Advanced Clinical

WHITE PAPER

The Importance of GCP and GMP Audits to Verify Clinical Trial Compliance

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Introduction

Auditing is an essential element and key function within the pharmaceutical industry, offering information about the state of study trials, quality of products and effectiveness of systems and processes.[1] Regular audits help companies ensure patient and product safety, avoid gaps in compliance, and prepare for regulatory inspections. Within the clinical trials environment, Good Clinical Practice (GCP)[2] and Good Manufacturing Practice (GMP)[3] intersect with investigational product (IP), therefore there is a need for understanding the requirements for both. The fundamentals and general process for audit performance are similar whether conducted for GCP or GMP audits. However, areas of review and assessment are different for each. Authored by experts from Advanced Clinical, this white paper examines the key steps in audit performance—planning, preparation, conduct, reporting, follow-up and closure—outlining the differences and similarities in process and scope of review between GCP and GMP-focused audits.

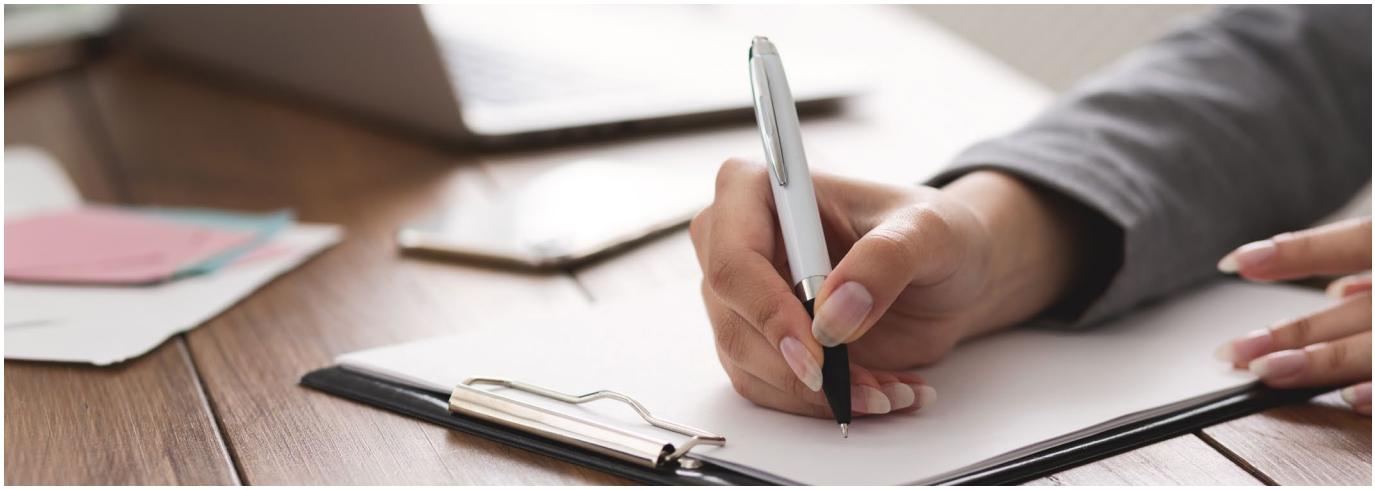
Areas of focus for GCP and GMP audits

GCP site audit objectives and key focus areas include:

- Patient safety and verification of Principal Investigator (PI) oversight
- Documented evidence of a Quality Management Systems (QMS), including site procedures and evidence of training
- Compliance with all study protocol requirements, including relevant regulations (see sidebar for examples), Institutional Review Board (IRB)/Ethics Committee (EC) requirements and IP management

GMP vendor audit objectives and key focus areas include:

- Verification of compliance with country and product-specific regulatory requirements (see sidebar for examples of applicable US regulatory requirements) for manufacturing, packaging, labeling, storage, testing, and shipment of pharmaceutical products to ensure product safety, identity, strength, purity, quality, and efficacy (SISPQE).
- Documented evidence that a robust QMS is in place and ensures that staff is adequately trained; detailed procedures are specified and followed; documentation of work is completed in a timely manner; facility, environmental, system, cleaning, equipment, process, and product control via validation and testing; and there is adequate management oversight. Although a GCP QMS may also cover some of these areas, GMP facility and process standards are seen as more rigid to ensure the SISPQE of the product.



U.S. Regulatory Requirements

GCP [4]

Compliance with all study protocol requirements, including those related to:

> US 21 CFR Parts 11, 50, 54, 56, 312, and 314 (Code of Federal Regulations – Applications for FDA Approval to Market a New Drug)

> ICH (E6) R2 Harmonized Tripartite Guideline for GCP

> FDA Bioresearch Monitoring (BIMO) Compliance Program[5] Guidance Manual (CPGM) 7348.811

GMP [6]

Compliance with regulations that apply to GMP facilities include several that fall under the 21 Code of Federal Regulations

> Parts 210 & 211 – cGMP in Manufacturing, Processing, Packing, or Holding of Drugs and Finished Pharmaceuticals

> Part 11 Electronic Records; Electronic Signatures

> Part 820 Quality System Regulation

> Part 600 Biological Products

> Part 812 Requirements for Clinical Trials for Medical Devices

> ICH Q7 Good Manufacturing for Active Pharmaceutical Ingredients

> ICH Q10 Pharmaceutical Quality System

There are six key steps associated with performing audits (planning, preparation, conduct, reporting, follow-up and closure). Similarities and differences between GCP and GMP audits for each of these steps are outlined below.

Step 1 - Planning: Contract Review and Definition of Audit Scope

GCP and GMP audit planning involves similar approaches.

The Quality Auditor meets with the client to review contract details and define the audit scope. During this meeting areas of focus or concern, a detailed review of services provided by the auditee, a review of relevant historical information, information on electronic systems to be accessed during the audit, and identification of a point of contact at the site/facility are discussed.

The Quality Auditor reviews specific requirements for visiting the site/facility (for example: COVID-19 policies, requirements for Personal Protective Equipment [PPE], confidentiality agreements, access badge and/or screening and facility/campus layout) to ensure an on-time start and optimization of time allotted to perform the audit.

An audit plan and/or audit confirmation letter is developed based on contract requirements and the area(s) of focus discussed during the initial meeting with the client. These documents serve to fully outline the purpose, scope, focus, regulatory references and timing of the audit and provide the auditee with a high-level agenda. They also ensure mutual agreement and understanding of the details to be covered during the audit and the timeframe for audit completion.

Step 2 - Preparation: Checklist and Tool Development

Preparation for GCP and GMP audits differ in several ways.

GCP Site Audits:

The Quality Auditor should request and review applicable documentation from the client/sponsor, including the protocol, investigator brochure, protocol deviations list, serious adverse events (SAEs) list, monitoring plan and interim monitoring reports. In reviewing the protocol, the Quality Auditor should be alert for anything atypical compared with similar studies in terms of protocol synopsis, inclusion/exclusion criteria, schedule of assessments and key changes that occurred over the course of the study. A copy of the protocol should be available for reference during the audit. This documentation should also be readily available during the audit.

An audit checklist and other tools should be prepared to support the audit. These should contain as much information as possible, including versions of the protocol, investigator brochure, and informed consent forms that will be reviewed at the site. A tool should be developed for the review of patient files and other source documentation, for example, a schedule-of-assessments print-out for notes on each subject or a table should be added to the audit checklist to ensure all applicable information is captured. All tools should be user-friendly and streamline the auditor's review process.

GMP Vendor Audits:
Similar to GCP audits, documentation should be requested from the client and/or auditee in advance of the audit. Typical pre-audit requests involve documentation outlining site overview details, including services/capabilities, shifts/hours of operation, a facility layout diagram, process flow, details of computerized systems in use at the site and their functions, a current organizational chart, the quality manual and quality policy, a Standard Operating Procedure (SOP) master list, and regulatory inspection history details, including any observations and criticality rankings.

An audit checklist and tools should be prepared to assist during the audit and should outline areas of review and capture notes with as much information as possible.

If the GMP audit will be conducted virtually, the Quality Auditor should ensure access to a secure document sharing platform and the ability to perform a live virtual tour of the facility or review pre-recorded videos.

Step 3 - Conduct: Audit Etiquette and Areas of Focus

Preparation for GCP and GMP audits differ in several ways.

GCP Site Audits:
When conducting a GCP audit, an opening meeting is held (which can oftentimes be brief and informal) to meet the site staff, discuss the audit agenda, the flow of the audit, and understand staff availability. The Quality Auditor should ensure access to any electronic systems, submit known requests for documentation to be reviewed, and be shown how to access source data such as electronic medical records.

Significant audit focus areas include:

- Facility tour of clinic areas related to the study in order to examine the process for patients participating at the site, in addition to key areas used for consent, patient assessments, equipment, sample processing/shipping, document storage areas and IP storage, which may be within a pharmacy depending on the size and complexity of the site.
- Examining documents such as the:
- Delegation of Authority (DOA) log documenting appropriate PI oversight of the study
- Patient screening log, along with initial informed consents to ensure these were given freely prior to any study assessments
- Other patient-related files, such as inclusion/exclusion criteria, source documentation, electronic data capture (EDC) and compliance with the protocol assessment schedule and requirements
- Investigator site file review, including the protocol and protocol signature pages, investigator brochure and acknowledgment of receipt pages, FDA Form 1572, financial disclosure forms, IRB approvals, IRB-approved templates of informed consent forms and any relevant correspondence
- Site-specific SOPs, such as the informed consent process, IP handling/storage/accountability/disposition and record retention; there may be various levels of SOPs and QMS development depending on the site
- Staff qualifications, education and experience, and training (study-specific, GCP, and Health Insurance Portability and Accountability Act [HIPAA])

A closing meeting should be held to share any unclassified audit findings and to discuss the audit reporting process and timelines. An audit certificate is generated by the lead auditor following completion of the audit and forwarded to the client and/or auditee (as defined in the contract).

GMP Vendor Audits
GMP audits are generally more structured and formal. An opening audit presentation is typically given by the audit host(s) and/or relevant subject matter experts (SMEs). A dedicated team typically supports audit documentation requests, organizes a facility tour, and coordinates SME interviews when questions arise that cannot be answered directly by the host(s).

Significant GMP audit focus areas may include:

- Facility tour, following the process flow of material receipt, storage, sampling, release, processing, testing and shipment (as applicable to services performed for the client/sponsor)
- Assessment that an adequate QMS is in place for production, packaging and labeling, equipment and facilities, materials, laboratory and quality systems at the facility

- Data integrity and adherence to 21 CFR Part 11 requirements
- Demonstrated and/or documented evidence of adherence to: established processes (such as batch record instructions during manufacturing/packaging), SOPs (including gowning requirements, pest control, security measures such as restriction on access), COVID policies (such as mask-wearing and temperature checks), testing protocols, methods and specifications
- Documented evidence that the facility is adequately staffed and appropriately trained for assigned work prior to completing duties associated with staff roles
- Demonstrated and documented evidence of adequate control of the facility, electronic systems, process, materials, and product
- Documented evidence of proper management structure (including an independent quality unit), management commitment, oversight, assessment, and engagement to address identified risks and trends as well as continuous improvement opportunities

A closing meeting is held to summarize the audit and review potential unclassified findings with the audit team, facility management and/or relevant SMEs. An audit certificate is generated by the lead auditor following completion of the audit and forwarded to the client and/or auditee (as defined in the contract).

Step 4 - Reporting: Summarizing Interviews, Documents, and Findings

The process for drafting GCP and GMP audit reports is the same, providing a summary of areas and documentation reviewed, interviews conducted, as well as any findings noted. Following approval, the audit report and/or findings table are sent to the auditee for review and feedback. Audit responses, including an explanation of any Corrective and Preventive Actions (CAPA) to be taken, should be provided to the lead auditor by the auditee, typically within 30 business days.

Step 5 - Follow-up: Ensuring Completion of CAPA Commitments

For both GCP and GMP, the lead auditor (unless otherwise stated in contract details with a client/sponsor) reviews the responses received, accepts responses and any action to be taken, or requests additional assessment or clarity to address any pending concerns. Once responses and CAPA (where applicable) are agreed to, the lead auditor follows up to verify that any commitments are completed by the target date in the response.

Step 6 - Closure: Verification and Notification

This process is the same for GCP and GMP audits; following verification of CAPA completion or commitment to follow-up during a future audit, the audit is closed, and an audit closure notification sent to the client and/or auditee.

Conclusion

Key Takeaways

Lack of compliance with regulations has a potential impact in GCP and GMP environments as well as on the overall success of a clinical trial. GCP and GMP compliance for clinical trials is required for proper IP production, handling, and management. While there are general similarities with the processes for conducting GMP and GCP audits, the focus, preparation, audit approach and depth have significant differences. Clients/sponsors can benefit from working with an external partner with GCP and GMP experience, which allows for collectively evaluating phase-appropriate requirements in each type of audit.

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- BBA from Morehead State University
- 20+ years of Quality experience in GMP (solid oral dosage manufacturing, packaging, labeling and cold chain distribution)
- 1 year of GCP - CRO Quality auditing experience (associated with site and TMF audits for phase II and III clinical trials)

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- BS in Natural Science from University of Pittsburgh – Greensburg
- 25+ years of quality experience in Good Laboratory Practice (GLP – toxicology, environmental fate, plant metabolism, etc.), Good Manufacturing (GMP – solid oral dosage contract manufacturing organization) and Good Clinical Practice (GCP – clinical research organization [CRO])

Resources

1. https://ispe.org/training/online-learning/gmp-auditing-pharmaceutical-industry
2. https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/good-clinical-practice
3. https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps
4. https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials
5. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-manual/bioresearch-monitoring-program-bimo-compliance-programs
6. https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations

