WHO Prequalification Medicines Inspection (GMP/GCP) Update and Q&A

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Outline

1. Prequalification (PQ) Medicines:
   - PQ website, process and scope

2. PQ Medicines Inspection Process
   - PQ inspections, inspection teams, types, scope, timeline
   - Use of inspection reports from other NRAs (desk review)
   - Main components of cGMP

3. Risk-based approach to PQ inspections

4. Norms and Standards

5. PQ Inspection Experience

6. Summary
PQ of Medicines: Process
https://extranet.who.int/prequal/
https://extranet.who.int/prequal/
Prequalification of Medicines- Process

Expression of Interest

Product dossier SMF

Assessment

Additional information and data

Acceptable

Inspections

Corrective actions

Compliance

Prequalification

Maintenance and monitoring

QUALITY MEDICINES FOR EVERYONE
Scope of Prequalification

- Limited to priority medicines as published in Invitations for Expression of Interest (EOI) on PQT website
- 8 Therapeutic areas
  - HIV/AIDS
  - Malaria
  - Tuberculosis
  - Reproductive Health
  - Influenza
  - Acute diarrhoea in children (zinc)
  - Neglected Tropical Diseases (NTDs)
  - Hepatitis B and C
  - Insulin
- Potential for other categories if there is the need.
PQ Medicines Inspection Process
The evaluation of a medicine for prequalification (not manufacturing site) includes inspection of Finished Pharmaceutical Products (FPP) and Active Pharmaceutical Ingredients (API) manufacturing sites, and Contract/Clinical Research Organizations (CROs), i.e. **no dossier, no inspection**;

The sites must be cGMP (current Good Manufacturing Practices), GCP (Good Clinical Practices) or GLP (Good Clinical Practices) compliant (as appropriate) for a product to be prequalified;

Inspections are conducted **during** the assessment process, on an **on-going basis** and **in special circumstances**;

Inspections conducted by an “SRA” (now WHO listed authorities) are **taken into account** when planning inspections;

The need for inspections of FPP sites, API sites and CROs are decided on a case by case risk basis.

WHO reserves the right to inspect all manufacturers, clinical and bioanalytical sites listed in a product dossier - to assess compliance with WHO cGMP, GCP and GLP.
Types of GMP inspections

1. **Routine inspection:** This is a full inspection of all the applicable components of GMP.

2. **Concise inspection:** Concise inspections can be performed when a desk assessment of SRA/WHO-listed authority inspection reports was performed but the scope of the SRA/WHO-listed authority report was found not sufficiently comprehensive to fully cover the WHO product.

3. **Non-routine inspection:** These include follow-up inspections and special inspections.

   - **Follow-up inspection:** Depending on the nature of the defects and the work required, follow-up inspections are conducted 6 weeks to 6 months after the first/initial inspection.

   - **Special inspections:** Special inspections are spot checks focusing on one product, a group of related products, specific operations, e.g. mixing, labelling. Such inspections could be announced or unannounced.
Inspection team and scope

- By a team of qualified and experienced inspectors
  - WHO representative (qualified and experienced inspector)
  - Inspector from well-established inspectorate (Pharmaceutical Inspection Cooperation Scheme countries – PIC/S)
  - Product assessor, where required
  - National inspector/s invited to be part and observe the inspection
  - Observer from recipient/developing countries (nominated by DRA of the country)

- Scope:
  - Compliance with guidelines:
    - cGMP for API and FPP sites,
    - GCP for CROs,
    - GLP for FPP/API factory, QCL, CRO-BAL (bioanalytical lab), NQCL
  - Data integrity verification – data manipulation, falsification, (validation, stability, clinical, bio-analytical)
Main components of cGMP

5 P’s of GMP
- People
- Premises
- Procedures
- Processes
- Products

Only valid if Data Integrity is there too
Key components of a Bioequivalence (GCP) study inspection?

**Clinical Part:** Consists of verifying how the study was actually conducted on trial subjects, particular attention given on ethics committee, subject safety and well-being, monitoring

**Bioanalytical Part:** Consists of verifying how the subject's samples were handled, processed, tested and how plasma/blood drug concentrations were calculated for each subject

**Other:** Statistics, quality assurance, communications between departments, archiving, etc.
PQT-m: Inspection timelines

- **First inspection**: 6 months from dossier acceptance (*PQ reference number*) for assessment or from site confirms it is ready.
- **Routine inspection**: 1 – 3 years and ± 3 months from due date.
- **Notification**: 1 – 2 months 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.
Use of inspection reports from other NMRAs:

DESK REVIEW

- Inspectorates whose reports are recognized:
  - PIC/S member inspectorates
  - EU (EDQM + EMA)
  - USFDA – member of PICS

- What GMP evidence to submit:
  - SMF – Up-to-date
  - Inspection report - conducted **NMT 2 years**
    + CAPAs to deficiencies + final conclusion
  - Product Quality Review – not more than 1 year old
  - List of documentary evidence (see next slide)

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

- PQT 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
Documentary Evidence

Desk assessment involves a detailed assessment of specified documentary evidence provided by the applicant. The level and extent of documentation depends on the complexity of the site and its operations as well as on the type of agreement with the inspecting authority.

- Site master file (SMF)
- List of all products manufactured
- Copy of most recent inspection report by the competent NRA (confidentiality, restrictions)
- Copy of most recent inspection report by local NRA (confidentiality, restrictions)
- CAPA and proof of CAPA implementation
- Most recent product quality review of the concerned product(s)
- Completed batch manufacturing / packaging record including analytical part
- List of any recalls in the last three year
- A confirmation by senior QA representative regarding self-inspection or external audit, copy of warning letter or regulatory action issued by any authority
- Any other documents, as necessary.
Risk-based approach to PQ inspections (GMP/GCP)
Risk-based approach to inspections

Ref: SOP: Inspection Frequency and Scheduling

Inspections are scheduled using a risk based approach, taking into account all known factors that could affect quality, safety and efficacy, including the following:

- results of previous WHO inspections
- results of inspections by other National and International Regulatory Authorities
- type of APIs, products and dosage form manufactured or activities performed
- recalls or complaints since last inspection
- results of product testing
- significant changes within the manufacturer, e.g. changes to key personnel, buildings, equipment, products etc.
- any other relevant information (e.g. variations)
- For clinical and BE studies, recommendations from clinical and BE assessors and external authorities are considered
Risk assessment form for active pharmaceutical ingredients within the WHO Prequalification Programme (1 of 2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Risk = 2</th>
<th>Risk = 1</th>
<th>Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Polymorphism</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>2 Solubility in water</td>
<td>Low</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>3 Synthesis</td>
<td>Complex</td>
<td>Not complex</td>
<td></td>
</tr>
<tr>
<td>4 Solvents</td>
<td>High Risk</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>5 Impurities</td>
<td>High Risk</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>6 Sterile</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>7 Fermentation</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>
### Risk assessment form for active pharmaceutical ingredients within the WHO Prequalification Programme (2 of 2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Risk = 2</th>
<th>Risk = 1</th>
<th>Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 Toxicity</td>
<td>High</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>9 Activity/potency</td>
<td>High Risk</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>10 Particle size</td>
<td>High Risk</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>11 Other property consideration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Site compliance information (WHO/EDQM/Other)</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
</tr>
</tbody>
</table>

**Total Risk Score**

**General remarks:**

<table>
<thead>
<tr>
<th>Last inspection date</th>
<th>Outcome</th>
<th>Compliant</th>
<th>Not Compliant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Inspection prioritization</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>
Risk assessment for clinical/contract research organizations within the WHO Prequalification Programme

1. Recommendations from the BE assessors
2. New CRO (not inspected before by WHO listed authorities)
3. Prior GCP/GLP compliance history
4. Large number of subjects enrolled
5. Large number of screen failures
6. High drop-out rates
7. Adverse events reported
# Guide to inspection frequency (IN MONTHS)

Ref: **SOP 401: Inspection Frequency and Scheduling**

<table>
<thead>
<tr>
<th>RISK CATEGORY:</th>
<th>GMP Compliance Rating:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acceptable:</td>
</tr>
<tr>
<td></td>
<td>Good</td>
</tr>
<tr>
<td>Critical (C)</td>
<td>24</td>
</tr>
<tr>
<td>High (H)</td>
<td>30</td>
</tr>
<tr>
<td>Medium (M)</td>
<td>36</td>
</tr>
<tr>
<td>Low (L)</td>
<td>48</td>
</tr>
</tbody>
</table>
# Inspection duration guide (On-Site Days)

Ref: SOP 401: Inspection Frequency and Scheduling

<table>
<thead>
<tr>
<th>Manufacturer Size</th>
<th>C</th>
<th>H</th>
<th>M</th>
<th>L</th>
<th>C</th>
<th>H</th>
<th>M</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial Inspection</td>
<td>Re-inspection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Major</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Standard</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
# Guide to manufacturer risk classification

Ref: **SOP: Inspection Frequency and Scheduling**

<table>
<thead>
<tr>
<th>PRODUCT TYPE / ACTIVITY</th>
<th>RELATIVE RISK CATEGORY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRITICAL</td>
</tr>
<tr>
<td><strong>Finished Products:</strong></td>
<td></td>
</tr>
<tr>
<td>Sterile finished products</td>
<td></td>
</tr>
<tr>
<td>Non-sterile finished products</td>
<td></td>
</tr>
<tr>
<td><strong>APIs:</strong></td>
<td></td>
</tr>
<tr>
<td>Sterile APIs</td>
<td></td>
</tr>
<tr>
<td>Non-sterile APIs where there is a special risk (e.g. isomerism, polymorphism, special risk of harmful impurities, etc)</td>
<td></td>
</tr>
<tr>
<td>Other non-sterile APIs</td>
<td></td>
</tr>
<tr>
<td><strong>National QC Laboratories</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Contract Research Organization (CRO)</strong></td>
<td></td>
</tr>
</tbody>
</table>
Deficiencies are descriptions of non-compliance with GMP requirements.

A distinction is made between deficiencies as a result of:
- a defective system or,
- failure to comply with the system.

Deficiencies may be classified as:
- Critical Observation – potential risk harm to the user
- Major Observation – major deviation from GMP/GCP
- Minor or Other Observation – departure from good practice
Risk-based approach in:
Conclusion following an inspection

✅ When there are "other" observations only:
  – considered to be operating at an **acceptable level of compliance** with WHO GMP.
  – The manufacturer is expected to provide CAPAs.
  – CAPAs are evaluation and followed up during the **next routine inspection**.

✅ When there are "other" and a few "major" observations:
  – **compliance with WHO GMP** is made after the CAPAs have been assessed.
  – CAPAs for majors to include documented evidence of completion.
  – CAPAs paper evaluated ± an on-site follow up inspection.

✅ When there are "critical" or several "major" observations:
  – considered to be operating at an **unacceptable level of compliance** with WHO GMP guidelines.
  – Another inspection will be required
Information put in public domain – available for use by NMRAs: WHOPIRs and NOCs

- These are published in response to the **WHA Resolution WHA57.14** of 22 May 2004, which requested WHO, among other actions:
  - "3. (4) to ensure that the prequalification review process and the results of inspection and assessment reports of the listed products, aside from proprietary and confidential information, are made publicly available;"

- A **WHO Public Inspection Report (WHOPIR)** reflects a positive outcome after an inspection

- A **Notice of Concern (NOC)** is a letter reflecting areas of concern where the non-compliances require urgent attention and corrective action by the manufacturer or research organization.
Norms and Standards (GMP/GCP)
Prequalification Programme: International norms, standards and guidelines used in inspection activities to ensure wide applicability

USP
BP
Ph. Eur.
Ph. Int., JP
Other guidelines e.g. ICH, ISO
### International norms, standards and guidelines used in inspection activities – GMP (APIs and FPPs)

- **GMP for Pharmaceutical Products containing Hazardous Substances.** WHO Technical Report Series, No. 957, 2010 Annex-3,
Handbook for Good Clinical Research Practice (GCP) Guidance for implementation
EMA Guideline on Bioanalytical Method Validation
FDA Guidance for Industry: Bioanalytical Method Validation
Production of Water for Injection (WFI) by means other than distillation

Good chromatography practices

Points to consider for manufacturers and inspectors: Environmental aspects of manufacturing practices for the prevention of antimicrobial resistance

Use of Health-Based Exposure Limits for determining selection of dedicated facility and cleaning validation

Manufacture of Sterile Medicinal Products (Annex-1 of EU GMP): joint initiative of EMA, PIC/S and WHO.
Manufacture of Sterile Medicinal Products

- **Pharmaceutical quality system**: emphasizes need for quality risk management, root cause analysis and impact assessment;
- **Personnel**: Emphasizes training and education and importance of staff behaviors, need for goggles in critical zone;
- **Premises**: Implementation of ISO 14644 and clarifies need for monitoring of 5 micron particles in cleanrooms, reinforces the importance of trending;
- **Equipment**: Emphasizes need to separate operators from process using RABs and isolators;
Utilities: Requirements for compressed air, prevention and removal of biofilms in water systems;

Production: Clarification on requirements on pre/post use filter integrity testing, lots of discussion on expectations for 100% or sampled tests container closure integrity;

Monitoring: Reference to rapid ID methods, clarification of expectations regarding viable and nonviable monitoring (e.g. frequency), risk assessment must be used to develop environmental monitoring regime;

Contamination Control Strategy (CCS): manufacturing process mapped and risk highlighted. For new facilities, CCS part of the design process and should be subject to regular review and update based on data and process knowledge.
PQ Inspection Experience: 2018-2019
Inspections performed in 2018: Medicines

- Initial: 21%
- Follow-up: 3%
- Reinspection: 58%
- Desk review: 18%

Total: 116 inspections

Inspection outcomes 2018: Medicines

- Compliant: 63%
- Non-compliant: 19%
- Awaits CAPA: 5%
- Follow-up required: 13%
FPP Inspections by country: 2018

- India
- China
- Europe (Eastern)
- Africa (Ethiopia, Kenya, Nigeria)
- Middle-East (Egypt, Jordan, Pakistan)
- Indonesia
- American continent (Mexico, Brazil)

Number of FPPs inspected per Disease category in 2018

- Reproductive Health
- Diarrhea
- HIV
- Tuberculosis
- Malaria
- Hepatitis
- Neglected tropical diseases
Top 10 Deficiencies for FPPs in 2018 - Number of deficiencies per category

1.6 Product Quality Reviews
5.8 Cross-contamination chemical/physical
6.1 Sampling procedures and practices - raw materials
8.2 Supplier and contractor audit - technical...
1.4 Documentation - Procedures and records
1.3 Quality Risk Management
1.1a Pharmaceutical Quality System - general
7.4 Cleaning validation
API inspections in 2018 by Country

- India: 40%
- China: 60%

API applications inspected in 2018 by Disease area

- Reproductive Health
- Diarrhea
- HIV
- Tuberculosis
- Malaria
- Hepatitis
- Neglected tropical diseases
- Influenza
Top 10 deficiencies for APIs in 2018: Number of deficiencies per category

1.6 Product Quality Reviews
1.8 Change Control
7.3 Process validation
7.4 Cleaning validation
7.5 Computerized Systems validation
1.5 Data integrity
1.3 Quality Risk Management
1.4 Documentation - Procedures and records
1.9 Deviations - Root cause investigations
3.1 Design, maintenance, cleaning and pest control of production premises
CRO inspections by type in 2018

- Desk assessments of SRA reports: 4
- Onsite inspections: 14

CRO inspections by outcome in 2018

- Compliant: 18
- Follow-up required: 1
Top 10 Critical/Major deficiencies for CROs in 2018 (13 onsite inspections)

1. Subject safety (premises unsafe, lack of preventive measures to ensure wellbeing etc.)
2. Lack of adequate access control to computerized systems
3. Inadequate archival of documents
4. Inadequate handling of study samples
5. Audit trails inadequate - Bioanalysis or other areas
6. Inadequate validation of computerized systems
7. Inadequate back up of computerized data
8. Pharmacy - Issues re Handling of medicinal products, access, logs
9. Issues with the database used for identification of volunteers
10. Informed consent process
## Statistics: Jan-Nov 2019

<table>
<thead>
<tr>
<th></th>
<th>ONSITE:</th>
<th>Desk Review:</th>
<th>Grand Total:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>API:</strong></td>
<td>23 routine, 2 initial, 1 follow up</td>
<td>32</td>
<td>58</td>
</tr>
<tr>
<td><strong>FPP:</strong></td>
<td>23 routine, 4 special, 5 initial, 1 follow-up</td>
<td>13</td>
<td>46</td>
</tr>
<tr>
<td><strong>CRO:</strong></td>
<td>3 initial, 2 routine, 1 special</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td><strong>QCL:</strong></td>
<td>20 routine, 1 follow-up, 4 initial</td>
<td>9</td>
<td>34</td>
</tr>
</tbody>
</table>
### Summary

- **GMP/GCP/GLP inspections** are fundamental elements of managing quality. The inspection contribute to the protection of public health in the pharmaceutical industry;

- **Risk management principles** are applied when scheduling, conducting and closing out inspections. Similarly, **abbreviated procedures** for innovators and generic products approved by the WHO listed authorities ("SRA") used in lieu of WHO inspections;

- WHO-PQ evaluation results show that there are still a lot of poor manufacturing and laboratory practices (e.g. understanding of requirements, inadequate development, poorly designed manufacturing processes and data integrity issues) out there;

- Most of the sites (APIs, FPPs and CROs) are located in China and India and do not comply with WHO requirements when inspected the first time;

- Encouraging to see a number of countries from developing world are coming forward; and

- Results show that **WHO-PQ** has made tremendous contribution in this respect.
Acknowledgement

Joey Gouws,
Group Lead, PQ Inspection Services