World Health Organization
Prequalification of Medicines
Manufacturers meeting April 2011

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WHO GMP

In this presentation:

- Background and Introduction – GMP
  - WHO – PIC/S – EU - USA

- Manufacturer survey 2010

- Discussion
GMPs

WHO GMP

- First WHO GMP published in 1967
- Revised on an ongoing basis
  - Revisions circulated for comment, informal consultations
  - Expert Committee – published in TRS
- Main principles
- "Supplementary" guidelines
- Used in over 100 countries

EU and PIC/SGMP

- Directives published in 1989
- Other "local" GMP existed well before this date
- PIC formed in 1970, PIC/S formed in 1995
- EU and PIC/S GMP similar
- PIC/S GMP based on WHO GMP
- 39 Participating authorities
### WHO and PIC/S GMP

#### WHO GMP
- Main principles
- Sterile product manufacture
- Heating, Ventilation and Air Conditioning (HVAC) systems
- Water for pharmaceutical use
- Quality Control laboratories
- Radiopharmaceuticals
- Good Storage Practices (GSP)
- Good Distribution Practices (GDP)
- Good Trade and Distribution Practices (GTDP)
- Sampling
- Herbal products
- Hazard Analysis and Critical Control Point (HACCP)
- Reference standards
- Validation
- GMP for APIs

#### PIC/S GMP
- Main principles
- Manufacture of sterile medicinal products
- Manufacture of biological medicinal products for human use
- Manufacture of radiopharmaceuticals
- Manufacture of veterinary medicinal products other than immunologicals
- Manufacture of immunological veterinary medical products
- Manufacture of medicinal gases
- Manufacture of herbal medicinal products
- Sampling of starting and packaging materials
- Manufacture of liquids, creams and ointments
- Manufacture of pressurised metered dose aerosol preparations for inhalation
- Computerised systems
- Use of ionising radiation in the manufacture of medicinal products
- Manufacture of investigational medicinal products
- Manufacture of products derived from human blood or human plasma
- Qualification and validation
- Parametric release
- GMP Guide for active pharmaceutical ingredients
### Examples

<table>
<thead>
<tr>
<th>WHO</th>
<th>PIC/S</th>
</tr>
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<tbody>
<tr>
<td><strong>16.17</strong> Means should be instituted of indicating failures of equipment or of services (e.g. water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. After use, production equipment should be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.</td>
<td></td>
</tr>
<tr>
<td><strong>16.18</strong> Time limits for storage of equipment after cleaning and before use should be stated and based on data.</td>
<td></td>
</tr>
<tr>
<td><strong>16.19</strong> Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.</td>
<td></td>
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</table>
## Examples

<table>
<thead>
<tr>
<th>WHO</th>
<th>PIC/S</th>
</tr>
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<tbody>
<tr>
<td>16.23</td>
<td>3.41</td>
</tr>
</tbody>
</table>

Measuring, weighing, recording, and control equipment and **instruments** should be **serviced** and calibrated at **prespecified** intervals and records maintained.

To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated, preferably on a label attached to the instrument.

Measuring, weighing, recording and control equipment should be calibrated and checked **at defined** intervals by **appropriate methods**. Adequate records of such tests should be maintained.
Manufacturer's survey done in 2010 – contracted party

Limited to identified manufacturers – with prequalified products - majority in India

Online questionnaire divided into four sections:
1. Previous PQP Experience
2. PQP Service Design (process)
3. PQP Service Delivery (people)
4. Other Aspects of the PQP

Section 2 (Design) is “custom” to the PQP – developed as a result of a process review with the WHO PQP Staff and a series of interviews with pharmaceutical manufacturers
- Two multi-item questions for both assessments and inspections
- Two separate multi-item questions each for assessments and inspections respectively

Section 3 (Delivery) is a widely-applied scale of service quality, SERVQUAL (Parasuraman, Zeithaml, Berry)\(^1\), developed in the 1980’s; refined and applied over past 25 years
- Five separate multi-item questions each for assessments and inspections respectively

Section 4 is also custom to the PQP and includes advocacy, training and compliance aspects of the PQP
Survey

- A list of potential survey participants was compiled by the WHO PQP Staff using internal records
  - Regulatory Affairs Professionals (assessment of product dossiers)
  - Quality Assurance Professionals (on-site inspections)
  - Inclusion criterion: participation in the PQP of Medicines 2006 - 2010

- Contact list represents “known population” of manufacturer PQP participants: 75 original contacts; later revised to 62 (30 regulatory, 32 QA)

- Sampling plan: census – all contacts received an e-mail invitation

- All invitations sent by e-mail with two reminders; some follow up telephone reminders

- 41 completed surveys received by 20 July (66% response rate)
  - Surveys oriented toward assessment of product dossiers: 18
  - Surveys oriented toward on-site inspections: 23
Survey

Providing clear explanations of good manufacturing practice deficiencies observed during inspection of a manufacturing site: 6.4*

Providing applicants / manufacturers with timely announcements of inspections: 6.0

Providing a site inspection plan that includes all the information needed to prepare for an inspection: 5.8

Providing direct access to inspectors to address technical questions or deficiencies: 5.3*

Providing an efficient process to resolve issues and questions raised during the inspection of manufacturing sites: 5.0*
<table>
<thead>
<tr>
<th>Question</th>
<th>Item</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q7C.1</td>
<td>Providing clear explanations of good manufacturing practice deficiencies observed during inspection of a manufacturing site</td>
<td>Review of pre-qualification dossiers and subsequent responses should be addressed on a fast track to help the FP manufacturer’s.</td>
</tr>
<tr>
<td>Q7C.1</td>
<td>Providing clear explanations of good manufacturing practice deficiencies observed during inspection of a manufacturing site</td>
<td>Inspection process is fair and up to the mark.</td>
</tr>
<tr>
<td>Q7C.1</td>
<td>Providing clear explanations of good manufacturing practice deficiencies observed during inspection of a manufacturing site</td>
<td>The deficiencies must be evaluated with risk to product, patient and process.</td>
</tr>
<tr>
<td>Q7D.1</td>
<td>Providing clear interpretation of GMP requirements</td>
<td>At least once in 6 months follow-up audit by QA professional of other organization. Example: Mylan labs QA head audit aurobindo facility or Aurobindo QA head audit Mylan facility</td>
</tr>
<tr>
<td>Q7D.1</td>
<td>Providing clear interpretation of GMP requirements</td>
<td>If more training programs for pharmaceutical manufacturers could be organized, it would be much better.</td>
</tr>
<tr>
<td>Q7D.1</td>
<td>Providing clear interpretation of GMP requirements</td>
<td>I am happy with the way pre-qualification program is conducted. No additional suggestions from me. The process of dossier evaluation and the process of inspection are transparent and people from WHO are approachable.</td>
</tr>
<tr>
<td>Q7D.2</td>
<td>Providing an efficient process to resolve issues and questions raised following the inspection of manufacturing sites</td>
<td>Interpretation of regulatory guidelines should be clear.</td>
</tr>
<tr>
<td>Q7D.3</td>
<td>Providing an inspection process that makes efficient use of manufacturers’ time</td>
<td>Should indicate inspection process earlier</td>
</tr>
<tr>
<td>Q7D.4</td>
<td>The clarity of questions asked during the inspection process</td>
<td>1. Thorough communication with the manufacturers; 2. Interpretation and application of GMP terms.</td>
</tr>
<tr>
<td>Q7D.4</td>
<td>The clarity of questions asked during the inspection process</td>
<td>On new aspects / update in expectation of regulatory, site team must be briefed</td>
</tr>
<tr>
<td>Q7D.4</td>
<td>The clarity of questions asked during the inspection process</td>
<td>We are simultaneously working for compliance with all regulatory authorities. Sometimes we come across discrepancies in standards of different authorities. At such times we expect guidance from WHO on which standards should be followed so that we have harmonised standards for all global regulatory authorities. For example guidance on tablets formulations by Dr. Van Zyl is available, we expect similar guidance for other formulations.</td>
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<tr>
<td>Q7D.4</td>
<td>The clarity of questions asked during the inspection process</td>
<td>Some of the questions could be more specific and practical. If the manufacturer’s response is not satisfactory, the inspector should say so on site and, if possible/appropriate, provide some further instructions.</td>
</tr>
<tr>
<td>Q7D.5</td>
<td>Including inspectors from your country or region on the inspection team</td>
<td>Out of 4 WHO inspections, only one time inspector from our country participated in the audit only for an hour. That's why rated 3. Need to have firm commitment from Ministry of Health for auditing facilities along with WHO Geneva auditors. A report from WHO auditors to ministry of health regarding presence of local inspector and on his performance may improve this.</td>
</tr>
<tr>
<td>Q7D.5</td>
<td>Including inspectors from your country or region on the inspection team</td>
<td>Inconsistencies between inspectors style and willingness to understand different implementations of GMP and means of achieving the same needs to be addressed.</td>
</tr>
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</table>
Survey: Comments in responses

- Providing clear explanations of GMP deficiencies observed during inspection of a manufacturing site
  - Review of dossiers and subsequent responses should be addressed on fast track
  - Inspection process is fair and up to the mark
  - Deficiencies must be evaluated with risk to the product, patient and process

- Providing clear interpretation of GMP requirements, resolving issues and clarity of questions
  - Satisfied. Transparent
  - If response is not clear on site (following inspectors questions) - then should say so on site and provide some suggestions
  - Inspectors inconsistent in willingness to understand different interpretations of GMP s
Survey: Comments in responses

Average Rating

Providing clear interpretation of GMP requirements 6.3
Providing efficient process to resolve issues and questions raised following the inspection of manufacturing sites 6.1
Providing an inspection process that makes efficient use of manufacturers’ time 6.3
The clarity of questions asked during the inspection process 6.2
Including inspectors from your country or region on the inspection team 5.5

Average Rating
Survey: Comments in responses

When asked how strongly they agree or disagree with the statement "WHO GMP requirements are more stringent than EU or US FDA GMP requirements", the majority of manufacturers indicated that they were more stringent.

**Comment**

It is quite descriptive and elaborative. Interpretation of WHO guidelines are very easy compared to others. Even minute points covered in WHO GMP.

The sampling plan and protocols should be made more strict.

Such as provisions about sampling and the approval of changes etc.

WHO is specifying, how to perform the activities alongwith scientific rationale and explanations.

The inspection takes a long time, it covers a wide range of areas.

The requirement of EU / MHRA is more as compared to WHO, it need to be harmonise.

Sometimes they ask us to perform certain studies thrice which are not required by any other regulatory bodies.

Regarding the aspects of safety and effectiveness very specific like one batch vs 3 batch requirement for filling.

eg. conducting all ID tests on each container even if a robust ID test is available for each container.

The guidance are more detailed, specific and useful such as Guidance on HVAC & Water System

All are respected.

Again this is a general comment where the guideline points are interpreted differently and understanding of the inspectors where guideline are general.

Each and every points of the WHO guideline are covered while the inspection & suggestions were provided with observations for compliance & sufficient time is give implementaion of corrective actions. All supporting documents were also required for compliance to closure of audit.

accelerated Stability data requirement is 6months in case of WHO and where as 3months with USFDA. 

Validation data of three batches is a part of PQF. where as one batch and a commitment in USFDA.

The way WHO regulations are laid out and implemented, takes into account best of both EU and US FDA GMP requirements. It covers overall GMP, products and processes.

The WHO requires 100% sampling from each container of a raw materia's lot when received for manufacturing a formulation even if the vendor is validated.

It focuses more on the operational levels, not just paper work or procedures evidence. It also emphsizes detailed practice and skills/capiblity of employees.
Comments (WHO GMP more stringent)

- Quite descriptive and elaborate. Interpretation of WHO GMP is very easy compared to others. Even minute points are covered in WHO GMP
- Guidances are more detailed, specific and useful such as HVAC and Water
- WHO guidelines take into account the best of EU and FDA. It covers overall GMP, products and processes
- WHO explains how to perform activities alongside with scientific rationale and explanations
- Sampling
  - The sampling plan and protocols should be made more strict
  - Provisions about sampling and the approval of changes
  - WHO requires 100% sampling from each container even if the vendor is validated
  - Asking all ID tests on each container even if a robust ID test is available
- Inspections take a long time and cover a wide range of areas
- It focuses more on operational levels not just paper work or procedure evidence
- The requirement of EU / MHRA is more compared to WHO - need to harmonize
- They ask us to perform some studies thrice while others don't
- Very specific like asking 3 batches for filing
- Regarding safety and effectiveness
- Accelerated stability data required for 6 months where FDA requests 3 months. Validation of three batches opposed to one batch data (FDA)
- Guidelines are general and different interpretations by inspectors
The way forward…

- Invite comments from the floor
- Discussion
- List recommendations

WHO Procedure:
- Secretariat will take it to the Expert Committee
- Discussion, recommendation: Action if needed
- Revision, comment, informal consultation, Expert Committee