Streamlining WHO Prequalification of Diagnostics

Dossier Assessment

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Primary Activities: Dossier Assessment Team

- Manage applications to PQDx
  - Review the pre-submission form
  - Provide review to support PQ prioritization decision
  - Communications with manufacturers regarding decisions for PQ and requesting documentation
  - Dossier screening
  - Coordination of dossier assessment
  - Review of dossier assessment and grading

- Preparation of guidance for manufacturers

- Clearly define screening, assessment and post-assessment phase
Previous Process: Dossier Screening
Streamlined Process: Dossier Screening

Application prioritized
- Fees paid
- Dossier requested

Dossier submitted
- Dossier screened
- Supplements requested

Round 1 supplements submitted
- Rd 1 supplements screened
- Supplements submitted

Round 2 supplements received
- Rd 2 supplements screened
- Dossier ready for assessment
Previous Process: Dossier Assessment
Streamlined Process: Dossier Review

- PQ commences
- Fees paid
- Dossier submitted to assessor

Dossier review
- Dossier rated
- CAP requested

CAP Rd 1 submitted
- Cap round 1 reviewed
- Revision requested

CAP Rd 2 submitted
- CAP round 2 reviewed
- Amendments requested

Amendments submitted
- Amendments reviewed
- PQ Decision
Implications of changes

• Clearly defined screening, assessment and post-assessment phase

• Process: Defined number of rounds of amendments, decision points

• Transparency, predictability

• Emphasis on communication
Streamlined Dossier Review Process

• Improve current instructions and provide better guidance to manufacturers and

• Define minimum requirements
Streamlined Dossier Review Process: Guidance

Sample dossier on WHO website

http://www.who.int/diagnostics_laboratory/140314_simu_poc_cd4_dossier_web.pdf?ua=1

Planned activities

Improved instructions for submitting a product dossier, including

- Reference to published relevant international guidance e.g. ISO, CLSI
- Clarification of definitions
- Clarification of requirements
Streamlined Dossier Review Process: guidance under development

- **Labelling**
  - e.g. IFU – claims must be supported by data
  - IFU must give clear test instructions; define ‘intended use’

- **Risk assessment**
  - include WHO recommended format/s

- **Design change**
  - define design changes
  - antigens needs new clinical trials
  - buffer bottle size needs stability studies
Streamlined Dossier Review Process: guidance under development

- Performance studies
  - minimal requirements – (including consumer field evaluations)
  - general/ specific requirements for various technologies
  - define comparator tests (e.g. 3rd generation HIV EIA)
  - considerations for ‘independent’ study

- Stability Studies
  - end user (ruggedness)
  - transportation studies)
  - panels used for stability testing – fit for purpose
  - bio-burden testing – preservative effectiveness
Introduction of dossier grading tool

- Define critical dossier sections with high impact on product quality, safety and performance
- Grade of non-conformities identified
- Purpose of dossier grading tool
  - To provide a standardized method for PQ staff to determine whether the dossier findings support prequalification
  - Tool is designed to grade the nonconformities noted in the assessment of evidence submitted by the manufacturer for each dossier requirement.
The dossier grading tool

The basic structure for the rating system has been developed by GHTF (GHTF/SG3/N19:2012 QMS-Medical Devices-Nonconformity Grading System for Regulatory Purposes and Information Exchange)

Step 1 Identify a Nonconformity

Step 2 Apply Grading Matrix

Step 3 Review Manufacturer’s response

Step 4 Apply Escalation Rules depending on Manufacturer Feedback

Step 5 Final Nonconformity Grade
The rating of manufacturers evidence of conformity is influenced by 2 aspects

- The **impact** of the requirement on the safety, performance and quality of the IVD when used in a WHO Member State.
- The quality and the amount of **evidence** demonstrating conformity to the requirement
Applying the Grading Matrix to Nonconformities

Apply Grades 1 to 4 to a non-conformity according to whether there is no evidence, insufficient evidence or evidence AND the impact level of the requirement.

Where there is sufficient evidence that a requirement has been fulfilled (conformity), a score of 0 is assumed.

<table>
<thead>
<tr>
<th>Impact Level</th>
<th>Complies</th>
<th>Insufficient Evidence of Quality Safety and/or Performance</th>
<th>No Evidence of Quality Safety and/or Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>0</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Medium</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Low</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
## The Final Grade

<table>
<thead>
<tr>
<th>Requirement Impact</th>
<th>NC Grade</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>5</td>
<td>CRITICAL NONCONFORMITY</td>
</tr>
<tr>
<td>Medium High</td>
<td>4</td>
<td>MAJOR NONCONFORMITY</td>
</tr>
<tr>
<td>Low Medium</td>
<td>3</td>
<td>MINOR NONCONFORMITY</td>
</tr>
<tr>
<td>Low</td>
<td>2</td>
<td>OBSERVATION</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>CONFORMITY</td>
</tr>
</tbody>
</table>
Implications of Change

PQ decisions relating to the dossier will be transparent, and based on scientific rationale that

- takes into account the importance of the requirement on safety, performance or quality (impact level)
- other PQ processes for verifying if the Mx or the IVD fulfill the requirement (if there are, the impact level is reduced)
- The amount of evidence provided by the Mx in the dossier in support of the requirement.
Review of Dossier Requirements: Redundant Sections

- Identified that the review of QMS-related documents requested in the dossier is best reviewed by PQ Inspection team
  - Quality Manual
  - Procedure/s for control of design and development changes
  - Procedure/s for the provision of advisory notices to customers subsequent to product delivery
  - Procedure/s for the corrective and preventative action for non-conformities relating to the product
Review of Dossier Requirements: Additional Sections

- Some additional sections will be required
- The review of manufacturing documents with high relevance to device design should be reviewed at dossier stage by technical expert
  - the manufacturer batch release criteria
  - in process calibration/titration criteria
  - quality control of received supplies (ingredients, components)
Implications of change

- Dossier assessors’ time is being directed to review of requirements critical for a quality product, that are most suited to their expertise.
Previous Fast Tracking Process

- Previously, fast tracking resulted in fewer documents in a product dossier being reviewed
  - Those aspects reviewed were those identified as being of great importance for ensuring the performance and safety of a diagnostic in a MS
  - but meant that there was duplication of activities already undertaken by a stringent regulator
## Previous Fast Tracking Process

<table>
<thead>
<tr>
<th>Section</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Product</td>
<td>Regulatory versions of this product, Product description including variants (configurations) and accessories, Risk analysis and control summary</td>
</tr>
<tr>
<td>8. Labelling</td>
<td>Labels, Instructions for use</td>
</tr>
<tr>
<td>9. Commercial History</td>
<td>Countries of supply, Adverse events and field safety corrective actions</td>
</tr>
<tr>
<td>10. Regulatory History</td>
<td>All of section.</td>
</tr>
</tbody>
</table>
Streamlined Abbreviated Review

Fast tracking has been replaced by abbreviated prequalification assessment

- Acknowledges that the majority of contents of a dossier have already been reviewed
- No dossier is required to be submitted to WHO for review
- Aspects of high relevance to ensuring performance and safety in Member States, including their specificities (e.g. genotype prevalence, stability issues) are reviewed by a technical expert during the abbreviated inspection.
Implications of changes

- Least burdensome approach for manufacturers that takes into account the evidence and its review by a stringent regulator

- Decreased PQ times

- No sacrifice to review of aspects of high impact and of high relevance with respect to the diagnostic and its use in WHO Member States.
The dossier assessment team looks forward to many fruitful collaborations to ensure quality IVDs for priority diseases are available sooner.

Thank you for your attention. Your feedback is welcomed.