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Title:: Effective GMP AUDITS for APIs and Formulation Pharma Companies

By

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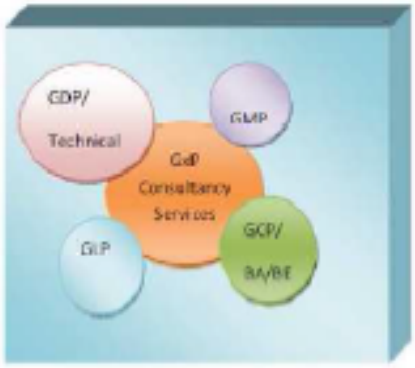

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GMP Audit

- Introduction:
- The independent third-party GMP audit is to evaluate GMP compliance status of the manufacturer in accordance with the current GMP requirements set forth in 21 CFR Part 210 & 211 ICH Q7 and EU GMP with its interpretations.
- The compliance status will be evaluated in terms of Quality compliance with respect to all the six GMP systems and hardware, software, and personnel. All deficiencies identified during the cGMP audits will be noted in the audit report with gap analysis and proposed corrective actions

GMP Audit Definition

- ***GMP inspection***: on-site assessment of the compliance with the GMP principles performed by officials of competent authorities or authorities found equivalent (Qualified inspectors).

- A systematic, independent and documented process for obtaining evidence and evaluating it objectively to determine the extent to which criteria are fulfilled.

GMP audit Related definition:

- ***Auditee :*** Persons from an organisation or organisational unit being audited.
- ***Auditor:*** A Qualified person with the competence to conduct an audit.
- ***Audit Team :***One or more auditors conducting an audit. Audit Unit An organisation or organisational unit (e.g. departments, plants, sites) to be audited.
- ***Audit Communication :***Is a process of exchanging information between two or more persons. Communication can be verbal and/or other means
- ***Competence :***The demonstrated ability to apply knowledge and skills.
- ***Compliance:*** GMP Applying to national/international GMP regulations. Compliance, regulatory Applying to statements made in the organisations own documents submitted to the authorities.

GMP Audit Benefits:

-The following benefits to the Pharmaceutical industry:

- Effective assessment of GMP Compliance
- Reduced costs
- Improved performance
- Facilitating harmonised guidelines for auditing
- Increased external confidence
- Inspection readiness Trouble free operation.

GMP Audit process:

- Following this document will provide the current “state of the art” in pharmaceutical auditing.
- **Before the Audit**:-Audit communication to understand the know how about the firm to be audited
- ***Pre-Audit Questionnaire*** Document requesting general information for the preparation of the auditors.
- ***Audit plan:*** Gives a general overview of the audit units, the frequency in which the audit units ought to be audited and provides a summary of the audit units to be conducted
- ***Audit schedule:*** Fixed dates at which the audit will take place for a pre-defined timeframe (usually a year). If not too complex, the Audit Plan and Audit Schedule can be combined to one document

GMP Audit process

- ***Letter announcing/requesting the audit*** :The auditee must be given the chance to organise himself. For this reason the auditor(s) should seek for an invitation well in advance of the planned/scheduled audit. This may be in form of a letter (mostly external) or memo (mostly internal) or even by e-mail.
- ***Audit agenda:*** An agenda agreed between auditor(s) and auditee, defining the topics to be focused and/or audited units.
- ***Secrecy agreement : (CDA/NDA):*** It is advisable to sign a secrecy agreement for external audits (supplier, contractor). Most often the auditor will be taken into sensitive areas, where a knowledge transfer, caused by the auditor, could lead to competitive disadvantages.

GMP Audit process

- ***Conduct of GMP audit:***
- The compliance status will be evaluated in terms of Quality compliance with respect to all the six systems and hardware, software, and personnel.
- All deficiencies identified during the cGMP audits will be noted in the audit report with gap analysis and proposed corrective actions. A pharmaceutical auditing process may include review of the following

- Documentation and Record Control
- Verification of data integrity and its control measures
- Manufacturing Process and Equipment
- Training
- Validation and Qualification

GMP Audit process:

- ***Audit report***: A detail report of audit report shall be prepared and sent to the Firm for CAPA
- ***Response to audit report***: A detail response letter from firm to the auditing agency with actions taken, CAPA details with covering letter sent to the regulatory agency.
- ***GMP Certificate/compliance:*** Statement: certificate with validity period and a statement of GMP compliance will be issued to the firm after satisfactory audit response letter.
- ***Monitoring:*** The firm internally monitoring the compliance status in their Quality meetings

GMP Audit Agenda (Plan):

- Firm details
- Objective
- Scope
- Schedule with period of audit
- Auditor information
- Supporting Documentation
- Assessment standards
- Audit process with proposed areas
- Concluding meeting requirements
- Audit arrangement requirements.

GMP Auditing Techniques

- **Introduction**
-
- Introduction of Company management and its facility
- Brief introduction of consultancy services
- Discussion of audit objective, plans, and schedule
- Overview of general site and facilities design and layout
- Facility tour of receiving, storage, sampling, dispensing, manufacturing, packaging, warehousing and shipping areas, following with material and personnel flow.
- QC Laboratory tour and microbial laboratory
- Quality systems: management review, documentation system, internal audit, training, change control, deviation management, Risk assessment validation approach, corrective and preventive action.
- Data Integrity in QC;QA and Production; Stores; Engineering.
- Environmental monitoring review
- Calibration and maintenance program
- Validation master plan and reports review
- Complaints and recall management

GMP Auditing Techniques

- We request availability of the following reference and discussion materials during the course of this audit: but not limited to.
- Site Master File and/or Quality Manual
- GMP, manufacturing, ISO or other certification
- List of products manufactured at the site
- Current Organisation Chart for the site.
- Facility floor plans
- Procedures to prevent mix-up in production and packaging
- Plans of Air handling (HVAC), Compressed air system, and any other service systems supporting packaging.
- Index of SOPs.
- Job descriptions for Key personnel

GMP Auditing techniques

- Training schedule and records
- Change Control
- Procedures for rework/reprocessing
- Recording of deviations and follow up
- Annual Product Review SOP
- Validation Master Plan for the site
- Validation Reports
- Qualification/Validation Reports for production equipment and areas
- Cleaning Validation Reports for equipment and areas used for production
- Starting material, in-process material and finished goods specifications and testing procedures
- Register for deviations
- Risk assessment
- Environmental monitoring summaries (trending) for packaging areas used for packaging
- Procedures, systems and reporting on audits to be conducted by firm for their suppliers,
- Vendor certification procedure for suppliers of materials used in manufacturing and packaging.
- Internal audit schedule
- Handling of complaints and recalls
- Calibration Program
- Preventative Maintenance Program

GMP Auditing Techniques

- 5 W and one H method-Who ,what, when, where, why and how?
- Interviewing/Interrogation
- Reviewing recorded information against raw data
- Analysing data and information against compliance

Assessing GMP compliance GAP

- Availability (and if necessary translations) of key documents
- Assessment of Team on co-ordinate preparations and answers
- Composition, organisation and responsibilities of the team
- Availability of key staff, and involvement of senior and/or top management (provide correct partner for discussions)
- Training of staff in what to expect, and how to respond to an auditor's questions
- Data integrity and its compliance

Audit observations and its classification

Deficiencies are classified as follows:-

1. Product Quality / Patient Safety Related deficiency (**Critical**)
2. Significant cGMP Deficiency but with no **direct impact** on Product Quality /Patient Safety (**Major**)
3. GMP deficiencies that are either considered to be minor isolated examples or there is insufficient information to classify them as Major (**Other**)

Table 2

Classification of deficiencies.

Critical	A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal. *Examples:* • *Mix-ups (active ingredients, excipients, bulk product)* • *Mixing (active ingredients, excipients, bulk product, printed packaging material)* • *Contaminants/microbiological contamination of sterile products* • *Deviations/changes (missing active ingredient, wrong dosage of active ingredient with consequences that are harmful to health or life-threatening)* • *Contamination with serious medical consequences (solvents, pesticides)* • *Defect/deficiency that represents an offence requiring intervention by the authorities* • *Significant deviations in the content of the quality documentation (DMF)* • *Iterated appearance of major deviations*
Major	A non-critical deficiency which has produced or may produce a product, which does not comply with its marketing authorisation; or which indicates a major deviation from EU Good Manufacturing Practice; or (within EU) which indicates a major deviation from the terms of the manufacturing authorisation; or which indicates a failure to carry out satisfactory procedures for release of batches or (within EU) a failure of the Qualified Person to fulfil his legal duties; or a combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such. *Examples:* • *Significant non-compliance with the GMP rules or significant deviations from the EU GMP Guidelines* • *Inadequate discharge of the responsibilities of specialists from Quality Assurance* • *Significant deviations of the product from the DMF content* • *Deviations that may result in residues that are harmful to health (Critical/Major, depending on the substance and therefore the risk)*
Other	A deficiency, which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice. (A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as a major or critical). *Examples:* • *Non-conformance to the GMP rules or deviations from the EU GMP Guidelines* • *Deviations of production and testing from the DMF* • *Deviations and changes* • *Missing documentation for processes proven to be correct*

Audit report

- Upon completion of the audit, the lead auditor will compile the findings and provide the section representatives with a preliminary report. This preliminary report is a synopsis of the findings and provides section personnel with an opportunity to voice any objections. If valid objections are raised, the audit team should adjust their findings accordingly.
- lead auditor assimilates all data from the audit and prepares an audit summary report. After receipt of this this audit report, CAPA actions and follow-up activities are discussed and a response letter will be prepared by firm.

CAPA plan for compliance

- The firm QMS Manager assimilates all data from the audit and prepares an audit summary report. The audit report, corrective actions and follow-up activities are discussed [Frequency (e.g. weekly)] during management meetings.

- Resolution report of corrective actions taken and follow-up activities is prepared by the QMS Manager through the [Name] to the [Name] and staff

- In the event, the audit identifies a problem associated with incorrect procedures, invalid action or invalid data, immediate corrective action will be taken. The QMS Manager will notify the [Name] to determine the most efficient method of notifying the client (i.e. by telephone, email, fax or letter). This notification will be documented. Corrected reports will be issued.

- A detailed Response letter citing the CAPA evidence will be sent to the agency

Auditor Qualification

- Auditors should have sufficient scientific, technical and other experience to enable them to perform an adequate and thorough audit of the active substance/formualation manufacturer, as related to the planned scope of the audit.
- Where a proposed auditor lacks an appropriate level of direct experience in the field of active substance manufacture, he or she should undergo a documented training and assessment programme in the areas that are relevant to the audit, taking into account the auditor's anticipated role in the audit and the technologies that are likely to be encountered during the audit.
- Auditors must also be trained and assessed in their knowledge and understanding of EU GMP and in auditing techniques in general. The training and assessment should be fully documented.
- The qualification and experience of contracted auditors are the same as the requirements for the manufacturing-authorisation holder's own auditors.

APIC Guide

- Companies should have an internal scheme setting the criteria to qualify as auditor and to maintain this qualification status.
- Typically this would be :
- Active involvement in a GMP related activity preferably for a minimum of two years
- Have participated in at least three audits as auditee
- Have followed an auditor training programme for example the APIC Certified Auditor Training course that is organised by the API Compliance Institute
- Conducts at least one audit per year

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- Thanks for your Attention and any questions?