Structured GMP Audits

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ABSTRACT

Although Good Manufacturing Practices (GMP) audits are common both for internal and external customers, a structured approach to planning and execution can result in a successful well-executed audit. There are a variety of audit types (GMP baseline, GMP risk-based, due diligence, product-specific, procedures, area-specific, etc.) that may be scheduled for a variety of reasons (preventative or remedial, Regulatory Agency findings, inspection readiness, product or process failures, complaints, deviations, routine assessments of systems, etc.). The proper planning, management, facilitation and execution of an audit are critical to a successful audit. A complete and concise report of the exercise provides maximum benefit to the customer.

INTRODUCTION

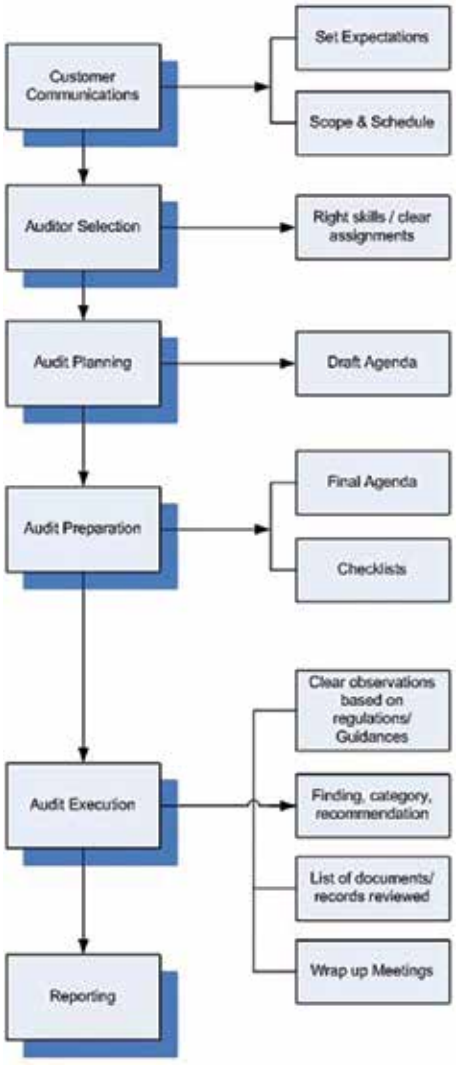
GMP audits are an important activity in a site compliance program. An organization that initiates a GMP audit has clear objectives and expectations for the audit. A significant amount of time, personnel effort, and cost is expended in a GMP audit. Audits that are properly planned, structured, and executed should yield maximum benefit to the organization. A successful audit will result in the appropriate level of coverage, clear direction, guidance, communication, controls, appropriate auditor skills for the respective site areas, clear observations, good recommendations, and customer satisfaction that audit objectives and expectations are met.

A properly planned audit should be carefully structured to comprise several defined activities. These include

- Customer communication. Customer objectives set the objectives, tone, focus, and technical scope for the audit.
- Auditor selection. Competent auditors with appropriate expertise (technical, regulations, industry practices, etc.) must be selected. Multiple auditors may be required to successfully audit widely divergent technical areas.
- Audit planning. Early communication and sharing of any manufacturing, facility, and customer information. A proposed agenda and audit focus is determined.
- Audit preparation. The proposed agenda is reviewed with the customer to finalize specific audit activities. Site documents to be reviewed in the audit are requested.
- Audit execution. The actual audit is performed as planned and prepared in prior discussions.
- Audit report. Results of the audit are communicated to the customer.

Figure 1 describes the sequence of activities in a structured GMP audit.

Figure 1: Structured Audit Approach



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CUSTOMER COMMUNICATION

The customer requesting an audit may be a client, internal department, or external group or firm. Understanding the customer reasons and concerns must set the tone for the focus of the audit. If client is external, ensure a Confidential Disclosure Agreement (CDA) is in place before the final audit planning since a customer may be reluctant to disclose known internal issues.

It is critical to understand the basis for the audit. For examples, audits may be routine, voluntary, prior to merger or purchase, product or process failures/focus, deviations, complaints, Regulatory-Agency driven, and other types. Pre-audit discussions must include participation from customer compliance or Quality Assurance (QA) contacts. It is fairly common for initial customer contacts to be with executive management or with operations management representing the site who may not have a strong Quality/Compliance background. These individuals may not be able to clearly express any compliance-related concerns and focus for the audit.

Mock audits may be conducted to prepare and make ready a site for a future regulatory agency audit. These mock audits require a trust-based relationship between the customer and auditors to ensure all potential risk areas are addressed without bias or prejudice. The customer is provided with a complete report that identifies areas of compliance risk before they become investigation findings or present a risk to product safety at the completion of the mock audit.

A firm date and time should be set as well as the duration of the audit and number of auditors. Specific and special needs of the customer should be identified, such as internal resource issues when multiple systems are audited concurrently.

Audit Types and Approach

General pharmaceutical Good Manufacturing Practices (GMP) audits, risk-based assessments, due diligence, and baseline audits contain many of the same requirements for audits. These audits may vary in length of time, depth of the audit, number of auditors, and perhaps focus. They may be limited to a specific product, area, or procedures. There are many different approaches to performing audits. One of the more common approaches is to take a systems approach in assessing the six systems described in the FDA "Code of Federal Regulations", Good Manufacturing Practices:

- Quality Systems
- Facilities and Equipment System
- Materials Controls System
- Production Controls System
- Packaging and Labeling System
- Laboratory Controls System

Sub-systems would include any requirements listed in the CFR within the above system categories. For example, a facilities and equipment system audit might assess the following sub-systems: Physical facility space, maintenance and repair function, utilities qualification, temperature/humidity controls, equipment qualification, cleaning validation, and other related systems.

Audits should be conducted for compliance with 21 CFR Parts 210/211/11, ICH (International Conference on Harmonisation) Q10, Pharmaceutical Quality Systems; ICH Q9, Quality Risk Management; ICH Q8, Pharmaceutical Development; and any relevant US FDA Guidances such as process validation, stability, Active Pharmaceutical Ingredients (APIs), aseptic manufacturing, and so on. Additional requirements for compliance with any international regulatory agencies should be clarified with the customer.

AUDITOR SELECTION

Auditors should be subject matter experts (SME) with focused areas of expertise. It is rare to identify someone who has the technical qualifications and can successfully audit all of the systems listed above with a comprehensive knowledge of the requirements, industry practices, and regulatory guidance recommendations. This expertise should extend to the customer products manufactured – oral sold dose, API, sterile products, OTC (over-the-counter), etc. Also extremely important are the personal communication skills of the auditors. An audit is not based on opinion or preference, but on compliance with the regulations and guidance documents. An audit should ultimately result in knowledge transfer from the SME to the customer in a partnering, helpful, and non-threatening fashion.

With the more common audit addressing the six systems, and the most common risk-based audit being conducted in 3-5 days, the best results for appropriate SME coverage are by assignment of at least three auditors. All of the auditors should be experts in the regulations and their applications, and have years of auditing experience. For any audit including a laboratory, one of the three auditors must be a chemist. The remaining five systems should be divided among the auditors based on their qualifications, capabilities and experience. All must have GMP expertise and working knowledge of their specific expertise and applications.

Oral solid dosage and aseptic manufacturing may require specific skills and expertise in production and facilities. An auditor with technical microbiology background should be engaged to conduct the microbiology lab audit for aseptic processing.

Once auditors are selected and audit dates are confirmed, copies of the respective auditor CVs/resumes and auditor contact information are provided to the customer.

AUDIT PLANNING

Early communication and sharing of any manufacturing, facility, and customer information with the auditors is a key to the success of the audit. Plan a conference call with the auditors ahead of the audit, for which customer background has been provided in advance of the call. Assign a lead auditor to provide audit guidance and cohesiveness of the audit team, answer auditor questions, report concerns, and act as primary communicator between the customer and the team. A draft agenda should be reviewed with the auditors for the opportunity to identify additional areas of concern or focus to be assessed. Timing should also be reviewed with the auditors to ensure they are comfortable with the time allotted to each area. Preliminary responsibilities should be assigned and discussed. It may be beneficial to mix responsibilities

across systems based on technical qualifications. This should be clearly delineated, documented and shared with the auditors to ensure the responsibilities are understood and the sub-system assessments are fully covered.

AUDIT PREPARATION

Audit preparation based on above plans is the next phase of the structured audit. Once finalized, the proposed agenda is provided and reviewed with the customer for comment. The agenda should include a brief overview presentation of the site and products by the customer and a tour of the facilities to fully acclimate the auditors. Each audit day should end with a status meeting with auditors and appropriate site personnel. The schedule should include time for auditor preparation prior to end-of-day wrap-up discussions. The end-of-day discussions present the most significant findings and observations from the day to the customer.

A brief list of documents for the customer to provide to the auditors ahead of the audit and during the audit should be developed. This will allow the auditors to come prepared and allow the customer to begin retrieving documents. One of the most helpful documents is an organizational chart to identify responsible heads of the systems groups. Past inspection reports and responses can be beneficial to understanding the areas of highest compliance risk. Each auditor must devote a few hours of time ahead of the audit to prepare and review for the audit.

The agenda is finalized and distributed to the primary customer contacts and auditors prior to the actual audit day. Final dates, location, times and contact information are distributed to all involved.

Detailed checklists should be prepared which follow the GMP requirement sections in the CFR to assess the quality system sub-systems. These may be tailored to focus on potentially problematic areas for the customer if applicable. For example, if commitments have been made in the past two years to a Regulatory Agency, it may be beneficial to include a review of the status of those commitments for verification of completion. Checklists should be further tailored for the audit type. Shorter risk-based and due diligence audits will focus on the areas of highest potential compliance risk. This requires the preparer to have a full understanding of the customer compliance status, as well as knowledge of industry compliance trends and regulatory agency key focus points. A well-structured checklist ensures that all scheduled sub-systems are assessed and there is appropriate coverage of the topics defined by the audit type and focus.

AUDIT EXECUTION

Actual performance of the audit as planned and prepared is then initiated. It can be beneficial for the auditors to meet in person ahead of the audit to discuss any concerns and additional questions they might have. If external auditors, they should arrive on site together and plan enough time to sign onto the site in advance of the scheduled start time. Internet connections should be available to them when they arrive and set-up time should be allowed to minimize disruptions when the audit starts.

Unless the customer prefers to lead the opening meeting, the lead auditor should be prepared to initiate the audit. This should include brief introductions from auditors and customers. The auditors should focus on relevant background, expertise, and areas each will be involved in assessing. A review of the agenda and responsibilities with all involved should be performed.

The auditors should provide additional lists of documents required for review in their relevant areas to their customer contact at the beginning of each audit day. The status of each of the documents requested, when requested, and when received should be documented. All site procedures should be readily available to all of the auditors on day one of the audit. Rapid retrieval of information is an important factor in Regulatory Agency audits.

The auditors must maintain a list of documents reviewed by title, number, version, and effective date for listing in the final report. It is recommended that the auditors address higher compliance risk sub-systems first in case more detailed review is required requiring more the originally allotted time. Time constraints may then preclude auditing of other areas as previously planned. The lead auditor should be kept informed of the status of such constraints if sub-systems must be re-assigned during the audit.

A review of the audited area standard operating procedures (SOPs) is necessary to understand the customer's requirements. If not compliant with regulatory requirements or agency guidances, this should be noted as a finding. Evidence of the execution of the SOPs must also be reviewed to ensure the SOP is being followed in practice. Any SOPs, records, logs, other documents reviewed as supporting evidence must also be identified. While conducting the audit, ensure that documented evidence of any findings are reviewed and references noted. Findings related to observations must be referenced by document title, date, area, and book and/or page number such that the customer is able to locate and correct the observation as applicable. Too many audits draw conclusions about the compliance of a system without looking beyond the SOPs to the actual execution of the SOPs in practice.

Thorough audits cannot be conducted solely from a review of documentation unless such limited focus is specifically requested. Plant walk-throughs can uncover a host of problems not evident unless the auditor is actually present on the plant floor or in the laboratory. Physical maintenance, operational cross-contamination risks, people flow and gowning, material and product flow, and storage issues may be readily identified – but only if the auditor devotes sufficient time to the actual operations area. Discussions with and observing activities of operators and analysts can also identify processes which are not represented in an SOP or activities which are not compliant.

A daily wrap-up meeting each day is recommended to review significant findings of the day. The meeting ensures that the customer understands the nature of the findings. It also provides the customer an opportunity to refute any findings with additional information that might not have been originally available to the auditors.

AUDIT REPORT

The audit report provides finding of the audit team for review and initiation of remediation by the customer. The lead auditor should obtain copies of the facility/product overview presented by the customer at the beginning of the audit. This may be summarized in the report to include a description of the facility, types of products manufactured, previous regulatory agency inspection dates, and any other pertinent information audit information.

Each finding should be accompanied by document/record evidence of the inadequacy or non-compliance associated with the observation as applicable which require a review of associated records. The finding must be stated as a finding -- not a recommendation -- and based on clear, referenced evidence. Some customers prefer to have the regulatory reference provided in the report as well. Auditors should take care not to provide a personal opinion. It may be that the typical industry practice is to implement a process in a certain way, but if the customer process is different and compliant, it is simply a personal opinion and not a requirement. If industry practice differs from the manner in which the customer performs a task, it might be noted by the auditor as a consideration but not cited as a regulatory finding.

Findings should be identified individually and categorized is a risk manner (minor, major, critical or low, medium, high) depending on the customer's requirements. Each finding should be accompanied by a recommendation for action to be taken to mitigate the finding. The more detail that can be provided in the recommendations relative to actions required, the more benefit to the customer, and the easier it is for the customer to generate a corrective action plan from the report details.

The report is combined from respective auditor inputs and reviewed to ensure findings are based solely on regulatory requirements and not on auditor opinions. Any inconsistencies are reconciled and overlaps combined. For example, a review of the deviation management process in the quality system may result in the conclusion that the system might not be fully compliant based on the SOP and records reviewed, while a sampling of selected production system-specific deviation records may have been properly reported and investigated.

Sub-systems that could not be addressed due to time constraints but were listed on the original agenda should be identified in the report.

Since many audit reports can be quite lengthy based on the areas covered and number of findings, an executive summary is beneficial to customer management who may require a high level brief reporting of the critical findings.

CONCLUSION

Consistent, well-planned, and executed GMP audits not only provide the auditors with the necessary structure to ensure all required areas are assessed, but also benefit the customer for the same reasons. From one audit to the next, even if the focus is adjusted, similar materials may be used with the same approach. Standardizing and structuring the manner in which the audit is planned and executed can ensure consistent, successful, and beneficial audits and reports.

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About the Author

Carol Brandt has over 30 years of experience in the pharmaceutical industry as a professional with expertise in strategic insight and extensive knowledge of quality assurance and computer Compliance in the healthcare industry. She holds a M.S. degree in Analytical Chemistry from Purdue University and is currently a Managing Partner in GMP Compliance with NNE Pharmaplan. For several global pharmaceutical and biological sciences companies, Ms. Brandt has managed systems operations across a global organization, supporting regulated quality assurance operations, diagnostic computer system groups, electronic record systems, manufacturing and production systems. She has held VP positions in the life sciences industry in Quality Assurance operations as well as Senior Director consultant roles, planning and executing complex compliance projects. Her responsibilities have included site licensure, FDA inspections, inspection preparation, regulatory responses and compliance with pharmaceutical State, local, FDA, CBER, CLIA and European regulations in compliance 21 CFR Parts 210, 211, 111, 820 and 11. She has also been responsible for compliance development of Quality Systems, processes, policies and procedures for OTC, dietary supplement, pharmaceutical and medical device industry leaders firms.