Medicines inspections technical updates:
Finished pharmaceutical product inspections

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TALKING POINTS

- WHO Prequalification Team (PQT)
- International Norms, Standards & Guidelines
- PQT Medicines (PQTm) Inspection Process
- Use of Risk-Based Approach
- Analysis of Inspection Findings
- Development of Guidelines
- Concluding Remarks
STRUCTURE OF DEPARTMENT OF ESSENTIAL MEDICINES & HEALTH PRODUCT

Essential Medicines and Health Product [EMP]

- Policy, Access and Use [PAU]
- Regulation of Medicines and other Health Technologies [RHT]
- Public Health, Innovation and Intellectual Property [PHI]

- Technologies Standards and Norms [TSN]
- Regulatory Systems Strengthening [RSS]
- Prequalification Team [PQT]
- Safety and Vigilance [SAV]
STRUCTURE OF THE PREQUALIFICATION TEAM
https://extranet.who.int/prequal/
Prequalification Programme: International norms, standards and guidelines used in inspection activities to ensure wide applicability

USP  
BP  
Ph. Eur.  
Ph. Int.  
Other guidelines e.g. ICH, ISO
PREQUALIFICATION PROCESS

Expression of Interest

Screening

Product dossier + site master file

Assessment – Q & E

Additional information and data

Acceptable

Inspections

Corrective actions

Compliance

Prequalification/Listing

Maintenance and monitoring
-handling complaints, variations, requalification
PQTm INSPECTION PROCESS
INSPECTIONS (GMP)

• The evaluation of a medicine for prequalification includes inspection of FPP and API manufacturing sites, and CROs, i.e. no dossier, no inspection

• Inspections conducted by an SRA are taken into account when planning inspections

• WHO reserves the right to inspect all manufacturers and clinical sites listed in a product dossier - to assess compliance with WHO GMP, GCP and GLP

• The need for inspections of API sites and CROs are decided on a case by case risk basis.
INSPECTION TEAM AND SCOPE

- By a team of qualified and experienced inspectors
  - WHO representative (qualified inspector)
  - Inspector from well-established inspectorate (Pharmaceutical Inspection Cooperation Scheme countries – PIC/S)
  - 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:
  - GMP for API and FPP sites,
  - GCP for CROs,
  - GLP for FPP/API factory QCL, CRO-BAL, NQCL, IQCL

- Data integrity verification – data manipulation, falsification, (validation, stability, clinical, bio-analytical)
WHO-PQT-RX: INSPECTION TIMELINES

- **First inspection**: 6 months from dossier acceptance 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:
SOP 424 DESK REVIEW

Inspectorates whose reports are recognized:
- √ PICS 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

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
USE OF RISK-BASED APPROACH TO INSPECTIONS
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 Regulators
- 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)
## GUIDE TO MANUFACTURER RISK CLASSIFICATION

**Ref: SOP 401: 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>
</tbody>
</table>

### Finished Products:

- Sterile finished products
- Non-sterile finished products

### APIs:

- Sterile APIs
- Non-sterile APIs where there is a special risk (e.g. isomerism, polymorphism, special risk of harmful impurities, etc)
- Other non-sterile APIs

### QC Laboratories

### CROs
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>
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</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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<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inspection prioritization</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## 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>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acceptable:</td>
<td>Good</td>
<td>Satisfactory</td>
<td>Basic</td>
</tr>
<tr>
<td>Critical (C)</td>
<td></td>
<td>24</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>High (H)</td>
<td></td>
<td>30</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Medium (M)</td>
<td></td>
<td>36</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>Low (L)</td>
<td></td>
<td>48</td>
<td>36</td>
<td>24</td>
</tr>
</tbody>
</table>

Unacceptable: Determine on a case by case basis.
## INSPECTION DURATION GUIDE (ON-SITE DAYS)

Ref: SOP 401: Inspection Frequency and Scheduling

<table>
<thead>
<tr>
<th>Manufacturer Size</th>
<th>Risk</th>
<th>C</th>
<th>H</th>
<th>M</th>
<th>L</th>
<th>Risk</th>
<th>C</th>
<th>H</th>
<th>M</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial Inspection</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Large</td>
<td>Re-inspection</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>
<td>2</td>
</tr>
<tr>
<td>Major</td>
<td></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>
<td>2</td>
</tr>
<tr>
<td>Standard</td>
<td></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>
<td>2</td>
</tr>
</tbody>
</table>
RISK-BASED APPROACH IN:
definition and classification of deficiencies

• 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.
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.
ANALYSIS OF INSPECTION FINDINGS - FINISHED PHARMACEUTICAL PRODUCTS
WHO-PQT MEDICINES INSPECTIONS

All inspections 2016

- **FPP**: 38
- **API**: 29
- **QCL**: 17
- **CRO**: 7
- **Total**: 91
WHO-PQT MEDICINES INSPECTIONS

FPP inspections 2016 per country

- India: 17
- China: 2
- Kenya: 3
- Brazil: 2
- Korea: 1
- Marocco: 1
- Egypt: 1

Initial GMP status FPP 2016

- Awaits CAPA: 7
- Non Compliant: 5
- Compliant: 26
Critical deficiencies (routine, non sterile sites) 2016

- Computerised systems – data integrity
- Computerised systems – data manipulation
- Contamination &c cross-contamination
- Design, maintenance and cleaning of productions premises
- Documentation – SOPs and records
- Productions premises

Critical deficiencies (routine, sterile sites) 2016

- Computerised systems – data integrity
- Contamination &c cross-contamination
- Handling and control of staring materials
- Production and packaging operations
- Sterility Assurance - Aseptic Practices
- Sterility Assurance - Media Fill
- Pharmaceutical Quality System
Top major deficiencies routine inspections year 2016

- Product quality review (PQR)
- Stability studies
- Equipment qualification/calibration - production
- Computerised systems – documentation and control
- Production and packaging operations - API
- Process validation
- Documentation – batch processing records
- Design, maintenance and cleaning of equipment
- Computerised systems – validation
- Quality risk management (QRM)
- Computerised systems – data integrity
- Cleaning validation
Top common deficiencies comparison 2013 (29 sites) - 2014 (32 sites) - 2015 (21 sites) - 2016 (36 sites)
DEVELOPMENT OF GUIDELINES
UPCOMING NEW AND REVISED GUIDELINES

Guidance on Good Practices for Desk Assessment for Compliance with GMP, GCP and GLP for Marketing Authorization of Medicinal Products

Guidance on GMP: Validation:

- Appendix 1: Validation of HVAC (under revision)
- Appendix 2: Validation of Water Systems for Pharmaceutical use (under revision)
- Appendix 3: Cleaning Validation (no change)
- Appendix 4: Analytical Method Validation (under revision)
- Appendix 5: Validation of Computerised Systems (under revision)
- Appendix 6: Qualification of systems and equipment (under revision)
- Appendix 7: Non-sterile process validation (revised)

Guidelines on GMP for heating, ventilation and air conditioning systems for non-sterile pharmaceutical dosage forms (under revision)
GUIDANCE ON GOOD PRACTICES FOR DESK ASSESSMENT FOR COMPLIANCE WITH GOOD MANUFACTURING PRACTICES, GOOD LABORATORY PRACTICES AND GOOD CLINICAL PRACTICES FOR MARKETING AUTHORIZATION OF MEDICAL PRODUCTS

(April 2017)

WORKING DOCUMENT QAS/17.713
April 2017
Consultation document

GUIDANCE ON GOOD PRACTICES FOR DESK ASSESSMENT FOR COMPLIANCE WITH GOOD MANUFACTURING PRACTICES, GOOD LABORATORY PRACTICES AND GOOD CLINICAL PRACTICES FOR MARKETING AUTHORIZATION OF MEDICAL PRODUCTS

Draft for Discussion

Should you have any comments on the attached text, please send these to: Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms, World Health Organization, 1211 Geneva 27, Switzerland; email: kopp_s@who.int; fax: (+41 22) 791 4730; and to Mrs Wendy Bonny (bonnyw@who.int), by 21 September 2017.

Working documents are sent out electronically and they will also be placed on the Medicines website for comment. If you do not already receive directly our draft guidelines please let us have your email address (to bonnyw@who.int) and we will add it to our electronic mailing list.
IN SUMMARY

1. Collaborative and risk management principles are applied to ensure efficient use of available resources.

2. WHO-PQ evaluation results show that there are still a lot of poor manufacturing practices out there. Collaborative effort and skills are needed to ensure access to medicines of assured quality.

3. Most of the sites (FPPs) are located in China and India. Most of the sites (FPPs) do not comply with WHO requirements when inspected first time.

4. Encouraging to see a number of countries from developing world are coming forward.

5. Results show that WHO-PQP has made tremendous contribution in this respect.
Thank you for your attention!

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