Technical updates medicines inspections: Finished Pharmaceutical Products (FPP)

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- Prequalification Inspection Process
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- Dossier Submission Requirements versus GMP Compliance on Process Validation (PV)
- Examples of Good and Unacceptable CAPAs
- Recommendations
Prequalification Programme: norms, standards and guidelines used...


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Key elements of WHO GMP for FPP:

- Pharmaceutical Quality System (QRM and PQR)
- Good manufacturing practices for pharmaceutical products
- Sanitation and hygiene
- Qualification and validation
- Complaints
- Product recalls
- Contract production, analysis and other activities
- Self-inspection, quality audits and suppliers’ audits and approval
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Good practices in production
- Good practices in quality control
WHO Prequalification Programme (PQP) Inspections-1

- Manufactures are inspected by WHO PQ on a routine basis using an internal procedure and risk based approach;

- Before inspection, inspector is required to verify objective of inspection to be carried out;

- Inspector determines what the scope and depth of the inspection will be based on product dossier assessment report and findings of previous inspection;

- WHO PQ conducts system based inspection but also covers product specific elements (e.g. dossier data integrity verification);

- It is possible to prequalify a product which was not specifically covered during an inspection but is produced on the same production lines inspected.
WHO Prequalification Programme (PQP) Inspections-2

- Review Site Master File (SMF);
- Review variation list, complaint register;
- Prepare tentative inspection plan;
- Opening meeting covering introduction and brief presentation of site
- Inspection to cover on-site verification of facility and data verification

- Observations are based on ‘RED’
  - Requirement
  - Evidence
  - Deficiency
Top Ten Observations from 2013 FPP Inspection

1. Quality management – product quality review
2. Documentation - procedures/SOP
3. Supplier and contractor selection/monitoring/audit
4. Investigation of anomalies – OOS
5. Documentation – specifications and testing
6. Quality control - chemical
7. Design, maintenance and cleaning of equipment
8. Complaints
9. Equipment qualification - laboratory
10. Design, maintenance and cleaning of premises

Number of inspections: 34
Top Ten Observations from 2014 FPP Inspection

1. Quality management – product quality review
2. Computerised systems – data integrity
3. Quality control – chemical
4. Personnel issues – training
5. Process validation
6. Cleaning validation
7. Investigation of anomalies – deviations
8. Quality management – change controls
9. Supplier and contractor selection/monitoring/audit
10. Documentation control

Number of inspections: 18
(Jan-Jun)

- Critical: 22
- Major: 91
- Others: 146

2014
Dossier submission requirements versus GMP compliance on PV

- It is not a requirement to submit PV report during submission of dossier

- A protocol and commitment to conduct PV at the commercial scale is submitted in lieu of PV report

- Once a robust validation system is demonstrated to be in place, it is possible to get GMP approval even when certain products have not been validated at the commercial scale and have not been commercialised. It however MUST be demonstrated that:
  - the site has adequate product and process knowledge acquired from development and pilot scale, and
  - there are firm commitments and arrangements to place the first commercial batches on validation and the report shared with PQ.

- Submission of validation data may trigger an inspection to verify the validation data but, in any case, the next due date of such a site would normally be set to 6 - 12 months.

- Finished product batches cannot be marketed without PV
Example of Good and Unacceptable CAPA!

Observation: Inspection of a laboratory failed to establish, implement and maintain policies, systems, procedures and controls to ensure reliability and integrity of data.

For example:

- Audit trail disabled,
- Disabling of audit trail when manually integrated,
- No procedure available on manual integration,
- Common password used among several analysts,
- “Trial System Suitability” not part of report,
- Analysts allowed to delete files without control and justification,
- No control on issuance of analytical worksheets
Bad / Unacceptable CAPAs

- No root cause analysis with respect to individual observations
- Incomplete, superficial response with no objective evidence to support action plan
- No impact analysis, no correction, and proposal of unjustifiable timeline
- Usual CAPAs i.e. Retraining without establishing root cause especially associated with human errors
- Being defensive or in denial with no commitment for compliance and seriousness taken to address findings
Good CAPAs to include

- Remedial corrections of an identified problem
  - Correction: repair, rework or adjustment relating to the disposition of an existing discrepancy

- Root cause analysis with corrective action to help understand the cause of the deviation and potentially prevent recurrence of a similar problem
  - Corrective action: Action to eliminate the cause of a detected non-conformity or other undesirable situation

- Preventive action to avert recurrence of a similar potential problem
  - Preventive action: Action to eliminate the cause of a potential non-conformity or other undesirable potential situation
Recommendations!

- Understand the requirements
- Learn from your and others’ mistakes
- Learn from information available in the public domain (NOC, warning letters, import alerts etc)
- Response should tell the whole story and stand on its own!
- Most important to demonstrate commitment to compliance and seriousness taken to address observations in a timely manner
Thank you for listening!