WHO Technical Briefing Seminar
Essential Medicines and Health Technologies
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WHO Prequalification Team (WHO-PQT)

Introduction to medicines inspections technical updates

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In this presentation:

✓ Position of inspection services within the PQT
✓ Inspection process as part of the PQTm process
✓ Inspection eligibility, triggers and timelines
✓ Announced and unannounced inspections
✓ Reliance on others, joint inspections and sharing reports
✓ Inspection statistics
✓ Worrying and promising trends
✓ Impact of root-cause analysis
✓ Revised guidelines
✓ How to access inspection information on the PQTm website
✓ Take-home messages
✓ How to contact the inspection team
Inspection Group within the Prequalification Team
The Inspection Services Group

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Group Lead, PQT Inspections

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CROs/CRM

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Vaccines

Kim Richards
Diagnostics

Under Recruitment

Lead Inspector Diagnostics

Makomani Siyanga
Rotational, ZaZiBoNa

Hilton Katz
Rotational, NVISA, Brazil

To report in January 2016

Pending Recruitment

Nomination awaited
Rotational, China/India

Ana Garcia Miguel
Secretary

Inspections within the WHO-PQTm process

Expression of Interest

Product dossier SMF

Assessment
Additional information and data

Acceptable

Inspections
Corrective actions

Compliance

Prequalification

Maintenance and monitoring

FPP: GMP API: GMP CRO/BE: GCP/GLP

Follow-up NOC
Closing letter WHOPIR

Routine inspections Special inspections Handling complaints

WHO-PQ Inspections

• **Eligibility for WHO-PQ inspections:**
  – companies that are producing or intend to produce products invited under EOIs and
    • have submitted dossiers to WHO-PQ for assessment.

• **Trigger for inspection:**
  – Only following submission of the product dossier.

• **Target:**
  – within 6 months of dossier acceptance for assessment and preferably after 1\textsuperscript{st} round of assessment.
WHO-PQT-Rx: Target Inspection Timelines

- **First inspection:** 6 months from dossier acceptance for assessment or from site confirms it is ready.
- **Surveillance/Routine monitoring inspection:**
  - **due date:** risk-based, 1 – 3 years from date of previous inspection
  - **Actual date:** ± 3 months from due date.
- **Notification:**
  - Announced: 1 – 2 months before inspection.
  - Unannounced/shot announced: 0 – 7 days before inspection
- **Onsite days:** 3 – 5 days.
- **Report:** 30 days from last date of inspection.
- **CAPAs:** 30 days from receipt of report (max 2 rounds, comprehensive, on CDs and not hard copies)
- **Closing of inspection:** 6 months from inspection.
- **Follow-up inspection:** 6 months from inspection
Announced and Unannounced inspections

✓ WHO Guidelines provide for Announced and Unannounced inspections: WHO TRS823, Annex2

WHO TRS823, Annex2:
http://www.who.int/entity/medicines/areas/quality_safety/quality_assurance/InspectionPharmaceuticalManufacturersTRS823Annex2.pdf?ua=1

✓ WHO-PQT procedures provide for Announced and Unannounced inspections: published on PQT website

General information on inspections

The WHO prequalification team plans and coordinates the performance of inspections (announced or unannounced) of the site(s) of manufacture of selected Active Pharmaceutical Ingredients API(s), the Finished Pharmaceutical Product (FPP), and of selected clinical testing units or Contract Research Organization (CRO).

Norms and Standards

Manufacturers and CROs will be assessed through inspections (announced or unannounced) for compliance with WHO norms and standards including Good Manufacturing Practices (GMP), and Good Clinical Practices (GCP) and Good Laboratory Practices (GLP) as appropriate.
International Collaboration has been enhanced

- Share the workload and promote avoiding duplicative inspections.
- Facilitation of harmonization through joint inspections and sharing of outcomes.
- Capacity building of NMRAs inspectors.
- Facilitating use of WHO-PQ inspection results in national regulatory environment for information and decision making.

**Joint Inspections**
- Mainly EU Inspectorates
- EAC NMRAs

**Co-inspectors**
- PICS Inspectorates
- Independent Experts

**Observers**
- Host country inspectorates
- Recipient country NMRAs

**International API inspection Collaboration**
- USFDA, EMA, TGA, WHO
- EU NCAs (UK, FR, IT, GER, IR)
- EDQM

**Collaboration in handling GMP related crises**
- Teleconferences
- Joint investigations
- Coordinated actions, press releases
WHO-PQT-Rx: Use of Inspection reports from other NMRAs - SOP 424.1 Desk Review

➡ Inspectorates whose reports are recognized:
  ✓ PICS member inspectorates
  ✓ EU (EDQM + EMA)
  ✓ USFDA – new member of PICS

➡ What GMP evidence to submit:
  – SMF – Up-to-date
  – Inspection report - conducted NMT 2 years – validity 3 years from inspection date
    • + CAPAs to deficiencies + final conclusion
  – Product Quality Review – not more than 1 year old

➡ Review of the report:
  ✓ scope covered the specific FPP or API
  ✓ Is comprehensive and supports the final outcome.

➡ PQP reserves the right to inspect the FPP/API manufacturer – as long as product is active in WHO-PQP.

➡ on-going GMP compliance will be confirmed by WHO
Joint Inspections

❖ Benefits:

✓ Share the workload and promote avoiding duplicative inspections.
✓ Responds to industry’s concerns about inspection fatigue.
✓ Avoid potential different outcomes associated with independent inspection

❖ Within PQT, joint inspection may be initiated under the following circumstances:

➢ International API inspection Collaboration
➢ Collaborative procedure with NMRAs under regional harmonisation, e.g. EAC
➢ NMRAs approached for co-inspectors but find common interest in the site, e.g. EU NCAs, TGA and USFDA.
➢ Follow-up inspection of a site of international interest following regulatory action by one of the NMRAs.

❖ Contradictions: Refusal of joint inspections – 3 this year

➢ Possible reason for issuance of a Notice of Concern (NOC)
Sharing inspection reports and outcomes with NMRAs and International Procurers

- **Benefits:** similar to those from joint inspections
- **Supported by confidentiality agreements and MoUs**
- **WHO-PQT procedures provide for sharing inspection reports with NMRAs:** WHO TRS961, Annex10

> With a view to coordinating inspection activities, avoiding duplication and promoting information sharing without prejudice to the protection of any confidential and or proprietary information of the applicants and manufacturers in accordance with the terms of this procedure, WHO may disclose inspection related information to regulatory authorities of WHO Member States as well as to regulatory authorities that are members of the PIC/S.

> Notwithstanding the foregoing, WHO reserves the right to share the full assessment and inspection reports with the relevant authorities of any interested Member State of the Organization and interested United Nations agencies.
Inspection statistics: 2014

2014: Number of inspection per category

Medicines: 39
Diagnostics: 24
Vaccines: 10

- QCL
- CROs
- API sites
- FPP Sites
2014: Type of inspection per category

<table>
<thead>
<tr>
<th></th>
<th>Number of sites</th>
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<tbody>
<tr>
<td><strong>FPP Sites</strong></td>
<td>19</td>
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<tr>
<td>API sites</td>
<td>24</td>
</tr>
<tr>
<td>CROs</td>
<td>3</td>
</tr>
<tr>
<td>QCL</td>
<td>7</td>
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<tr>
<td>DIAGNOSTICS</td>
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</table>

**Geneva, Switzerland 23-27 November 2015**
### 2014: Compliance status per category

<table>
<thead>
<tr>
<th>Category</th>
<th>Non-Compliant</th>
<th>Awaits CAPAs</th>
<th>Compliant</th>
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<tr>
<td>FPP Sites</td>
<td>6</td>
<td>27</td>
<td>6</td>
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<tr>
<td>API sites</td>
<td>1</td>
<td>26</td>
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<td>CROs</td>
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<td>DIAGNOSTICS</td>
<td>6</td>
<td>11</td>
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**Geneva, Switzerland 23-27 November 2015**
Worrying Trends – signs of hope

Media is awash with NOCs, warning letters, import alerts, statements of non-compliance, complaints, recalls, etc.

➢ Data integrity and falsification
  ❖ The honest way is always the "right way"
  ❖ unbalanced focus on QC (quality built in – not tested in).
  ❖ New very good guidelines - WHO and MHRA

➢ « Show-case » and « shadow » industries.

➢ « Knee-jerk » responses to inspection observations.

➢ Many « Awaits CAPAs » on routine inspection:
  ❖ poor maintenance of quality systems
  ❖ work hard to pass first inspection and then go on holiday
RESPONSES TO INSPECTION OBSERVATIONS (1)

- An inspection is a sampling exercise and by consequence not all aspects of the manufacturing process may be inspected.
  - The manufacturer is encouraged to take the information provided in the inspection report as examples and to consider **vertical and horizontal analysis** of the issues.
  - nonconformities described in the report that are designated to be of lesser degree of severity, may **increase in severity if not satisfactorily addressed in a timely manner**.
RESPONSES TO INSPECTION OBSERVATIONS (2)

- The manufacturer is required to submit an action plan in response to the observations and all nonconformities noted in the final inspection report within **30 days after receipt of the report**.

- **It is suggested that the action plan incorporates:**
  - root cause analysis (**how/why did this happen**),
  - analysis regarding related areas (**is this same issue impacting/occurring elsewhere**),
  - correction (**fix now**) with completion dates,
  - corrective action (**to prevent recurrence**) with completion dates and,
  - The plan for **demonstration of effectiveness** of the actions taken.
New Format for Submission of CAPAs

<table>
<thead>
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<tbody>
<tr>
<td>Unit number</td>
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<tr>
<td>Production Block</td>
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<tr>
<td>Physical address</td>
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<tr>
<td>Contact person(s) and email address</td>
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<tr>
<td>Date of inspection</td>
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<tr>
<td>Inspector(s)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Observations</th>
<th>Root cause analysis (Additional information may be attached as annexes)</th>
<th>Correction and proposed corrective action (Additional information may be attached as annexes)</th>
<th>The steps that have or will be taken for the demonstration of effectiveness of the actions taken</th>
<th>Timeline</th>
<th>Assessment by inspector</th>
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</thead>
<tbody>
<tr>
<td>Critical</td>
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—we need this in MS Word format – template for assessing CAPAs for traceability.

—we need feedback on use of this format.
Impact of Root-cause analysis:

- The need for and the number of follow up inspections has reduced.

- Number of site complying after first CAPAs has increased.
Revised Guidelines

- Good data management
  - ALCOA principles – See back up slides for more elaboration

- Supplementary guidance on GMP: non-sterile process validation
  - linked to quality risk management (QRM) and quality by design principles
  - focus is now on the life-cycle approach.
    - Process design
    - Process qualification
    - Continued process verification

- Guidance for organizations performing in vivo bioequivalence studies
  - Enhanced management responsibilities & Bio-analytical requirements

- Classifications for inspection deficiencies – new guidance for inspectors
  - joint discussion with PIC/S

- Model inspection report
  - format in line with PIC/S but maintaining sections according to WHO GMP Guidelines

- GMP for APIs (Q&As) – collaboration with ICH IWG – update
  - a link to the document on the ICH website to be established on the WHO website
Selected GMP topics for manufacturers and GMP inspectors

Nairobi, May 9 - 12, 2011


http://apps.who.int/prequal/assessment_inspect/info_inspection.htm#2/

Inspections

This section provides information on Inspection activities in the Prequalification Programme. The following topics are covered:

- General Information on Inspections
- Norms and Standards (e.g., GMP, GCP)
- Meetings with Inspectors - Meeting Request Form
- Training material
- Inspection reports and WHOPIRs
- Notice of Concern (NOC)
- Collaborative procedure with National Medicines Regulatory Authorities (NMRAs) in inspection activities
- Points to consider for inspections of biowaver data
- Frequently asked Questions and Answers

General information on inspections

The WHO prequalification team plans and coordinates the performance of Inspections (announced or unannounced) of the site(s) of manufacture of selected Active Pharmaceutical Ingredients API(s), the Finished Pharmaceutical Product (FPP), and of selected clinical testing units or Contract Research Organization (CRO).

The inspections of the manufacturing site(s) are conducted to assess compliance with Good Manufacturing Practices (GMP) for Finished Pharmaceutical Products (FPPs) and GMP for Active Pharmaceutical Ingredients (APIs) as recommended by WHO. A Site Master File (SMF) submitted by the applicant will be reviewed before an inspection is performed. (Please note that a SMF should be submitted on a CD or DVD at the same time a product dossier is submitted for assessment. See Q&A). Data and information submitted in dossiers and SMFs will be verified during inspections.

The inspections of clinical testing units or organizations are carried out to assess compliance with GCP and GLP, and to perform data...
Take-home messages:

✓ WHO Inspection is an important process towards and for maintaining WHO prequalification status – which facilitates international procurement and national registration.

✓ International collaboration is a cornerstone of WHO-PQT inspections which comes with benefits; it needs your support.

✓ There have been worrying trends observed during WHO-PQT inspections but there is also reason for optimism.

✓ WHO-PQT is continuously improving its guidance – please consult them.

✓ There is a lot of information on the WHO-PQT website – please visit it often.
HOW TO CONTACT US

For specific information requests, please contact the following focal points:

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