Inspections Overview
Inspections Overview

- Stage 1 Inspection:
  - Desktop review of QMS;
  - Or onsite one day inspection ONLY if inspectors are in the region;
  - Report provided to the company.
- Stage 2 Inspection
  - Generally a 3 day inspection onsite;
  - Lead Inspector and at least one other inspector (Technical expert or co-inspector);
  - A draft report is left onsite at close of meeting, with a detailed report sent to the manufacturer within 30 days.
Objectives

• Harmonisation (with PQ Medicines/Vaccines/Vector Control and MDSAP)
• Transparency (clarify rules and requirements)
• Adhering to set timelines (time to schedule, onsite and PQ requirements).

• Current turn around time for the entire process is
  • 350 - 270 days for full review
  • 100 - 180 days for abridged
Reference and Guidance documents

• PQDx_014 Information for Manufacturers on the Inspection of Manufacturing Site(s)

• ISO 13485:2003 and 2016 Medical Devices-Quality management systems – Requirements for regulatory purposes

• ISO 14971:2007 Medical devices-Application of risk management to medical devices

• IMDRF and GHTF Documents
Assessment Types
Full Assessment

Priority product

Yes

Dossier screening

Dossier incomplete

Dossier complete

Dossier screening

Dossier review

Site inspection

Laboratory evaluation

Priority product

Yes

Dossier complete

Maintenance of PQ Status

Dossier incomplete

Dossier screening

PREQUALIFICATION DECISION

Copenhagen, Denmark 18-21 September 2017
Abridged procedure

Priority product

Yes

Laboratory evaluation

Review on-site dossier aspects

Site inspection

PREQUALIFICATION DECISION

Maintenance of PQ Status

Copenhagen, Denmark  18-21 September 2017
Requirements for Inspection

• 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 must 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 with the transition to 2016 version underway
- 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
Risk management

- Risk management to meet ISO 14971:2007
  - Throughout product lifecycle
- Risk management for product realisation (design, manufacturing, storage, transportation), user and patient
- Risk management file
- Risk management plan
- Risk analysis
- Risk evaluation and control
- Residual risk acceptable?

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Product Stability

• Product stable to meet "harsh" conditions (hot, wet, dry, dusty)
• Transportation studies (simulate "worst" conditions)
• Long term stability at limiting conditions
• In-use stability studies (open vial)
• Data to support all claims available on-site
• Note: product labelling (component, kit and shipping box)
Routine Manufacturing

- Transfer from R&D to production completed
- Established and evaluated suppliers
- Validated processes (acceptance ranges determined, in-process controls established)
- Trained personnel (requirements determined, training plan, records)
- Standard batch sizes
- Established "out-of-specification" process
- Batch manufacturing records established (include all manufacturing information, full traceability of material and equipment)
Inspection Process

Stage 1
- Plan
- Ready for Inspection
  - Yes
  - Compliant (<7 level 4 NC)
    - 2 rounds CAP
      - Yes
      - Recommendation for PQ
        - (Seek techn. assistance)
      - No
        - Terminate
    - No
      - 2 rounds CAP
      - Yes
        - Terminate
      - No
        - Terminate

Stage 2 Inspection

Dossier Screening
- Dossier Review
  - Compliant?
    - Yes
    - List of questions
    - 2 rounds CAP
    - Yes
    - Terminate
    - No
    - Terminate
  - No
    - Terminate
Onsite Inspection

- Application
- Dossier review (QM documentation part)

**Inspection Cycle:**

- Evaluation of readiness for inspection (stage 1)
  - Desktop of additional documentation (Certificates, recent audit reports, quality procedures, SOP, summary of sold product...)
  - Stage 1 inspection (1 inspector day to inspect state of QMS implementation, facility, competence of staff, critical suppliers incl. outsourced activities, internal audit and management commitment / review)

- Initial (Stage 2) Inspection

- Special inspection (confirm implementation of CAP); onsite inspection, if required

- Re-Inspection (risk based, after 3-5 years)
Abridged Inspection
• Aim:
  • To avoid duplication
  • Reduce time
  • Reduce cost

• When:
  • If a stringently assessed regulatory version is submitted for prequalification
  • If a non-stringently assessed (rest of world) regulatory version of the product is submitted for prequalification assessment but a stringently assessed regulatory version also exists (no difference between the two versions)
• Stringently Assessed
  • Approved by a GHTF founding member regulatory authority and assessed at a level comparable to that required by WHO
  • Competent Authorities from the Member States of the European Union
    • Directive 98/79/EC on in vitro diagnostic medical devices
  • Associated Notified Bodies
  • FDA
  • Health Canada
  • Japanese Ministry of Health, Labour and Welfare
  • TGA
# Full and Abridged Inspections

<table>
<thead>
<tr>
<th>PQ Stage</th>
<th>Full assessment</th>
<th>Abridged assessment</th>
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<tbody>
<tr>
<td>Dossier review</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Site inspection</td>
<td>Full Inspection</td>
<td>Abridged inspection (information package requested)</td>
</tr>
<tr>
<td>Laboratory evaluation</td>
<td>Yes</td>
<td>Yes</td>
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Objectives of Abridged Inspections

• Less time spent on site
• Fewer inspectors (usually one inspector and one technical expert)
## Required information – Full and Abridged Inspection

<table>
<thead>
<tr>
<th>Element</th>
<th>Required documents</th>
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</thead>
<tbody>
<tr>
<td>Quality Management System</td>
<td>Quality Manual&lt;br&gt;Staff organigram&lt;br&gt;Change control procedure&lt;br&gt;Complaint handling and vigilance procedure&lt;br&gt;Audit report of most recent regulatory inspection/audit&lt;br&gt;Current certificates</td>
</tr>
<tr>
<td>Product</td>
<td>Labelling (IFU, component labels and box labels)&lt;br&gt;Photographs of kit, box including contents, kit components and accessories</td>
</tr>
<tr>
<td>Manufacturing</td>
<td>Floor plan&lt;br&gt;Manufacturing flowchart including in/process control points&lt;br&gt;List of significant suppliers (including type of supply)&lt;br&gt;Outsourses processes</td>
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Inspection planning

- Inspection team determined
- Communication with manufacturer (suitable inspection dates, required documentation)
- Manufacturer to agree on the inspection team (Brief CVs provided)
- Inspection plan provided one to two week prior to the inspection
The onsite Inspection

- Opening meeting, end of day discussions, full transparency
- Open exchange of information between WHO and Manufacturer throughout the entire process
- Inspection and tour of the site to review the manufacturing process
  - Manufacturing of the WHO product is required
- Accessibility to all requested documents and records
- Sampling process with risk based emphasis
- Review and confirmation of raw data related to the dossier submission including all validations, stability studies and performance data
End of Inspection

• Closing meeting to discuss any findings
• A list of findings is left onsite for the manufacturer to begin CAPA preparation
• A report is issued within 30 days of the site inspection unless otherwise informed.
• Grading of any nonconformities is independently reviewed before the final report is released
Post Inspection

- Reports are complied by the lead inspector
- Approval and release of the report is by the WHO authorized approver
Corrective action plan

- Required to be submitted within 30 days of receipt of report
  - Root cause analysis
  - Correction
  - Corrective action
  - Timeline and responsible person/department
  - Evaluation of the effective implementation of the corrective action

- Two rounds of CAPA are allowed
Grading of nonconformities

- Based on the GHTF Model

GHTF/SG3/N19:2012
‘Quality management system – Medical devices – Nonconformity Grading System for Regulatory Purposes and Information Exchange’.

Grading nonconformities - Levels 1 to 5.
How the grading works

Grading is a two-step process:

**Step 1: Grading matrix**

The clauses of the ISO 13485 standard are divided into two categories:

1. **Indirect QMS impact**: ‘ISO 13485:2003 clauses 4.1 – 6.3’:
   - enablers for the QMS processes to operate
   - considered to have indirect influence on medical device safety and performance
   - *Starts at Level 1.*

2. **Direct QMS impact**: ‘ISO 13485:2003 clauses 6.4 – 8.5’:
   - direct influence on design and manufacturing controls
   - have direct influence on medical device safety and performance.
   - *Starts at level 3.*
**Step 2: Escalation Rules** – raises NC up one level

- subsequent inspection - same finding
- absence of documented process
- nonconforming product on the market

*Note: Fabrication of information / data is graded as Level 5 and the inspection can be terminated.*
Determination of critically defective QMS

- If the following findings occur:
  - One or more level 5 nonconformities or
  - Seven or more level 4 nonconformities

- Result:
  - Corrective action plan review
  - Possible follow-up inspection
  - Notice of Concern (NOC)
Inspection statistics

Number of inspection

- 2017: 7
- 2016: 11
- 2015: 14

Number of products reviewed

- 2017: 35
- 2016: 25
- 2015: 33
Where to find information

• Contact us by email prequalinspection@who.int

• Sign up for our mailing list By emailing diagnostics@who.int

• Check our website http://www.who.int/diagnostics_laboratory/evaluations/en/