World Health Organization

WHO Prequalification of In Vitro Diagnostics & Male Circumcision Devices

23rd AHWP Annual Meeting 22 – 25 October 2018

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The Prequalification Team

The prequalification team is responsible for the quality-assurance of IVDs, MCDs, FPPs, APIs, QCLs, vaccines, immunization devices, VCPs and VCIs

Diagnostics (Dx) assessment of in vitro diagnostics (**IVD**) & male circumcision devices (**MCD**)

Medicines (Mx) assessment of finished pharmaceutical products (**FPP**) & active pharmaceutical ingredients (**API**)

Vaccines (Vx) assessment of vaccines & immunization devices (**ImD**)

Vector control (VCx) assessment of vector control products (**VCP**) & vector control ingredients (**VCI**)

Inspections
of manufacturing sites

Laboratory evaluation & testing
of Dx, Mx & Vx

&

Laboratory prequalification
of Mx quality control laboratories (QCLs)

Technical assistance
to manufacturers, NRAs and other stakeholders

Facilitation of National regulatory approval
for Dx, Mx & Vx

PQ: aim, scope and impact

- The aim of PQ 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**
- The findings of PQ generate **independent** technical information on **safety, quality and performance** of IVDs and MCDs, principally used by other UN agencies, WHO Member States and other interested organizations
- The PQ 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 and MCDs**

HIV

Malaria

Hepatitis C

Hepatitis B

HPV

G6PD

Cholera

Syphilis*

*As of January 2019

Male circumcision devices

What does PQ do differently to national regulators?

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

BUT

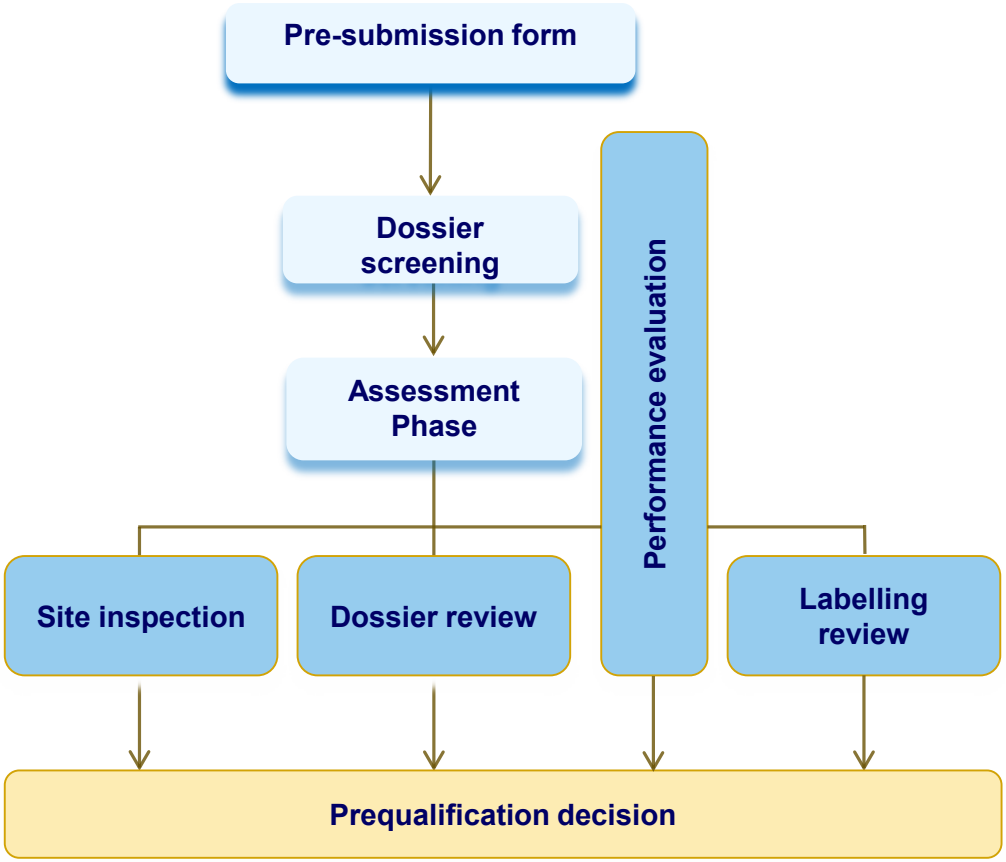
PQ review is of aspects of particular relevance for resource-limited settings.

PQ References
International Organization for Standardization (ISO)
Global Harmonization Task Force (GHTF)
International Medical Device Regulators Forum (IMDRF) - replaced GHTF
Clinical and Laboratory Standards Institute (CLSI)

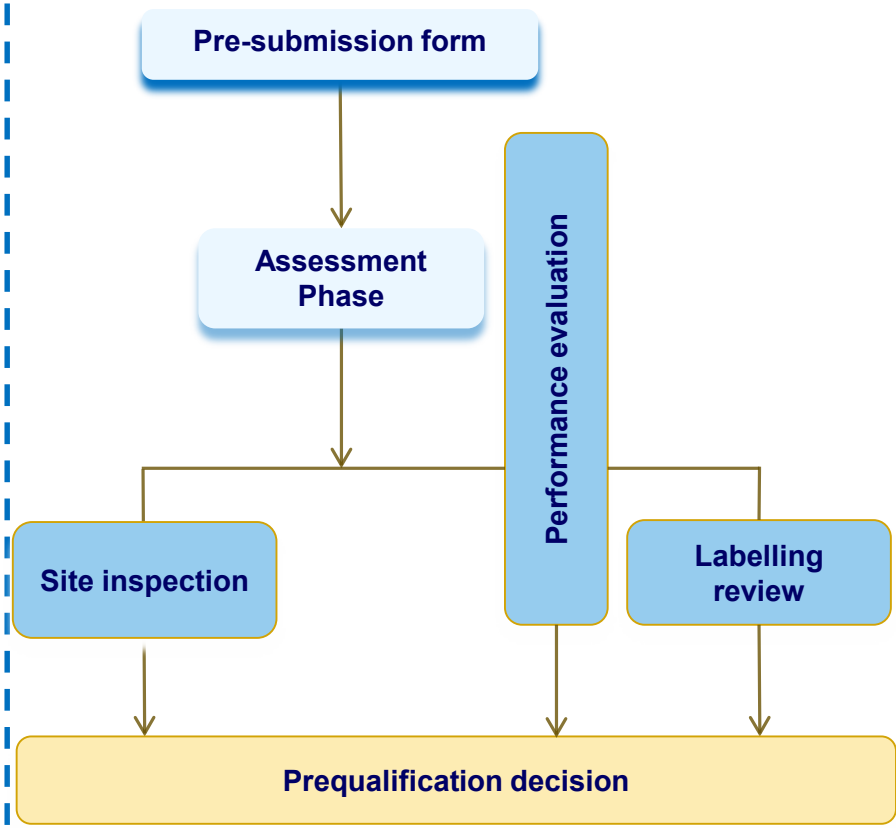
WHO Prequalification of IVDs

World Health Organization

Full prequalification assessment



Abridged prequalification assessment



Post PQ Activities: commitments to PQ, re-inspection, post market surveillance, changes, annual reporting

Purpose of the dossier – unique PQ characteristics

- Purpose: Demonstrate that the manufacturer has considered the quality, safety and performance of its product in the countries where WHO PQ products are procured
- Programmatic suitability: specific emphasis on issues of particular relevance to resource-limited settings, such as:
  - Stability of products (e.g. heat and humidity)
  - Suitable specimen type
  - Labelling of products
  - Ease of use (e.g. training and material)
  - Performance evaluated in the global population
  - Life cycle management of products

Product Dossier contents

Take into account the intended use, testing population, user, and setting of use

Key Components
Product description
Design and manufacturing information
Product performance specifications & associated validation and verification studies
Labelling
Commercial history
Regulatory history
Quality management system

Requirements for Manufacturing site inspection

- Fully implemented quality management system (design & development, manufacturing including quality control, storage, distribution) as per ISO 13485
- Risk management to meet ISO 14971, taking into consideration its **intended user and intended use setting**
- Products undergoing prequalification have to be in routine manufacturing
- Sufficient capacity to ensure reliable delivery

Key Components
Quality management system including documentation requirements
Management responsibility including customer focus, quality policy
Resource management including human resources, work environment
Product realization including production and service provision, control of monitoring and measuring devices
Measurement, analysis and improvement including control of nonconforming product, improvement

Performance evaluation

- Independent **verification** of the **performance** characteristics of IVDs submitted for prequalification assessment
- Evaluation of **operational characteristics** with a focus on needs of resource-limited settings
- Assays are challenged with a **focus on their use in resource-limited settings** and in the context of WHO guidelines (SRA review has different priorities based on local populations and product use)
- Wherever possible, panels are representative of a **global population**
- The dataset obtained **complements the verification and validation data** submitted by the manufacturer in the product dossier and finding in the Site inspection
- Currently takes place in a WHO Prequalification Evaluating Laboratory

Performance evaluation pathways

Option 1: Performance evaluation coordinated by WHO

The performance evaluation will be scheduled by WHO as soon as the product is designated as meeting WHO prioritization criteria

Option 2: Alternative Performance Evaluation Mechanism

The manufacturer selects a laboratory from the list of WHO Prequalification Evaluating Laboratories

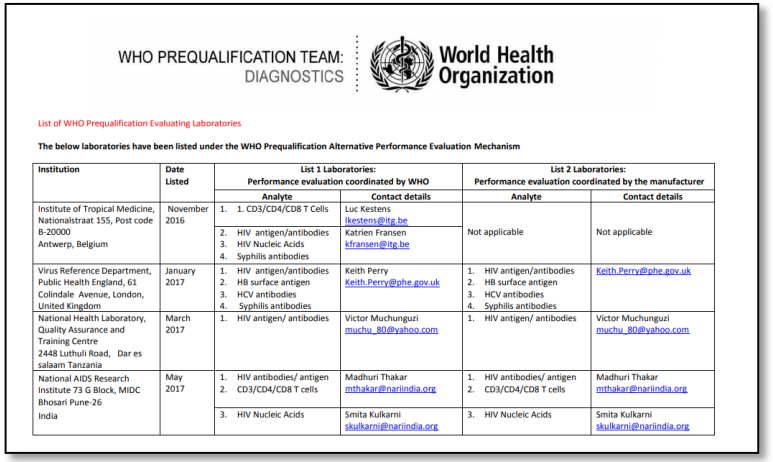
The manufacturer will bear the cost of the evaluation and be responsible for coordinating it directly with the laboratory

WHO Prequalification Evaluating laboratories

WHO audits laboratories against predefined requirements based on ISO 15189 and ISO 17025

2 lists of laboratories:

- **List 1** - laboratories working with WHO and participate in Option 1
- **List 2** – laboratories working directly with manufacturers and participate in Option 2
- Laboratories may choose to be listed under both lists



WHO PREQUALIFICATION TEAM: DIAGNOSTICS

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List of WHO Prequalification Evaluating Laboratories

The below laboratories have been listed under the WHO Prequalification Alternative Performance Evaluation Mechanism

Institution	Date Listed	List 1 Laboratories: Performance evaluation coordinated by WHO		List 2 Laboratories: Performance evaluation coordinated by the manufacturer	
		Analyte	Contact details	Analyte	Contact details
Institute of Tropical Medicine, Nationalstraat 155, Post code B-20000 Antwerp, Belgium	November 2016	1. 1. CD3/CD4/CD8 T Cells 2. HIV antigen/antibodies 3. HIV Nucleic Acids 4. Syphilis antibodies	Luc Kestens lkestens@itg.be Katrien Fransen kfransen@itg.be	Not applicable	Not applicable
Virus Reference Department, Public Health England, 61 Colindale Avenue, London, United Kingdom	January 2017	1. HIV antigen/antibodies 2. HB surface antigen 3. HCV antibodies 4. Syphilis antibodies	Keith Perry Keith.Perry@phe.gov.uk	1. HIV antigen/antibodies 2. HB surface antigen 3. HCV antibodies 4. Syphilis antibodies	Keith.Perry@phe.gov.uk
National Health Laboratory, Quality Assurance and Training Centre 2448 Luthuli Road, Dar es salaam Tanzania	March 2017	1. HIV antigen/ antibodies	Victor Muchunguzi muchu_80@yahoo.com	1. HIV antigen/ antibodies	Victor Muchunguzi muchu_80@yahoo.com
National AIDS Research Institute 73 G Block, MIDC Bhosari Pune-26 India	May 2017	1. HIV antibodies/ antigen 2. CD3/CD4/CD8 T cells	Madhuri Thakar mthakar@nariindia.org	1. HIV antibodies/ antigen 2. CD3/CD4/CD8 T cells	Madhuri Thakar mthakar@nariindia.org
		3. HIV Nucleic Acids	Smita Kulkarni skulkarni@nariindia.org	3. HIV Nucleic Acids	Smita Kulkarni skulkarni@nariindia.org

Any laboratories interested in becoming a WHO PQ Evaluating Laboratory may submit an Expression of Interest at any time. Information available at: http://www.who.int/diagnostics_laboratory/evaluations/alternative/en/

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
  - Meeting the acceptance criteria for the laboratory evaluation
- WHO PQ 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

IVDs prequalified

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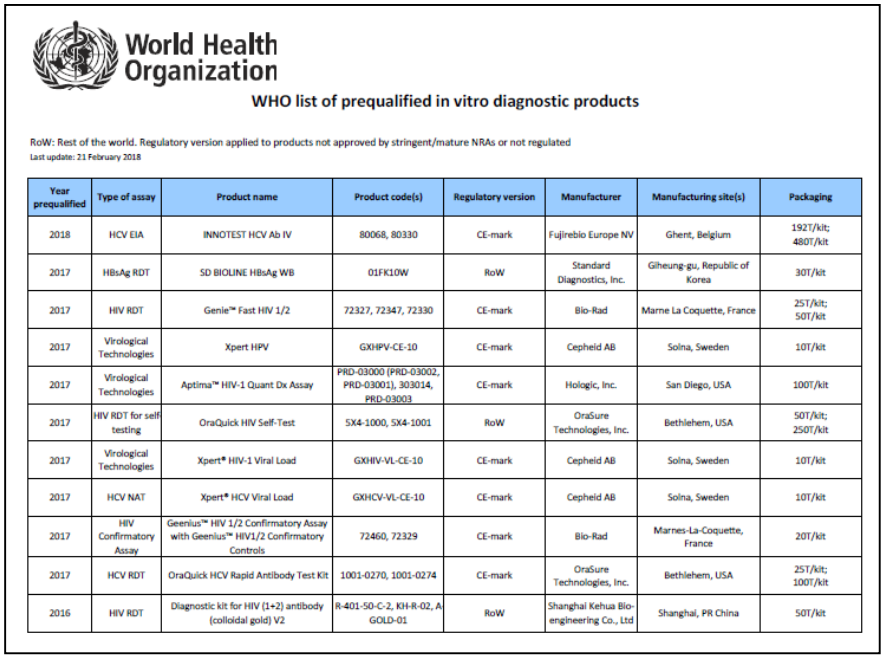
75 IVDs listed as of October 2018

New IVDs in 2018:

- CyFlow® Counter System with CD4 easy count kit and CD4% easy count kit
- Vikia HBsAg
- careHPV Test
- Muse Auto CD4/CD4% kit
- INNOTEST HCV Ab IV
- OraQuick HIV Self-Test
- Xpert® HCV Viral Load
- Xpert HPV



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WHO list of prequalified in vitro diagnostic products

RoW: Rest of the world. Regulatory version applied to products not approved by stringent/mature NRAs or not regulated

Last update: 21 February 2018

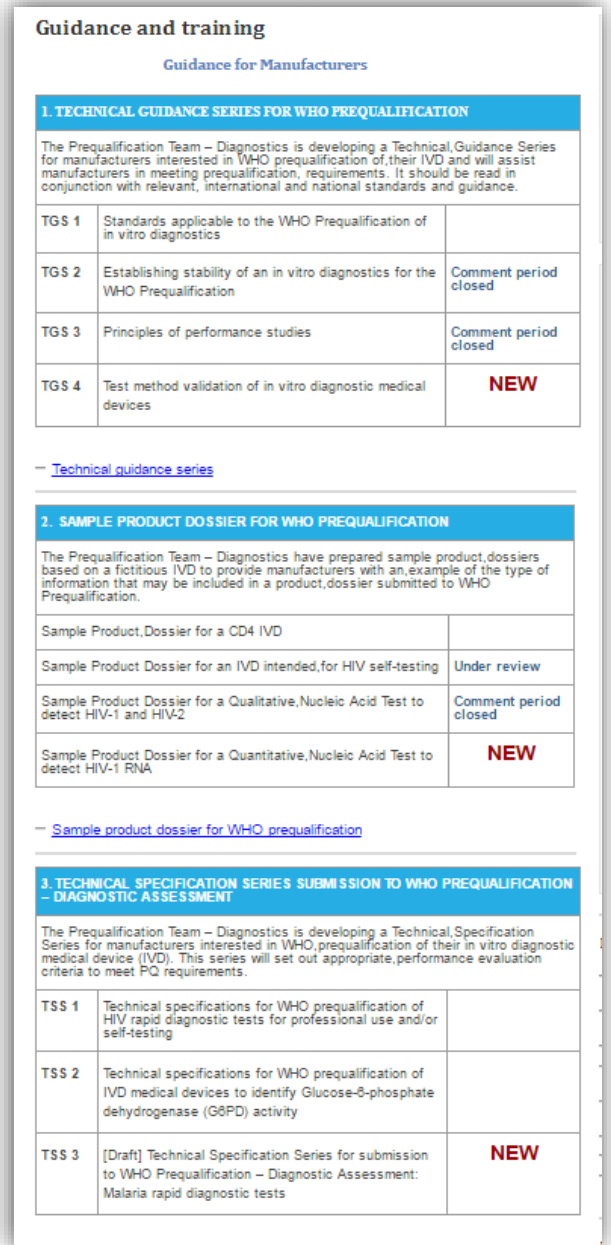
Year prequalified	Type of assay	Product name	Product code(s)	Regulatory version	Manufacturer	Manufacturing site(s)	Packaging
2018	HCV EIA	INNOTEST HCV Ab IV	80068, 80330	CE-mark	Fujirebio Europe NV	Ghent, Belgium	192T/kit; 480T/kit
2017	HBsAg RDT	SD BIOLINE HBsAg WB	01FK10W	RoW	Standard Diagnostics, Inc.	Giheung-gu, Republic of Korea	30T/kit
2017	HIV RDT	Genie™ Fast HIV 1/2	72327, 72347, 72330	CE-mark	Bio-Rad	Marne La Coquette, France	25T/kit; 50T/kit
2017	Virological Technologies	Xpert HPV	GXHPV-CE-10	CE-mark	Cepheid AB	Solna, Sweden	10T/kit
2017	Virological Technologies	Aptima™ HIV-1 Quant Dx Assay	PRD-03000 (PRD-03002, PRD-03001), 303014, PRD-03003	CE-mark	Hologic, Inc.	San Diego, USA	100T/kit
2017	HIV RDT for self testing	OraQuick HIV Self-Test	5X4-1000, 5X4-1001	RoW	OraSure Technologies, Inc.	Bethlehem, USA	50T/kit; 250T/kit
2017	Virological Technologies	Xpert® HIV-1 Viral Load	GXHIV-VL-CE-10	CE-mark	Cepheid AB	Solna, Sweden	10T/kit
2017	HCV NAT	Xpert® HCV Viral Load	GXHCV-VL-CE-10	CE-mark	Cepheid AB	Solna, Sweden	10T/kit
2017	HIV Confirmatory Assay	Geenius™ HIV 1/2 Confirmatory Assay with Geenius™ HIV1/2 Confirmatory Controls	72460, 72329	CE-mark	Bio-Rad	Marnes-La-Coquette, France	20T/kit
2017	HCV RDT	OraQuick HCV Rapid Antibody Test Kit	1001-0270, 1001-0274	CE-mark	OraSure Technologies, Inc.	Bethlehem, USA	25T/kit; 100T/kit
2016	HIV RDT	Diagnostic kit for HIV (1+2) antibody (colloidal gold) V2	R-401-50-C-2, KH-R-02, A GOLD-01	RoW	Shanghai Kehua Bio-engineering Co., Ltd	Shanghai, PR China	50T/kit

Guidance for manufacturers

Increased focus on guidance to manufacturers

- Sample dossiers
- Technical Guidance Series
- Technical Specification Series
- Reportable Changes to Prequalified Products

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



Guidance and training

Guidance for Manufacturers

1. TECHNICAL GUIDANCE SERIES FOR WHO PREQUALIFICATION		
The Prequalification Team – Diagnostics is developing a Technical,Guidance Series for manufacturers interested in WHO prequalification of,their IVD and will assist manufacturers in meeting prequalification, requirements. It should be read in conjunction with relevant, international and national standards and guidance.		
TGS 1	Standards applicable to the WHO Prequalification of in vitro diagnostics	
TGS 2	Establishing stability of an in vitro diagnostics for the WHO Prequalification	Comment period closed
TGS 3	Principles of performance studies	Comment period closed
TGS 4	Test method validation of in vitro diagnostic medical devices	NEW

– Technical guidance series

2. SAMPLE PRODUCT DOSSIER FOR WHO PREQUALIFICATION	
The Prequalification Team – Diagnostics have prepared sample product,dossiers based on a fictitious IVD to provide manufacturers with an,example of the type of information that may be included in a product,dossier submitted to WHO Prequalification.	
Sample Product,Dossier for a CD4 IVD	
Sample Product Dossier for an IVD intended,for HIV self-testing	Under review
Sample Product Dossier for a Qualitative,Nucleic Acid Test to detect HIV-1 and HIV-2	Comment period closed
Sample Product Dossier for a Quantitative,Nucleic Acid Test to detect HIV-1 RNA	NEW

– Sample product dossier for WHO prequalification

3. TECHNICAL SPECIFICATION SERIES SUBMISSION TO WHO PREQUALIFICATION – DIAGNOSTIC ASSESSMENT		
The Prequalification Team – Diagnostics is developing a Technical,Specification Series for manufacturers interested in WHO,prequalification of their in vitro diagnostic medical device (IVD). This series will set out appropriate,performance evaluation criteria to meet PQ requirements.		
TSS 1	Technical specifications for WHO prequalification of HIV rapid diagnostic tests for professional use and/or self-testing	
TSS 2	Technical specifications for WHO prequalification of IVD medical devices to identify Glucose-6-phosphate dehydrogenase (G6PD) activity	
TSS 3	[Draft] Technical Specification Series for submission to WHO Prequalification – Diagnostic Assessment: Malaria rapid diagnostic tests	NEW

Currently published or in draft

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Technical Guidance Series

TGS 1	Standards applicable to the WHO Prequalification of in vitro diagnostics	
TGS 2	Establishing stability of an in vitro diagnostics for the WHO prequalification	
TGS 2 annex	Establishing component stability for an IVD. Case study: single-use-buffer vials for rapid diagnostic tests	
TGS 3	Principles of performance studies	
TGS 4	Test method validation for an in vitro diagnostic medical devices	
TGS 5	Designing Instructions for use for in vitro diagnostic medical devices	
TGS 6	Panels for quality assurance and quality control of in vitro diagnostic medical devices	
TGS 7	Risk management	New

Technical Specifications Series

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	new
TSS 4	In vitro diagnostic medical devices (IVDs) used for the detection of high-risk Human Papillomavirus (HPV) types in cervical cancer screening.	new

Guidance on reporting changes to WHO

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- Increase clarity for manufacturers on what is to be reported
- Provide descriptive generic examples of the changes to be reported
- Overview of how to determine the severity of a change and the WHO change assessment process

+30 changes reviewed in 2018

International harmonization and convergence

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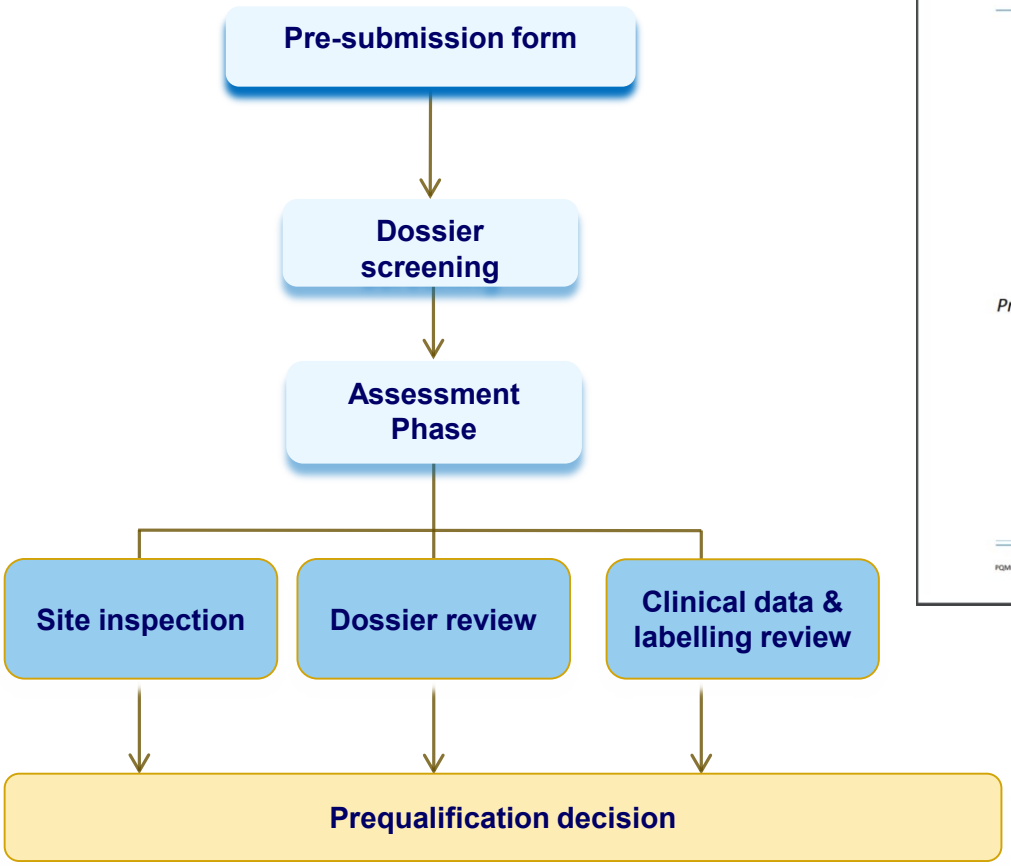
IMDRF-related convergence

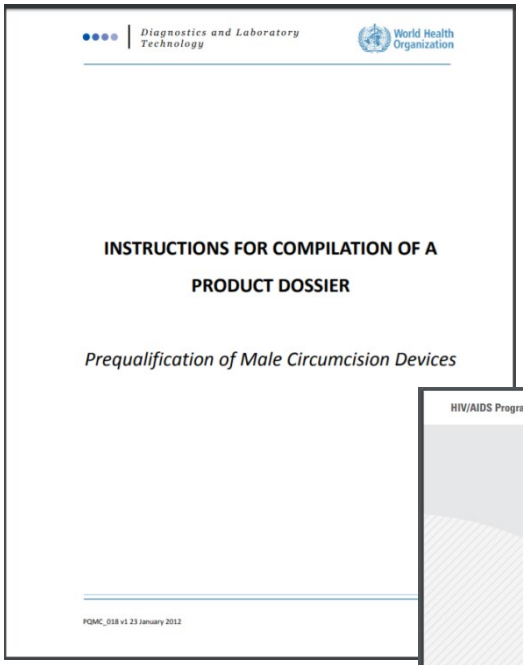
- EPs
- IVD ToC and dossier restructuring
- Report restructuring
- GRRP: new reliance mechanisms

AHWP-related convergence

- IVD Labelling
- IVD Changes

Prequalification of Male circumcision devices





Prequalified
Male circumcision devices

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Prequalified devices:

- ShangRing (2015)
- Prepex (2013)

Changes to MCDs:

- 12 Change requests since 2014

Thank you.

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WHO

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Switzerland