Stakeholder Forum
Stakeholder Session

WHO Regulatory Update

Joey Gouws, Group Lead: Inspections
17 September 2019
Overview

• Background:
  – WHO: Prequalification establishment
• PQT - Dx Assessment
• PQT - Safety
• PQT – Inspections
<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Medicines</th>
<th>Vaccines</th>
<th>Vector Control</th>
</tr>
</thead>
</table>
| **Origin:** Substandard performance of HIV assays in sub-Saharan Africa  
→ **Response:** HIV Test Kit Evaluation Programme (1988)  
**PQ beginning:** 2010 | **Origin:** Request by WHO MS to assess the quality, safety and efficacy of low-cost and new FDCs HIV/AIDS generic medicines  
**PQ beginning:** 2001 | **Origin:** Request by UNICEF and PAHO to evaluate quality, safety and efficacy of vaccines in the context of national immunization programmes  
**PQ beginning:** 1987 | **Origin:** WHOPES set up in 1960 for evaluation of pesticides for public health. In 2015, WHO initiated reforms to foster innovation, improve efficiency, assure quality and align with other PQ programmes  
**PQ beginning:** 2017 |

**WHO responded to the need of procurement agencies and WHO Member States for quality-assured health products, by creating and applying quality-assurance mechanisms**
Prequalification Process

Expression of Interest

Product dossier SMF

Assessment

Additional information and data

Acceptable

Inspections

Corrective actions

Compliance

Prequalification

Maintenance and monitoring
Update on Dx Assessment
Expanding the scope of prequalification

- Consultation conducted in Q4 2018 – Q1 2019: Feedback received from several stakeholders
- New methodology developed for determining priority – reflecting
  - EDL listing
  - WHO guidelines
  - Burden of disease (DALYs *Disability adjusted life years* i.e. heart disease, stroke, neonatal disorders)
  - Priority diseases (Blueprint diseases [i.e. Ebola, Zika, Lassa fever], eradicable diseases and NTDs (*Neglected Tropical Diseases*)
  - Associated health interventions (availability of curative treatment, preventative management and containment strategies).
- WHO to finalize priority ranking and communicate on new eligibility and timelines
- In the meantime HBV VL (*Viral Load*) will be added, expected in Q1 2020
PQ abridged assessment

- Procedure in place since 2014
- Leverages existing stringent reviews
- Undergoing revision
  - To reflect changes in regulations in jurisdictions recognized as performing stringent reviews
  - To explore opportunities to add new jurisdictions recognized as performing stringent reviews
  - To reflect evolving international harmonization initiatives,
    - IMDRF’s Medical Device Single Audit Programme (MDSAP)
  - Amended procedure expected early 2020
2019 Prequalification technical specifications development

Documents developed based on:

• international recognized best practice and standards
• using a consultative process during development to ensure
  – acceptance by manufacturers
  – confirmation on the practicality to implement
2019 Prequalification technical specifications development

- TSS documents planned for consultation and public comment in 2019
  - focus Hepatitis B/C

<table>
<thead>
<tr>
<th>TSS 13</th>
<th>Rapid diagnostic tests to detect hepatitis B surface antigen (HBsAg)</th>
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<tbody>
<tr>
<td>TSS 14</td>
<td>Immunoassays to detect hepatitis B surface antigen (HBsAg)</td>
</tr>
<tr>
<td>TSS 15</td>
<td>In vitro diagnostic (IVDs) medical devices used for the quantitative detection of Hepatitis B nucleic acid</td>
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</tbody>
</table>

- TSS documents planned for 2019/2020

| TSS 16 | In vitro diagnostic (IVDs) medical devices used for the quantitative detection of Haemoglobin |
2019 Prequalification technical specifications development

- Finalized Technical Specification Series (TSS) to be published in 2019

<table>
<thead>
<tr>
<th>TSS</th>
<th>Description</th>
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<tbody>
<tr>
<td>TSS 7</td>
<td>Rapid diagnostic tests to detect hepatitis C antibody or antigen</td>
</tr>
<tr>
<td>TSS 8</td>
<td>Immunoassays to detect HCV antibody and/or antigen</td>
</tr>
<tr>
<td>TSS 9</td>
<td>Immunoassays to detect HIV antibody and/or antigen</td>
</tr>
<tr>
<td>TSS 10</td>
<td>In vitro diagnostic (IVDs) medical devices used for the qualitative and quantitative detection of Hepatitis C RNA</td>
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<tr>
<td>TSS 11</td>
<td>In vitro diagnostic (IVDs) medical devices used for the quantitative detection of HIV-1 nucleic acid</td>
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<tr>
<td>TSS 12</td>
<td>In vitro diagnostic (IVD) medical devices used for the qualitative detection of HIV-1 and HIV-2 nucleic acid</td>
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PQDx IVD product dossiers – ToC format

• To date, WHO PQ applications, product dossiers have been provided and reported using STeD format

• WHO PQ Diagnostic Assessments to implement ToC format for dossiers and review reports:
  
  **Pilot, Q3/4 2019:**
  – as part of the Collaborative Registration Procedure for IVDs, a ToC-format dossier report has been generated and distributed to pilot participants
  – Dossier requirements, and dossier review documents being updated to reflect ToC

  **Transition period, 2020:**
  – Manufacturers requested to provide product dossiers in either STeD or ToC format; dossier reviews to be reported using ToC report templates
  – Training for assessors, and guidance for manufacturers, to be provided

  **Implementation, 2021:**
  – All product dossiers to be submitted in ToC format.
WHO reportable changes to prequalified medical devices

- WHO has published in Q2 2019 the final guidance document on management and classification of changes to a prequalified male circumcision device.  
  https://www.who.int/diagnostics_laboratory/180627_draft_mcd_guidance_for_comments_v01.4.pdf?ua=1

- WHO will launch a call for public comments of the guidance document on management and classification of changes to a prequalified in vitro diagnostic in Q3-Q4 2019.  
  https://apps.who.int/iris/bitstream/handle/10665/251915/WHO-EMP-RHT-PQT-2016.01-eng.pdf;jsessionid=A72C5B2D716245C92299ED653B367AD2?sequence=1
Update on Safety
WHO normative guidance

- Available in three languages
  - Spanish translation likely to be next
- Report templates harmonized with IMDRF and MEDDEV
- WHO offers 2-day workshop on how to engage stakeholder and implement guidance
How WHO will use IMDRF’s adverse event reporting terminology

• WHO will add IMDRF AER terms to ICD-11
  – Taking advantage of ICD’s governance, maintenance and translation functions

• WHO will host F2F meeting of AE reporting WG on 4-7 November 2019
Update on Inspection
Inspection types

• On site inspections
• Desk reviews
  – MDSAP inspection reports
    • Challenge limited due to delay in receiving reports
  – Stage 1 inspection – documents received from the manufacturer
On site Inspections

August 2018 – August 2019
• 21 IVD inspections completed
• 1 Male circumcision device (MCD)
  – Number of products reviewed = total 45 products

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<thead>
<tr>
<th></th>
<th>HIV</th>
<th>HCV</th>
<th>Malaria</th>
<th>HBsAg</th>
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<tbody>
<tr>
<td>Rapid</td>
<td>23</td>
<td>3</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>NAT (nucleic acid test)</td>
<td>6</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>EIA (enzyme immunoassay)</td>
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<td>3</td>
<td></td>
<td></td>
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<tr>
<td>Combo</td>
<td>1</td>
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Countries visited

- Ireland
- Belgium
- South Africa
- USA
- Japan
- India
- Italy
- South Korea
- UK
- China
- Thailand
- Malaysia

# manufacturers
Types of Non-conformities identified

• **Level 5**
  – Data integrity:
    • falsification of batch manufacturing records (BMR)
    • Falsification of QC testing results

• **Level 4**
  – Planning of product realization
    • Risks throughout product realization were not always documented (full life cycle of the product)
    • Lack of verification and validation activities specific to the product and product requirements
Prequalification technical guidance specifications series

• TGS 6 - Panels for quality assurance and quality control of in vitro diagnostic medical devices:
  – Purpose:
    • to provide IVD manufacturers with guidance on possible approaches in preparing validation panels for quality assurance (QA) and quality control (QC).
    • describes the WHO Prequalification expectations in terms of the QA and QC information provided for prequalification assessment.
TGS 7 - Risk management for manufacturers of in vitro diagnostic medical devices:

- Purpose:
  - to aid IVD manufacturers to develop appropriate risk management within their quality management system prior to:
    - compiling a product dossier for submission to WHO
    - in preparation for the site inspection.
Prequalification technical guidance specifications series

• TGS 8 - Quality control for in vitro diagnostic medical devices for WHO prequalification:
  – Purpose:
    • to aid IVD manufacturers in the development of Quality Control criteria focusing on:
      – identifying whether or not quality requirements for the product are being met
      – Identifying defects in the products that are produced.