



Internal GMP Audits (How to Conduct Internal Audits)

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Module Outcomes

On completion of this module participants should be able to:

- Organise audit plans and schedules
- Follow an audit process
- Classify observations, based on risk
- Conduct and exit interview and assign corrective action responsibility

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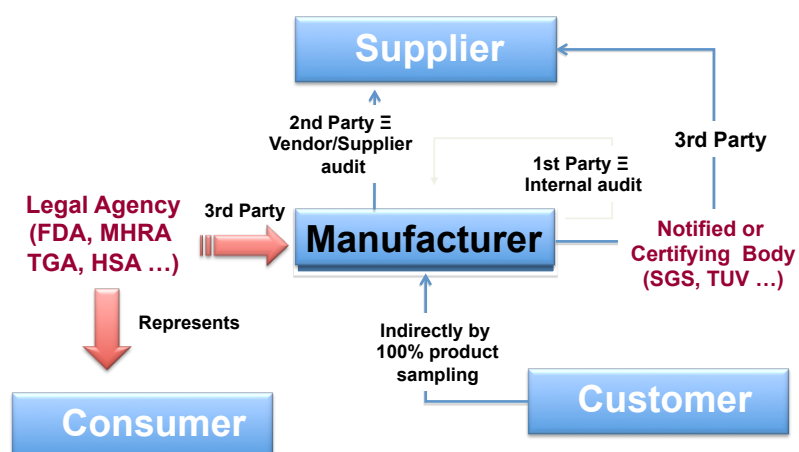
Module Topics



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Introduction 3

Different Types of Audits



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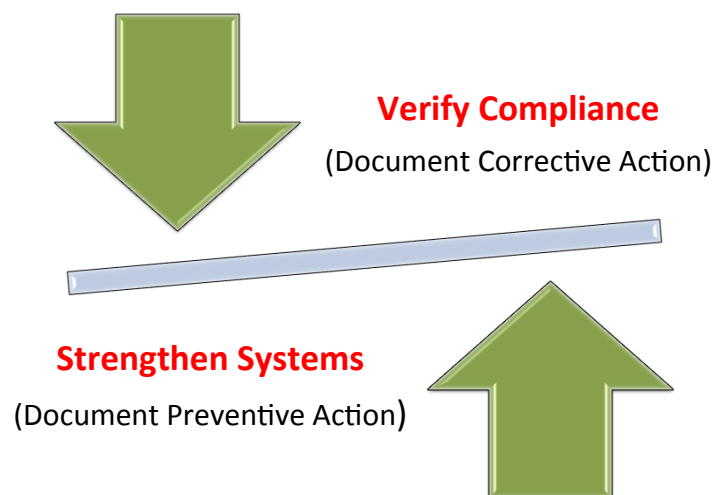
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Auditor Principles - ISO 19011

- **Ethical conduct:** the foundation of professionalism - Trust, integrity, confidentiality and discretion are essential to auditing.
- **Fair presentation:** the obligation to report truthfully and accurately
- **Due professional care:** the application of diligence and judgment in auditing
- **Independence:** the basis for the impartiality of the audit and objectivity of the audit conclusions
- **Evidence-based approach:** the rational method for reaching reliable and reproducible audit conclusions in a systematic audit process

Why do we conduct internal audits?



GMP Requirements for Internal Audits (Chapter 9)

Principle: Self inspections should be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice principles and to propose necessary corrective measures.

- 9.1 Personnel matters, premises equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self inspection, should be examined at **intervals following a pre-arranged program**
- 9.2 Self inspections should be conducted in an independent and detailed way by designated competent person(s) from the company. Independent audits by external experts may also be useful.
- 9.3 All self inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.

Audit Plans and Schedules

- Different companies do it differently – there is no one right way
- Annual “big bang” audit over several days
- Rolling audit based on cGMP chapters
- Rolling production line audits – follow the process
- Quality systems audits - Deviations and CAPA systems
- **GMP Requirements:**
 - SOP for conducting audits + audit record form
 - Annual schedule based on risk assessment – QA approved and updated
 - Record of when audits were conducted and by whom
 - Approved reports for each audit
 - Documented corrective actions

What Should be Audited ? (WHO Basic GMPs)

The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control.

Items for self inspection include:

- | | |
|--|--|
| (a) personnel | (h) documentation |
| (b) premises | (i) sanitation and hygiene |
| (c) maintenance of buildings & equipment | (j) validation / revalidation programmes |
| (d) storage of materials & finished products | (k) calibration of instruments |
| (e) equipment | (l) recall procedures |
| (f) production and in-process controls | (m) complaints management |
| (g) quality control | (n) labels control |
| | (o) results of previous self-inspections and any corrective steps taken. |

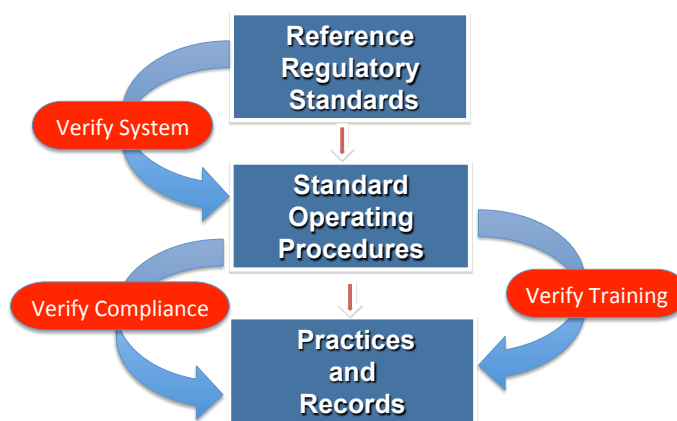
What Should be Audited ? (current areas of interest)

- Performance of the Quality System
- Adherence to Metrics
- How anomalies are resolved (Deviations, Complaints etc.)
- Data Integrity
- Cross – Contamination potential
- Annual Reviews:
 - AQRs for products
 - Water and EMs
- Supply Chain Integrity

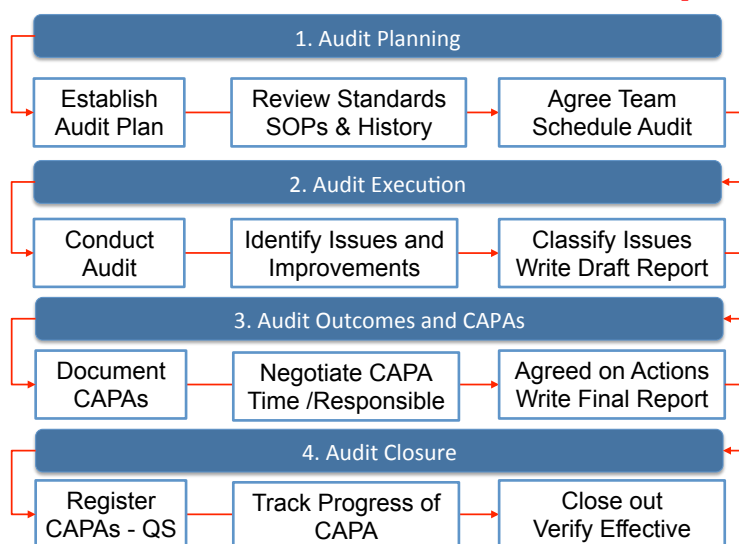
Example Audit Schedule

Document Number	RL xxxxxx		Internal Audit Register - Annual Schedule				Prepared By		Date	
Controlled Copy No										
Effective Date							Authorised By (QA)		Date	
Review	N/A									
Refer to SOP xxx - Internal Audit										
Report Number (restart each year)			Auditor(s)	Audit Topic / Area Audited	Planned Audit Date	Actual Audit Date	# NC	CAPAs	Agreed Close Out Date	Date Checked and Filled
IAR	Year	Sequence Number					(list # C/ M/ O)	Number these		
IAR	15	003								
IAR	15	004								
IAR	15	005								
IAR	15	006								
IAR	15	007								
IAR	15	008								
IAR	15	009								
IAR	15	010								
IAR	15	011								
IAR	15	012								

Top Down Auditing



Audit Process Flow – 4 Steps



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1. Planning – Research/Reference Industry Standards

Regulations and Codes

- cGMPs
- Industry Guidance Documents e.g. FDA OOS Guidance, PICS Utilities etc...
- Standards: Laboratory or ISO Standards eg ISO 14464, ISO 17025

Internal Documents

- Company Quality Policies,
- Standard Procedures and
- Master Instructions

Must be able to reference audit to aspects of published standards

Product and Material Specifications - BP/EP/USP

Product Registration Documents

- (A)NDA, BLA, IMPD, MD etc

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1. Planning – Research/Reference Industry Standards

- Can use Standard Checklists:
 - Advantages: Keep the audit focused and prompts auditor
 - Disadvantages: Limits investigative aspects – follow the lead
- Can use simplified “Audit Plans”
- Should provide an agenda to auditee in advance
- Company SOPs provide a very useful substitute for checklists

Audit Plans (Modified Checklists)

- List reference standards and relevant Company SOPs
- List Key Questions to be addressed
- List key SOPs and Records to be reviewed
- List monitoring or history records

Audit Plans (Example – Water System)

Reference Standards and Company SOPs

Doc #	Title
	SOP or Water Quality Manual covering sampling, maintenance, sanitation, monitoring, clean etc
	BP/EP and USP monographs for Purified, Highly Purified and WFI water
	BP/EP and USP Methods of Test for water samples (microbiological and chemical)
	FDA guide to inspection of purified water systems – 1993
	PICS Guide to Inspection of Utilities - 2002

Key Questions and Issues (also refer to PICS Guide to Inspection of Utilities – 2002 for critical questions)

1	Are there published current drawing describing the systems ? Show all units and sample points ?
2	Are the Sops for maintenance, sampling , operation, monitoring, start up/shut down, sanitation ?
3	Does a physical review of the system indicate same as drawings – are drawing “as built” and are units and piping to full GMP standards.
4	Are there records of physical monitoring units (DI/RO/UV/Filters etc), sanitation – complete ?
5	Validation/Qualification package for the system plus changes to the system ? System under change control program ?
6	Alert and action limits established for all steps (source, purification steps, storage, distribution) ? Consistent with regulatory and BP/EP/USP standards ?
7	Do history records/trends indicate control – are all out of limit conditions investigated/reports ? Are there annual reviews of performance ?
8	Are validated laboratory tests used and are organisms speciated regularly ? any pseudomonads ?

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Example – Critical Questions (Validation Programs)

- 1 Does the company have a published Master Plan ? Is the master plan comprehensive and include risk assessment?
- 2 Are the plans and protocols in line with regulatory requirements ? QA oversight ? Is there consideration of “worst case” ?
- 3 Does the company have specified responsibilities, a validation schedule & resource planning ?
- 4 How are validation deviations managed ?
- 5 Are reports signed off before next stage ?
- 6 Application of risk assessment ? Is it appropriate ?
- 7 Is raw data available and easily traceable ? Any omissions ?
- 8 Is there a filing and archive system ?
- 9 Is there a system for re-validation ?

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Audit Team Members

- Keep the teams small – minimum 2, no more than 4
- Appoint a Lead Auditor
- One member should have expertise in audit area
- Do not allow inexperienced persons to lead audits
- Audit must be objective – independence of audit team members from activities being audited
- Ensure there is no potential conflict of interest
- Ensure auditor and auditees can work co-operatively

2. Audit Execution – Important Tools

- Share the audit plan with auditees
- Clipboard, note pad and 2 pens
- Copy of cGMP handy
- Access to a calculator
- Have a good sense of humour !
- Be engaged in the audit – come prepared

2. Auditor Attributes

Good Auditor

- Objective and independent
- Knowledge of technology
- Organised and methodical
- Sticks to the timeframe
- Inquisitive – tell me more
- Good interpersonal skills
- Improvement atmosphere
- Good Listener

Poor Auditor

- Carries a bias
- Talks too much – opinionated
- Dis-organised – jumps topics
- Wastes time on trivia
- Doesn't take notes
- Mis-interprets evidence
- “Gotcha” atmosphere
- Too benign – “seems OK”

2. Auditor Interview Skills

- **Show Me !**
- **Please step me through the SOP !**
- **“A picture is worth 1000 words”** ... physically look at equipment and operations.
- Facts/Analysis only style – little discussion
- Conversational style – what if this happened ?
- Process style – follows SOPs and Records
- Mix of **Open** and **Closed** Questioning
 - Do you qualify your equipment ? (Closed)
 - How do you qualify your equipment ? (Open)
- Avoid self fulfilling questions - I assume this is done this way ?

2. Audit Sampling

- Auditing as a sampling exercise – cannot see everything
- All sampling by nature has inherent risks – drawing conclusions from very small sample sizes
- “Sample size of 1” when drawing conclusions is dangerous
- Too many samples means losing overall timeframe / objective
- General rule of thumb – sample 2 – 3 records to review:
 - if all OK - move on
 - If 1 is not OK, ask for more
 - If 2 - 3 are problems – move on

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2. Audit Note Taking

- Specific observations - not generalizations/no trivia
- Record Document and Ver #, Lot #, Interviewees, results etc
- Tip! have a code for issues e.g..
 - * = follow up issue
- OK or Tick = positive observation
- R = recommendation
- NC = cGMP deficiency
- Summarise at end of each day

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Classifying Observations (The hard part)

Critical	<ul style="list-style-type: none"> • Consumer Safety issue (Identity, Purity, Performance / Strength or Safety) • Directly observable
Major	<ul style="list-style-type: none"> • May impact safety “related or indirect” • Non compliance with basic GMP principles • Non compliance with Registration details
Minor/Other	<ul style="list-style-type: none"> • General Housekeeping • Unlikely to impact product quality

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Classifying Observations 25

Canadian HPB Risk Classification GMP Observations (Canadian Health Authority)

- Whereas it is recognized that it is impossible to encompass every situation that may generate a risk, the following principles should be considered:
 - The risk assigned will be in relation to the nature of the deviation as well as the number of occurrences.
 - Generally, when only **low risk products** are involved, a critical risk will not be assigned to observations described in Appendix 1, except for extreme situations such as fraud or widespread cross-contamination, infestation or unsanitary conditions.

HPB Guide 0023 Risk Classification of GMP Observations 2003

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Classifying Observations 26

HPB Risk Classification GMP Observations

(Canadian Health Authority)

- A critical product is one for which any of the following criteria may apply:
 - narrow therapeutic window
 - high toxicity
 - sterile product
 - biological drug
 - complex manufacturing process

HPB Guide 0023 Risk Classification of GMP Observations 2003

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Classifying Observations 27

Examples of Critical Deficiencies

- Lack of sterilisation validation (relevant to all sterile products)
- Inadequate segregation of manufacturing of high risk products, such as penicillins, cephalosporins, cytostatics, steroids, hormones, resulting in a risk of contamination
- (relevant to prescription medicine manufacturers but critical deficiency also if possibility of cross contamination to any other product)
- Evidence of gross pest infestation (relevant to all manufacturers)
- Falsification or misrepresentation of analytical results or records (relevant to all manufacturers)
- Raw materials not tested (including proper identification testing) to ensure compliance with specifications (relevant to all manufacturers)
- Release of materials or finished product not meeting specifications.
- No master batch documents (relevant to all manufacturers)
- Absence, falsification or misrepresentation of manufacturing and packaging records (relevant to all manufacturers)

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Classifying Observations 28

Examples of Major Deficiencies

- Lack of validation of critical processes (applicable to all medicines, but could be critical for low dose/high potency products; particularly sterilisation processes for sterile devices)
- No or grossly inadequate air filtration to minimise airborne contaminants
- Cleaning program not followed and evidence of dirty premises/equipment or non-validated cleaning procedures
- No data available to establish the shelf-life of registered medicines
- Damage (holes, cracks, peeling paint) to walls/ceilings in manufacturing areas where product is exposed
- Design of manufacturing area that does not permit effective cleaning
- Insufficient manufacturing space that could lead to mix-ups
- No raw material sampling area for medicine manufacturers)
- Deviations from instructions not approved
- No or inadequate internal inspection program

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Examples of Major Deficiencies

- Sanitary fittings not used on liquid/cream manufacturing equipment
- Stored equipment not protected from contamination
- Individuals in charge of QC/production not qualified by education, training and experience
- Inadequate initial and ongoing training and/or no training records
- Cleaning procedures not documented and/or no cleaning records
- Production equipment cleaning procedures not validated
- Reduced QC testing of raw materials without data to certify suppliers
- Test methods not validated
- Complex production processes for non-critical products not validated
- Unapproved/undocumented changes to master batch or equivalent documents
- No proper release for supply procedure

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Classifying Observations 30

Minor / Other Deficiencies

- Departures from cGMPs that are not classified as Major or Critical
- Repeated related minors equate to a Major if they are grouped.

Recommendations for Improvement

Auditors should consider recommendations for improvement where they can see an opportunity to improve efficiency or strengthening of a procedure.

Closing Meeting and CAPA

- Arrange a closing meeting with auditees as soon as the audit is complete
- Lead auditor should explain the outcome of the audit observations
- **State the “positives”**
- **List the negatives** – they are not classified at this time but indicate which are more significant and which less so
- Invite auditee feedback – they have opportunity to correct an error at this time.
- Most of the issues should be already known through the audit process – nothing new is tabled.

Preparation of Final Report

- Within maximum of 2 weeks from audit.
- All auditors contribute to final report
- **Must be balanced.** State positives as well as negatives
- No need for lengthy narrative/introduction
- Group related observations into one NC and list examples as evidence
- Must reference NC to a cGMP clause or SOP
- Unless previously agreed do not state CAPAs
- Publish the report and provide time for auditee to respond (weeks not months)

Grouping Observations

- The requirements of *Clause(s)# 1.1*, that *“the system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that...arrangements are made for the manufacture , supply and use of the correct starting and packaging materials , that “all necessary controls on intermediate products.. ... are carried out”* were not fully met – for example:
 - At any point in time, complete inventory records of raw materials and packaging materials - by identity (code and lot #), location and quantity - were not available.
 - FIFO was not utilised when issuing of raw materials & components for use in manufacturing.
 - Within the storage area of Factory X, the box of filters was labelled with Item Code and GIN, while the contents of the box were labelled with GIN only.

Grouping Observations

(Major) The Release for Supply step did not meet the requirements of the cGMP Clause 1.3 in that:

- (1) The release step relies upon an email list from the QA group to the warehouse group. The ERP status is changed later. It is considered that the email system is informal (outside the quality system) while the ERP system is the formal system i.e part of the quality system).
- (2) FRM Lab xxx (Product Release Checklist) which is used by QA to evaluate testing and batch records as part of the release step lacks sufficient detail checking steps. It is acknowledged that these checks do take place at the process control level but not verified at the final release step.
- (3) Warehousing/Production staff apply reject labels not a QA/QC representative.

Grouping Observations (FDA)

Critical Our investigator(s) observed specific violations, including, but not limited to following:

1. Failure to record all quality activities at the time they are performed.
 - a. On October 26 the investigator noticed that in the packaging area:

a production employee had recorded the final packed quantity of the batch in Step xxx even though the quantity was not yet known because the operator had not yet weighed the batch. Immediately after observing the incident, the investigator requested a copy of page 6 of the batch record containing Step xxx and was given a photocopy.

A full batch record provided later that day did not include the original page 6. Instead it included a new version of page 6.
 - b. The investigator observed at least two examples when a manufacturing step was recorded in the batch record before it occurred:
 - i. The production operator had already recorded the start time for step xxx and Step yyy as 12:15 PM on October 26, 2012, although it was still 11:00 AM when our investigator noticed this situation.
 - ii. For xxx at approximately 11:00 AM on the same date, a production officer had already recorded RM xxx used for the API aaa in the Batch record at step xxx, although the step had not yet occurred. The had not been pre-weighed or otherwise measured out in advance.

3. Audit Outcomes and CAPAs

- Auditee must consider what CAPA action is appropriate
- Should consult QA and Senior Management
- Can use the company CAPA record to do this
- Must respond quickly to a critical deficiency
- A CAPA is a commitment to correct something – Consider
 - Resources
 - The timeframe
 - Whether the CAPA fixes the system or only the symptom.
- State the **Corrective Action** and, if warranted, the **Preventive Action**
- Commit to negotiated timeframes for CAPA

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3. Audit Report – Suggested Layout

Internal Audit Report _____

Location/ Department: _____

Title of Audit: _____

Audit date/s: _____

Auditors: _____

Audit standard: _____ PIC/S cGMP or _____

Internal Audit Number:

COMPANY CONFIDENTIAL REPORT

Auditor to Complete		Auditee to Complete		QA to Complete	
#	Summary of Critical Deficiencies (reference cGMP or standard)	CAPA Actions		QA Review	Response Accepted Y/N
		Response Date: →			
		Identified Root Cause:	Proposed Completion Date		
		Intended CAPA action/s			
		1			
		2			
		3			
		Objective evidence provided:			

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4. Audit Closure

- Register CAPAs with CAPA Tracking Number
- Assign Responsibility for CAPA
- Agree on Close Out Date
- Agree on Objective Evidence needed to close out
- Agree on whether QA close out verification is required to check effectiveness
 - Critical NCs always
 - Major NCs by negotiation
 - Minor NC – not required
- QA schedule follow up meeting(s) to check progress with assigned persons

Some Regulatory Observations regarding Internal Audits

- The GMP audit was not conducted by trained individuals;
- Necessary corrective actions (including re-audits) were **not taken**;
- The quality audit (or re-audit) report was **not reviewed by management** having responsibility for the matters concerned;
- The audit findings and CAPAs were not reviewed and approved by QA;
- Corrective action commitments were not met in agreed timeframes;
- Senior management were not aware of critical audit findings;
- The Internal Audit /CAPA System was not effective .. In that multiple cGMP deficiencies were identified by Inspector that were **not part of the internal CAPA system.**

Final Disclaimer

- *“Since auditing is a sampling exercise, and it is not possible in a limited time to identify every area requiring attention, it is important that the issues raised be assessed as potentially symptomatic of additional items requiring attention.”*
- “Corrective action should address the specific non-conformity(ies) and any underlying cause(s).”
- “Items which were considered to be of a minor nature are listed for information only.”



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