WHO Prequalification of Diagnostics

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Regulation of diagnostics (IVDs)

- Regulation specifically for diagnostics is often poorly understood and/or poorly enforced

- Different categories of IVDs regulated differently
  - HIV IVDs, particularly for blood screening, attract greatest stringency
  - Degree of stringency is usually risk-based
  - Risk perception is different in different settings

- Procurement policies drive supply of quality assured products
  - often acting as de facto regulatory control
## Who sets international standards?

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
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<tbody>
<tr>
<td>International Organization for Standardization (ISO)</td>
<td>Certification of ISO compliance is made by an independent agency.</td>
</tr>
<tr>
<td>Global Harmonization Task Force (GHTF)</td>
<td>Comprised on national regulators &amp; industry. Issues guidance on specific topics related to medical devices including IVDs.</td>
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<tr>
<td>International Medical Device Regulators Forum (IMDRF) - replaced GHTF</td>
<td>Comprised on national regulators. Maintains GHTF guidance documents.</td>
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<tr>
<td>Clinical and Laboratory Standards Institute (CLSI)</td>
<td>Issues guidance documents specific for testing processes.</td>
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Role of WHO

- To provide normative guidance to Member States on when and how to use IVDs to guide clinical decision-making
  - WHO ART guidelines

- To provide recommendations on quality and performance of IVDs through the WHO Prequalification of Diagnostics programme according to international standards

- To increase in-country capacity to effectively regulate & to monitor quality of diagnostics in their market
Aim of WHO Prequalification of Diagnostics

- To promote and facilitate access to safe & appropriate diagnostic technologies of good quality in an equitable manner
  - Through adoption of GHTF guidance and ISO requirements

- Customers
  - WHO Member States
  - UN agencies
  - Funding and procurement agencies
Prequalification of Diagnostics

Application by Manufacturer

Dossier Assessment

Manufacturing Site Inspection

Laboratory Evaluation

Meets Requirements

Product Prequalified

Post Market Surveillance
## Prioritization of PQDx applications

<table>
<thead>
<tr>
<th>Current prioritization criterion</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Already listed on WHO/UN procurement scheme and procured by UN organizations in significant levels</td>
<td>Ensure continuity of supply and quality of products procured</td>
</tr>
<tr>
<td>Assist diagnosis of infection with HIV-1/HIV-2, or malaria</td>
<td>Focus on priority disease areas – highest historical procurement</td>
</tr>
<tr>
<td>Rapid test format</td>
<td>Bringing testing closer to the community</td>
</tr>
<tr>
<td>Original product manufacturers</td>
<td>Ensure known supply chain; no duplication of effort, best possible prices</td>
</tr>
<tr>
<td>Few other prequalified products exist in the product category such as CD4, VL</td>
<td>Focus on unmet market / procurement needs</td>
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Application: requirements

Relevant WHO documents:

1. Prequalification of diagnostics application form

2. Instructions for the completion of the application form

● Common issue
  – Poor information and/or wording in the IFU
  – GHTF/SG1/N43:2005 Labelling for Medical Devices criteria is applied
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Dossier: requirements

- Dossier must demonstrate that the IVD conforms to the Essential Principles of Safety and Performance of Medical Devices (GHTF/SG1/N41R9:2005)

**Key Components**

- Product description
- Design and manufacturing information
- Product performance specifications & associated validation and verification studies
- Labelling
- Commercial history
- Regulatory history
- Quality management system
Dossier: submission

- Read thoroughly the "Instructions for compilation of a product dossier" http://www.who.int/diagnostics_laboratory/evaluations/PQDxInfo/en/index.html

- Ensure clear well-organized with page numbers & the product dossier checklist as an index
  - English language, with certified translations

- Ensure the regulatory version submitted for prequalification is clearly stated
Dossier: submission

Clinical evidence to validate performance claims

- One clinical evaluation* performed by Manufacturer
- One clinical evaluation* performed independently
  - Must clearly relate to the product undergoing prequalification (same name, same product code, same regulatory version)

Performance characteristics

- Clinical (diagnostic sensitivity) including seroconversion sensitivity
- Clinical (diagnostic) specificity
- Positive and negative predictive values (high/low prevalence)
- Different clinical stages
- Geographical distribution (consider intended use setting)
- Genotypic differences

*The EC Common Technical Specifications (CTS) for IVDs 2009 are a useful guide
# Useful ISO references

<table>
<thead>
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<th>Relevant ISO standards</th>
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<tr>
<td>ISO 13485:2003</td>
<td>Medical devices - Quality management systems - Requirements for regulatory purposes</td>
</tr>
<tr>
<td>ISO/TR 10013:2001</td>
<td>Guidelines for quality management system documentation</td>
</tr>
<tr>
<td>ISO 14971:2007</td>
<td>Medical devices - Application of risk management to medical devices</td>
</tr>
<tr>
<td>ISO 17511:2003</td>
<td>In vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values assigned to calibrators and control materials</td>
</tr>
<tr>
<td>ISO 14155:2003 parts I and II</td>
<td>Clinical investigation of medical devices for human subjects</td>
</tr>
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## Useful GHTF references

<table>
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<tr>
<th>Relevant GHTF guidance</th>
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<tbody>
<tr>
<td>GHTF/SG1-N63:2011</td>
<td>Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices</td>
</tr>
<tr>
<td>GHTF/SG1/N41R9:2005</td>
<td>Essential Principles of Safety and Performance of Medical Devices</td>
</tr>
<tr>
<td>GHTF/SG1/N70:2011</td>
<td>Labelling for Medical Devices</td>
</tr>
<tr>
<td>GHTF/SG2-N54R8:2006</td>
<td>Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices</td>
</tr>
<tr>
<td>GHTF/SG2-N57R8:2006</td>
<td>Medical Devices Post Market Surveillance: Content of Field Safety Notices</td>
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## Useful CSLI references

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<tr>
<td>EP07-02</td>
<td>Interfering testing in clinical chemistry, 2nd edition</td>
</tr>
<tr>
<td>EP25-A</td>
<td>Evaluation of Stability of IVDs</td>
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Post Market Surveillance
The manufacturer must demonstrate that the IVD is produced under a functional quality management system e.g. conforms to ISO 13485:2003

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<td><strong>Quality management system</strong></td>
<td>including documentation requirements</td>
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<tr>
<td><strong>Management responsibility</strong></td>
<td>including customer focus, quality policy</td>
</tr>
<tr>
<td><strong>Resource management</strong></td>
<td>including human resources, work environment</td>
</tr>
<tr>
<td><strong>Product realization</strong></td>
<td>including production and service provision, control of monitoring and measuring devices</td>
</tr>
<tr>
<td><strong>Measurement, analysis and improvement</strong></td>
<td>including control of nonconforming product, improvement</td>
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Inspection: requirements

- Dossier submission data – to confirm is true
- QC and lot release
  - QC panels should be challenging enough to detect failure or drift
  - Independence and adequately staffed QA/QC department
  - Deviation reporting procedures observed
- WHO related/end user issues
  - IFU
  - stability (transport, in-use, expiry dates)
  - training
  - complaints reporting mechanisms
Prequalification of Diagnostics

1. Application by Manufacturer
   - Dossier Assessment
     - Manufacturing Site Inspection
     - Laboratory Evaluation
     - Meets Requirements
     - Product Prequalified

2. Post Market Surveillance
Laboratory evaluation

- Ensure two representative production lots are submitted
  - Batch manufacturing records will be verified upon inspection

- Ensure readiness for laboratory evaluation, if dossier assessment and inspection scheduling are underway

- Demonstration of test procedure by manufacturer may precede the commencement of the evaluation
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Post Market Surveillance
Post-market surveillance

- Complaint form for end users to report issues
- GHTF/SG2-N54R8:2006
  - Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices
- GHTF/SG2-N57R8:2006
  - Medical Devices Post Market Surveillance: Content of Field Safety Notices
Contact details for WHO PQDx

- WHO Prequalification of Diagnostics programme website
  http://www.who.int/diagnostics_laboratory/evaluations/en/

- Contact us early, if there is anything that is not clearly understood
  - Via our email address: diagnostics@who.int

- We are available for one-on-one sessions by teleconference or face-to-face meetings
Other WHO mechanisms: TB

- Strategic and Technical Advisory Group for Tuberculosis (STAG-TB)
  - gives technical advice to WHO on proposed recommendations such as endorsement for certain categories of tuberculosis diagnostics

- An Expert Group will meet to assess evidence for adoption or otherwise of a product for an intended use
  - E.g. WHO Expert Group on automated nucleic acid amplification technology for simultaneous and rapid detection of tuberculosis and rifampicin resistance: Xpert MTB/Rif system and WHO Expert Group on commercial serodiagnostic tests for diagnosis of tuberculosis
STAG-TB Recommendations

- The Expert Group reviews performance evaluation data (both published and unpublished) according to the GRADE criteria [http://www.gradeworkinggroup.org/index.htm](http://www.gradeworkinggroup.org/index.htm)

- The meeting report of the Expert Group is presented to the STAG-TB for their consideration

- This approach does not assess the quality management system used to manufacture the diagnostic i.e. no inspection or dossier assessment
  - Has been used for product categories that are currently poorly regulated compared to HIV
WHO endorsement: TB diagnostics

WHO endorsement of Xpert MTB/RIF assay on GenXpert platform for automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance.

Dr. John Doe, collaborated with the University of Medicine and Dentistry of New Jersey and the manufacturer (Cepheid, Sunnyvale, CA) to develop and validate the assay. ND coordinated the analytics studies, clinical validation studies, and field demonstration studies submitted to the Expert Group. Other published and unpublished data was also reviewed.
WHO endorsement: TB diagnostics

WHO evidence synthesis process confirmed a solid evidence base to support widespread use of Xpert MTB- or detection of TB and rifampicin resistance. It is therefore recommended that:

Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of MDR-TB or HIV-associated TB (strong commendation);

Xpert MTB/RIF may be used as a follow-on test to microscopy settings where MDR and/or HIV is of lesser concern, especially in smear-negative specimens (conditional commendation, recognizing major resource implications).
Differences between WHO endorsement and WHO prequalification

The unmet need was fulfilled by the introduction of Xpert MTB/RIF. This allowed for a quicker roll-out and ironing out implementation issues later. High cost has prohibited quicker roll-out, but recent reduced pricing and a more established market is more established with more interested buyers. Numerous RDT manufacturers, fewer POC CD4 and viral load manufacturers.
Differences between WHO endorsement and WHO prequalification

Endorsement relies on review of published literature and clinical trial with no inspection of quality management system.

Prequalification relies on the regulatory approach adopted by the HTF.

Serious issues for HIV and for TB products that are specifically developed for low and middle income countries require ad-hoc/inadequate regulatory review prior to market entry. Which approach? Probably not one size fits all.
You are welcome in Geneva

- Initiate discussions with us early
- Ask questions when unsure of the process or of the requirements
- Contact us by email

diagnostics@who.int