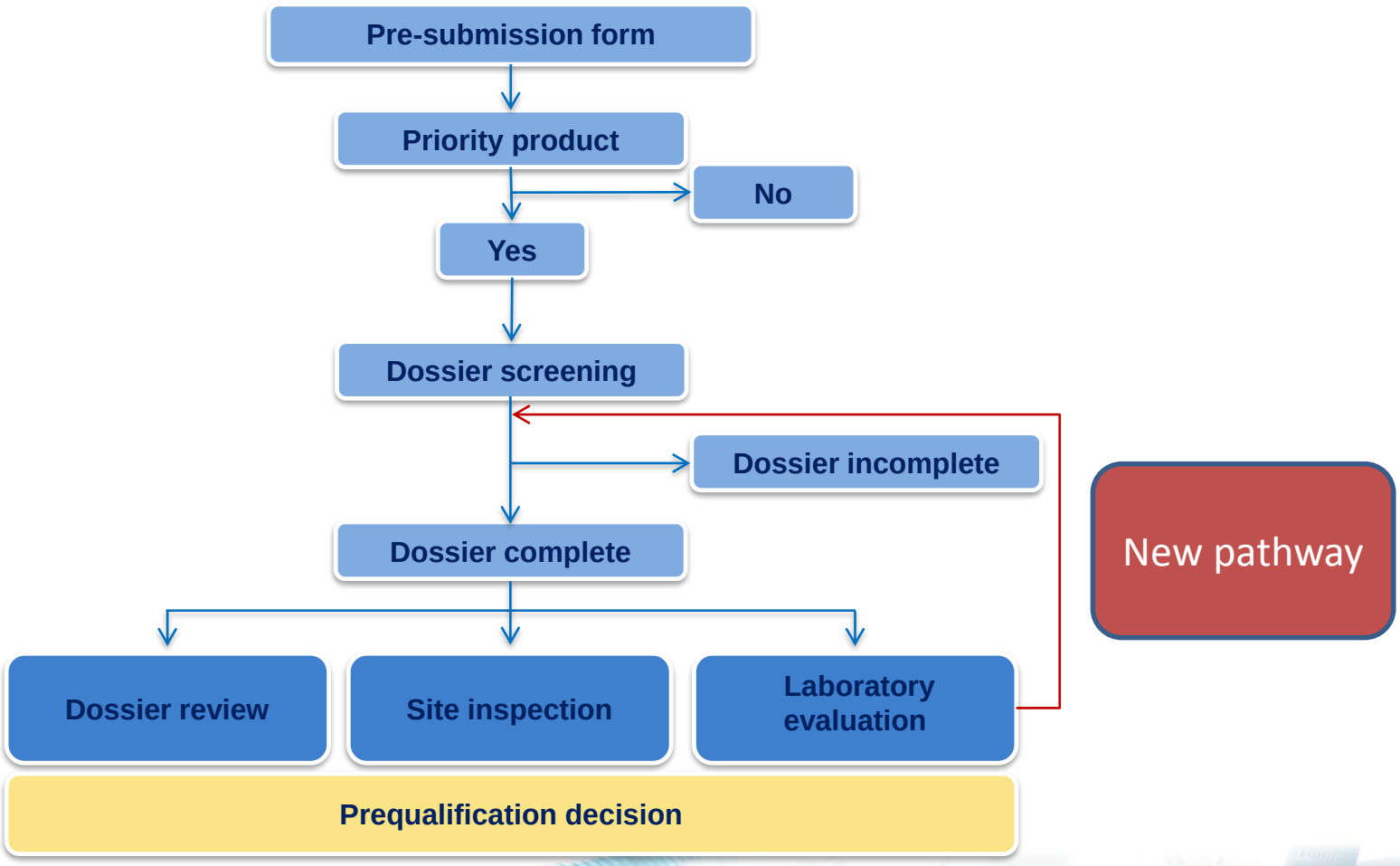
Assess products' regulatory versions intended for the global market

- Where a stringently reviewed versions exist, they are often not supplied to the global market – RoW versions differ from stringently assessed version in Mx site, QC, labelling, key suppliers, composition, intended use etc.

Review aspects of particular relevance for resource-limited settings

- Risk assessment, stability, flex studies, labelling, training and support network
- Take into account environment and user skills

WHO prequalification: Full assessment



WHO Prequalification: Abbreviated assessment Categories of products submitted to PQ

Scenario 1

Version submitted for PQ has been stringently assessed

Scenario 2

Version submitted for PQ has not been stringently assessed but a regulatory version exists that has been

Scenario 3

Version submitted to PQ has not been stringently assessed

Where stringent assessment has been conducted by founding member of GHTF

Determining eligibility for abbreviated assessment

- Submission and review of WHO pre-submission form
- Evidence of **prior** regulatory review of the product or a similar product manufactured by the same manufacturer
- Products will not be eligible for abbreviated assessment based on anticipated stringent regulatory review
  - ✓ Contact WHO to discuss before submitting pre-submission form

Scenario 1

If the regulatory version submitted for WHO PQ **has** undergone prior stringent regulatory review by a founding member of the GHTF

✓ Stringent regulatory review recognized as:

- CE; List A, Annex II
- FDA; PMA or BLA
- Health Canada; Class IV
- TGA; Class 4
- Japan; Minister's approval

Scenario 1

An abbreviated PQ assessment procedure will be followed:

1. No dossier requested by WHO
2. Abbreviated WHO site inspection
   - Information package requested to prepare for the inspection, including receipt of previous satisfactory audit report;
   - Shorter duration, fewer inspectors; to verify WHO customer requirements;
   - 1 inspector, 1 technical expert.
3. WHO laboratory evaluation of performance and operational characteristics to inform product selection

Scenario 2

If the regulatory version submitted for WHO PQ is the rest of world regulatory version but the manufacturer has a "similar" product that has undergone prior stringent regulatory review

✓ Stringent regulatory review is recognized as:

- CE (List A, annex II), FDA (PMA or BLA), Health Canada (Class IV), TGA (Class 4), Japan (Minister's approval)

Scenario 2

Procedure to be followed:

1. WHO pre-submission form reviewed

✓ Comparison of key differences between stringent regulatory version and ROW regulatory versions is made:

- Product description, intended use, test procedure, design, manufacturing site, key suppliers, labelling, instructions of use, quality management system, verification/validation studies, lot release criteria

✓ If substantial differences, usual PQ assessment procedure is followed (no abbreviated assessment)

✓ If no substantial differences, abbreviated PQ assessment procedure is followed

Scenario 2a

- If substantial differences between regulatory versions

  Usual PQ assessment

1. Dossier requested and reviewed by WHO
2. Site inspection
3. WHO laboratory evaluation of performance and operational characteristics to inform product selection

Scenario 2b

No substantial difference between regulatory versions

- Abbreviated PQ assessment

1. No dossier requested by WHO
2. Abbreviated WHO site inspection
   - Information package requested to prepare for the inspection, including receipt of previous satisfactory audit report;
   - Shorter duration, fewer inspectors; to verify WHO customer requirements;
   - 1 inspector, 1 technical expert.
3. WHO laboratory evaluation of performance and operational characteristics to inform product selection

Scenario 3

- ✓ Where no stringently assessed regulatory version exists
- ✓ Any regulatory review other than the following:
  - CE; List A, Annex 2
  - FDA; PMA or BLA
  - Health Canada; Class IV
  - TGA; Class 4
  - Japan; Minister's approval

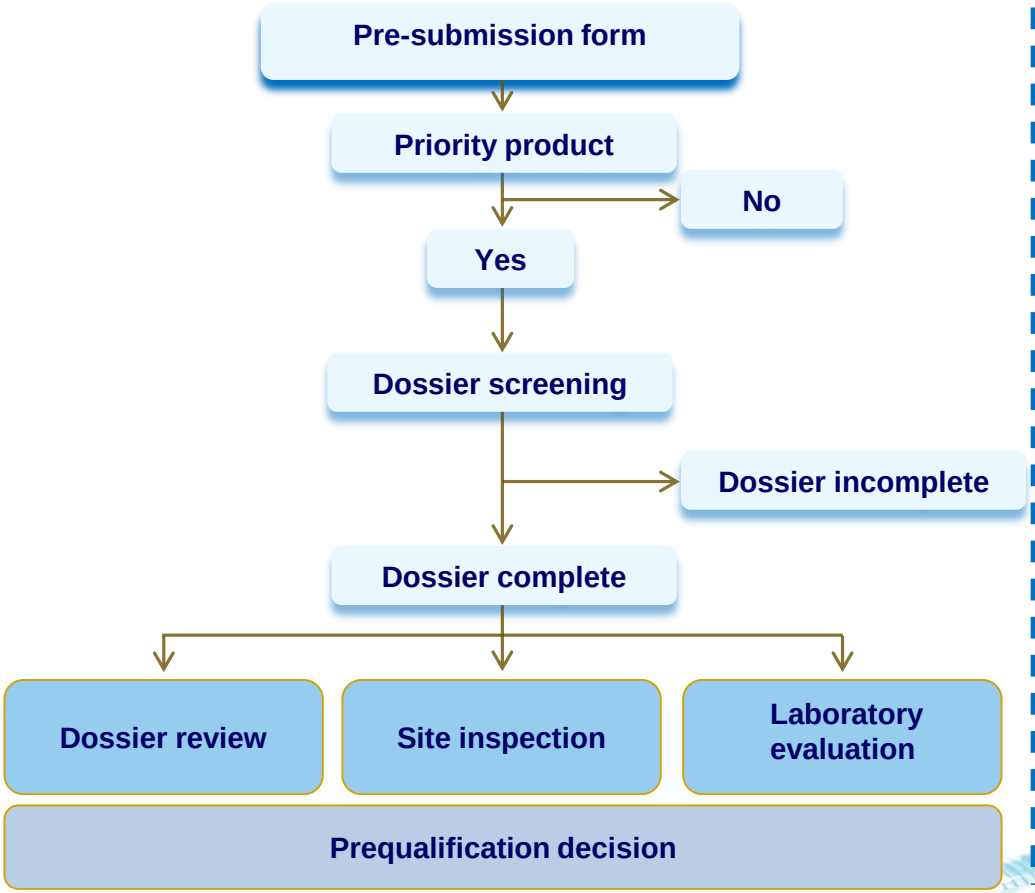
Scenario 3

- ✓ Usual PQ assessment procedure will be followed:

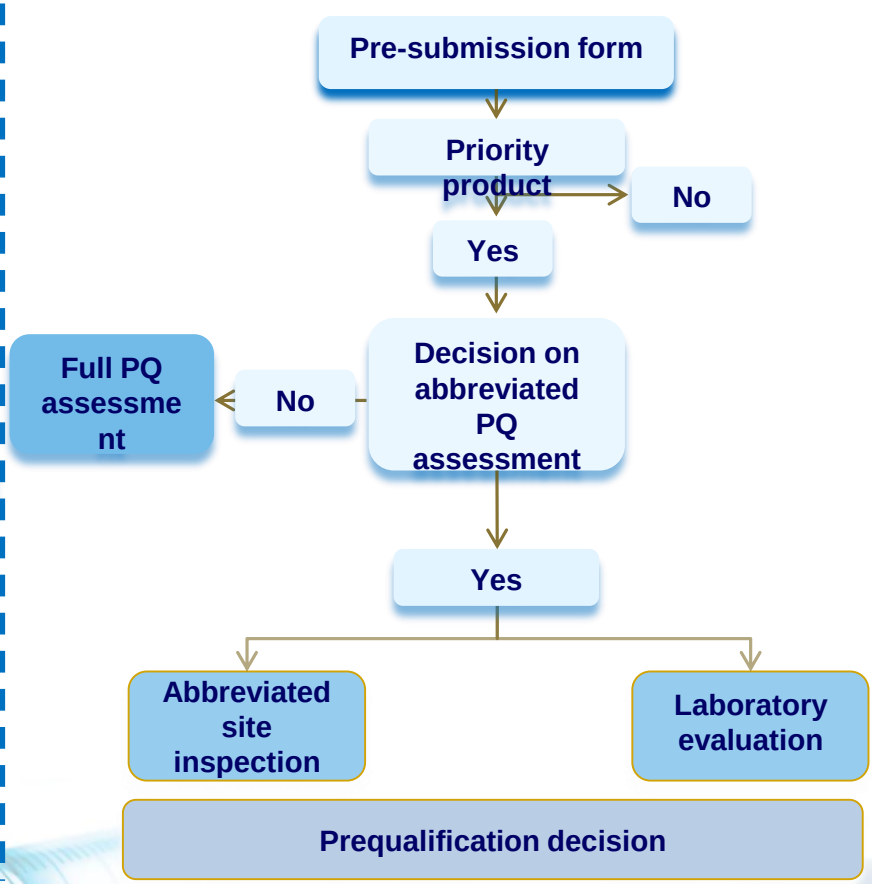
1. Dossier requested and reviewed by WHO
2. Site inspection
3. WHO laboratory evaluation of performance and operational characteristics to inform product selection

Prequalification of IVDs Programme

Full prequalification assessment



Abbreviated prequalification assessment



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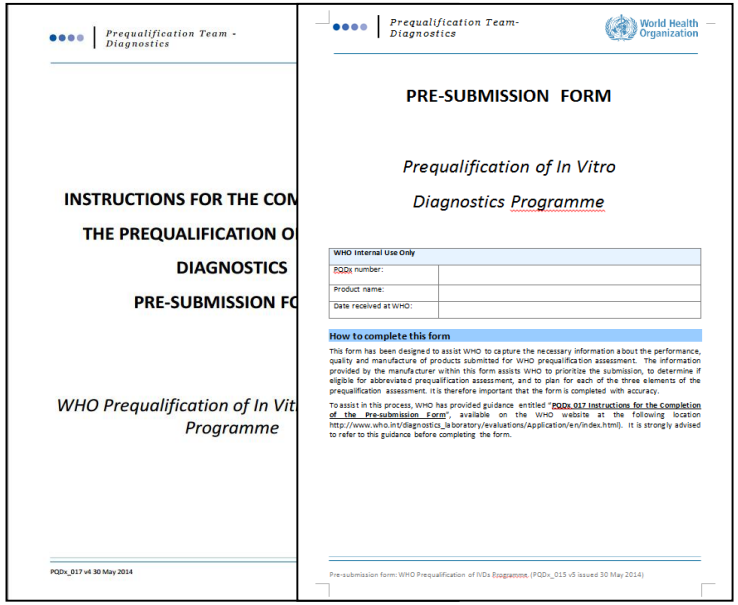
PQDx Product application

The Application Process

- Manufacturers can apply at any time
- Read the WHO PQDx_007 “Overview of the Prequalification of In Vitro Diagnostics”
- Complete the Pre-Submission Form (WHO PQDx_015), using the following guidance:

  WHO PQDx_017 “Instructions for the Completion of the Prequalification of In Vitro Diagnostics Pre-submission Form.”



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Programme

PQDx_017 v4 30 May 2014

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PRE-SUBMISSION FORM

Prequalification of In Vitro
Diagnostics Programme

WHO Internal Use Only	
PQDx number:	
Product name:	
Date received at WHO:	

How to complete this form

This form has been designed to assist WHO to capture the necessary information about the performance, quality and manufacture of products submitted for WHO prequalification assessment. The information provided by the manufacturer within this form assists WHO to prioritize the submission, to determine if eligible for abbreviated prequalification assessment, and to plan for each of the three elements of the prequalification assessment. It is therefore important that the form is completed with accuracy.

To assist in this process, WHO has provided guidance entitled "PQDx 017 Instructions for the Completion of the Pre-submission Form", available on the WHO website at the following location http://www.who.int/diagnostics_laboratory/evaluations/Application/en/index.html). It is strongly advised to refer to this guidance before completing the form.

Pre-submission form: WHO Prequalification of IVDs Programme (PQDx_015 v5 issued 30 May 2014)

The Pre-Submission Form

- Used to determine whether the application will be prioritized based on
  - Prioritization criteria
  - Programmatic suitability
- Used to determine whether the product is made by the original manufacturer (not rebranded)
- Used to determine the regulatory version of the device

Prioritization Criteria

Criteria	Rationale
Listed on the WHO procurement scheme and procured by UN organizations in significant levels	Ensure continuity of supply and quality of products procured
Assist in the diagnosis and/or monitoring of infection with HIV-1/HIV-2, the diagnosis and/or monitoring of infection with hepatitis C, and diagnosis of infection with malaria parasites, and diagnosis of infection with Human Papillomavirus for cervical cancer prevention	Focus on priority disease areas
Rapid test format and/or technologies that can be used at or near to point-of-care (POC)	Bringing testing closer to the community
Original product manufacturers	Ensure known supply chain; no duplication of effort, best possible prices
Few other prequalified products exist in the product category such as CD4, VL	Focus on unmet market / procurement needs
Adult Male Circumcision Devices	Focus on the needs of WHO disease programmes

Other criteria dependent on changing global health needs, the particular needs of WHO Member States, and the emergence of new and relevant diagnostic technologies.

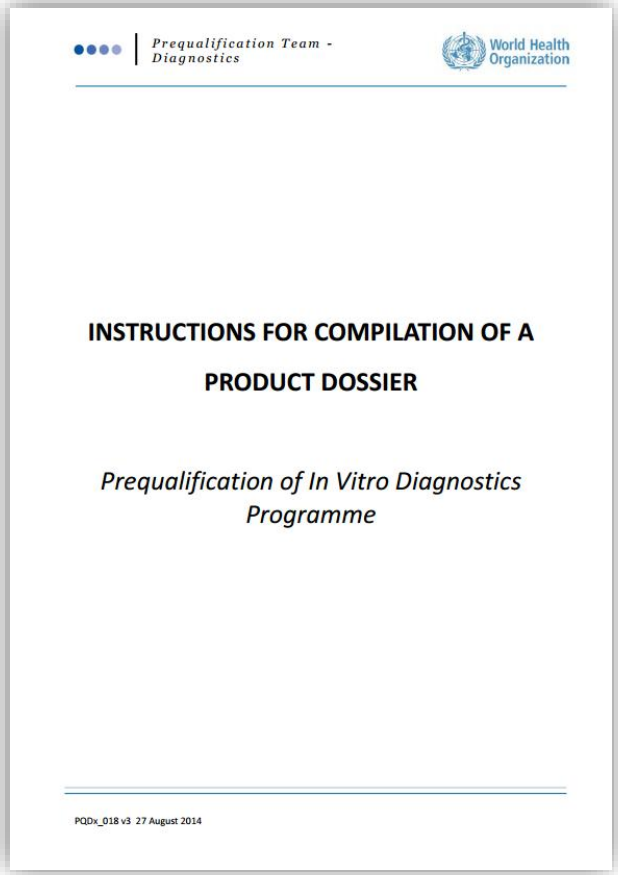
Outcome of application process

- WHO will send a letter informing of the outcome of the prioritisation process
- The letter will provide further instruction for those applications that are prioritised
  - First payment
  - Whether the application will be eligible for an abbreviated assessment
  - If for a full assessment, how and when to submit the product dossier

Dossier

Product Dossier Requirements

- Based on best international practice (ISO, EN, GHTF, IMDRF, CLSI…)
- Follows the content of the IMDRF MA IVD ToC (http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-140630-rps-ivd-toc.pdf)
- Dossier must demonstrate that the IVD conforms to the Essential Principles of Safety and Performance of Medical Devices (GHTF/SG1/N41R9:2005)
- Looks into critical aspects for WHO Member States often not dealt with from a local perspective by SRAs
  - stability, risk assessment, instructions for use, etc.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INSTRUCTIONS FOR COMPILATION OF A PRODUCT DOSSIER

Prequalification of In Vitro Diagnostics Programme

PQDx_018 v3 27 August 2014

Recurrent Issues - Dossier Screening Process

- Layout and format
- No clear identification of the product being submitted to PQ in the dossier documentation and reports
- Photos of the kits components are unclear/missing
- Some sections are not documented (e.g. design changes)
- Full study reports not submitted or too summarised
- Information on training and support network not available for countries where the assay is supplied
- Certificates requested are not certified
- No inspection reports submitted

Manufacturing site(s) Inspections

Requirements for Inspections

- Fully implemented quality management system (design & development, manufacturing including quality control, storage, distribution)
- Risk management to meet ISO 14971:2007
- Product stable to meet "harsh" conditions (hot, wet, dry, dusty)
- Products undergoing prequalification have to be in routine manufacturing
- Sufficient capacity to ensure reliable delivery

Quality Management System

Fully implemented quality management system (design & development, manufacturing including quality control, storage, distribution)

- Meets ISO 13485:2003 requirements (note: user requirements in areas of interest)
- Competence of personnel
- Work environment (determined and established)
- Quality control processes follow risk management results, quality control plan established, performance tested according to claims in instruction for use
- Storage conditions, temperature and humidity, validated for intermediates, components and kit, real time data required

Performance evaluation

Performance evaluation process

Preparation

- Successful dossier screening
- Identification WHO collaborating Centers
- Protocol is sent to the WCC and the manufacturer
- Ethical approval by the WCC
- Delivery of kits to the WCC

Testing

- WHO verify the Instruction for Use
- Manufacturer demonstration at the WCC
- Testing using approved protocol and manufacturer
- Draft lab evaluation report sent to WHO

Report

- WHO review the submitted draft report and submit to the manufacturer
- Mx submit comments to WHO within 30 days
- WHO send the final report to the Mx

Performance evaluation

- **Limited assessment of the clinical performance claims**

✓ Initial sensitivity and specificity (HIV, HBV, HCV, Syphilis)

✓ Accuracy: trueness and and precision (CD4 and HIV viral load)

✓ Operational characteristics: inter-reader variability and invalid rates (RDT)

- **Intended settings low and middle income countries (appropriate plasma panels)**

Specimen panels used

Assays	HIV serology	HIV serology (oral fluid)	Combined HIV/Syphilis serology	CD4 technologies	HIV viral load/EID
Specimen type	Plasma or serum	Linked plasma/serum and oral fluid	Plasma or serum	Whole blood	Plasma/Dried blood spots
Study type	Retrospective	Prospective clinic settings	Retrospective	Prospective clinic settings	Retrospective/ Prospective
Panels type	Characterized panels	Consecutive plasma + OF fresh exudates	Characterized panels	Consecutive fresh whole blood	Characterized panels **HIV subtypes**
Regional distribution	African, Asia, American, European	African, Asia, American, European	African, Asia, American, European	At least two regions	African, Asia, American, European

Seek ethical clearance for conducting the studies

Other Performance evaluation

- **HIV:**
  - Seroconversion sensitivity
  - Lot-lot variation
  - Mixed titre
  - WHO reference panel
  - p24 panel

Pass/Fail performance criteria

Assay	Initial sensitivity	Final specificity	Inter-reader viability	Invalid rates	Trueness	Precision	Others
Anti-HIV EIA, p24	100%	≥ 98%	≤5%	≤5%	N/A	N/A	
Anti-HIV RDTs p24	≥ 99%	≥ 98%	≤5%	≤5%	N/A	N/A	
anti-HCV EIA	100%	≥ 98%	≤5%	≤5%	N/A	N/A	
Anti-HCV RDTs	≥ 98%	≥ 97%	≤5%	≤5%	N/A	N/A	
HBsAg EIA, RDT	100%	≥ 98%	≤5%	≤5%	N/A	N/A	LoD
Anti trep	>85%	≥ 98%	≤5%	≤5%	N/A	N/A	
CD4	N/A	N/A	N/A	N/A	Bias <10%	CV<10%	

Prequalification: decision

- Final prequalification outcome depends on:
  - Results of dossier assessment and acceptance of action plan
  - Results of inspection(s) and acceptance of action plan
  - No level 5 nonconformities outstanding for either dossier or for inspection
  - Meeting the acceptance criteria for the laboratory evaluation
- WHO PQDx Public Report is posted on WHO website and product is added to the list of WHO prequalified products
- Product is then eligible for WHO and UN procurement

Contact us

Contact us by email

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Sign up to our mailing list

By emailing diagnostics@who.int

Check our website

http://www.who.int/diagnostics_laboratory/evaluations/en/

Спасибо!

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