

Auditing as a Component of a Pharmaceutical Quality System

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Conducting internal audits (or self inspections) and external audits of suppliers and outsourcing operations are key elements of a good quality system. Audits are an effective means of evaluating compliance with the objectives of the quality system and providing feedback to management as part of a continuous improvement program. This article explores the establishment of an auditing program for both internal audits and external audits including key elements to address when implementing an auditing program.

INTRODUCTION

Conducting internal audits (self inspections) and external audits of suppliers and outsourcing operations are key elements of a good quality system. One aspect of a quality system that is identified in the recently released International Conference on Harmonisation (ICH) Q10, “Pharmaceutical Quality System” (1), and in other quality system standards such as ISO 9001 (2), is that of conducting audits as a means of evaluating compliance with the objectives of the quality system. Implementation of the quality management system model defined in ICH Q10 should result in achievement of the three main objectives stated in ICH Q10: Achieve product realization, establish and maintain a state of control, and facilitate continual improvement. Auditing plays a key role in all three of these objectives. In order to achieve product realization, appropriate quality materials must be purchased from approved suppliers; supplier approvals may involve supplier audits. Establishment and maintenance of a state-of-control requires periodic reviews of operations and processes; auditing of such operations and processes may be used as a means of conducting such periodic reviews. Results of

periodic audits serve as important input into a continuous improvement program.

The following key elements from ICH Q10 provide strong rationale for conducting both internal and external audits:

- Include both internal and external audit results as part of the process performance and product quality monitoring system
- Implement corrective actions and preventive actions (CAPA) as a result of audit observations
- Include audit results as part of management review of the quality system
- Consider feedback from periodic internal audits and external audits in continuous improvement decisions.

REGULATORY PERSPECTIVE—INTERNAL AUDITS

Although the US drug current good manufacturing practices (CGMPs), 21CFR 210-211 (3), do not require internal audits to be conducted, most other international GMPs for drug products do require self-inspection programs (see Table I), and conducting internal audits is generally considered a regulatory expectation in the US. ICH Q7, “Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients” (4), likewise calls for internal audits to be performed. US medical device Quality System Requirements (QSR) (5), which are based on ISO standards, require internal audits to be conducted. US good laboratory practice (GLP) (6) regulations require audits (inspections) to be conducted by the quality assurance unit (QAU) to ensure the integrity of non-clinical studies. Although these internal audits are required by various regulations, they are intended to be used internally to improve operations, not by regulators to view a company’s dirty laundry.

TABLE I: International regulations for internal audits.

Regulatory Citation	Regulatory Text
Commission Directive 2003/94/EC (7)	Article 14 Self inspection The manufacturer shall conduct repeated self inspections as part of the quality assurance system in order to monitor the implementation and respect of good manufacturing practice and to propose any necessary corrective measures. Records shall be maintained of such self inspections and any corrective action subsequently taken.
EU GMPs 1.2 (ix)	The system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that: (ix) there is a procedure for self inspection and/or quality audit which regularly appraises the effectiveness and applicability of the quality assurance system.
EU 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.
Canadian GMPs C.02.012	C.02.012 1. Every fabricator, packager/labeller or distributor referred to in section C.01A.003, importer, and wholesaler of a drug shall maintain (a) ... (b) a program of self inspection.
ICH Q7 2.2.7	The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include, but not necessarily be limited to: 7. Making sure that internal audits (self inspections) are performed
ICH Q7 2.4	D. Internal Audits (Self Inspection) (2.4) To verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule. Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.
<i>Japanese Standards for Quality Assurance of Drugs, Quasi-drugs, Cosmetics and Medical Devices</i> (MHLW Ministerial Ordinance No. 136 Established as of September 22, 2004) Chapter 1 General Provisions (8)	Article 6 The licensing marketing approval holder of drugs shall prepare documents describing the following procedures in order to perform the quality assurance duties properly and efficiently (hereinafter referred to as “quality assurance duties procedures etc.” in this chapter). (5) Procedures for self inspection.

Under the Food, Drug, and Cosmetic (FD&C) Act, FDA has the authority to review internal audit findings; however, FDA has chosen not to exercise such authority except in the case of litigation. FDA understands that if companies know that FDA is planning to review internal audit findings, the audits will lose their value within the company. In the US, medical device company management may be required to certify in writing that audits have

been conducted and the results documented as a means of FDA verifying compliance with the audit provisions in the regulations.

REGULATORY PERSPECTIVE—EXTERNAL AUDITS

Most international drug product CGMPs (9, 10) require suppliers to be evaluated, although in some cases such as vendor certification or validation programs, audits are

required (see Table II). All CGMPs require that materials only be purchased from approved suppliers. Recent events, such as the recalls due to contaminated heparin, have focused attention on ensuring that the controls are in place for the entire supply chain. EU Directive 2004/27/EC (11) amended EU Directive 2001/83/EC (12) to require that drug product manufacturers use only active pharmaceutical ingredients (APIs) that are produced according to GMPs. Auditing of API suppliers is a key part of ensuring that the APIs are being produced according to GMPs and ensuring product is produced (product realization) using materials meeting the required quality characteristics.

US drug CGMPs do not address auditing of outsourced operations, although they do assign responsibility to the quality control unit for “approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.” Chapter 7 of the EU GMPs (13) defines a number of requirements for addressing contracted operations or services (i.e., outsourced operations) including the requirement that the outsourced operation be assessed to determine that the Contract Acceptor is competent to carry out the work required and to ensure that GMPs are followed. The EU GMPs further state that the contract between the Contract Acceptor and the Contract Giver should permit the Contract Giver to visit the Contract Acceptor’s facilities. The methods for evaluating or assessing outsourced operations are left up to each pharmaceutical company to determine. EU GMP Annex 8 provides the following useful items to include when evaluating a supplier, which can also be used for evaluating, outsourced, or contracted operations:

- The nature and status of the manufacturer and of the supplier or outsourcing operation and their understanding of the GMP requirements of the pharmaceutical industry
- The quality management system of the supplier or outsourcing operation
- The conditions under which the material is produced and controlled
- The nature of the material and the products in which it will be used.

AUDIT PROCEDURE

Like most operations within pharmaceutical companies the first step in establishing an auditing program, whether

for internal or external audits, is to have a written procedure describing the program.

The procedure should clearly define the objective for doing audits. Some potential objectives might include:

- Measure the effectiveness of the quality system
- Provide objective evidence that adequate controls are in place
- Assure that products and processes conform to specifications.

The procedure should define the frequency of audits. Although it is not necessary to specify that audits will be conducted at a specific frequency (e.g., monthly), the procedure should define how the frequency is determined and how the operations that will be audited are determined. Audit frequency and schedules should be risk based (14). Results of past audits should be included in the risk analysis. All aspects of the quality system should be audited annually, whether in one audit or spread out over several audits.

Responsibilities for conducting audits should be identified in the procedure. The procedures should also identify the management representatives responsible for reviewing the audit report and ensuring that observations are appropriately addressed in a timely manner. When defining audit responsibilities, audit teams should be identified. The audit leader should be independent of the operations being audited. Audit team members should be knowledgeable of the operations and procedures being audited. A representative from the operation being audited should be on the audit team, as it is likely that this representative will be the most knowledgeable person on the team in regards to the operation being audited. Audit teams may vary from audit to audit and the audit team leader may also vary. Audit team members should be trained in the audit procedure and in basic auditing skills. In addition, external sources (e.g., consultants) may also be used to conduct audits. Unfortunately, in small organizations, where it may not always be possible to assemble an audit team, audits tend to be conducted by one individual. Audits conducted by one person can result in limited coverage of processes due to time and auditor experiences. Such audits may also be affected by the lack of the auditor’s knowledge or experience in certain areas since auditors tend to focus on areas in which they have expertise.

TABLE II: International regulations for supplier and outsourcing audits.

Regulatory Citation	Regulatory Text
EU GMPs 7.3	7.3 The Contract Giver is responsible for assessing the competence of the Contract Acceptor to carry out successfully the work required and for ensuring by means of the contract that the principles and guidelines of GMP as interpreted in this Guide are followed.
EU GMPs Annex 8 Section 3	Under such a system, it is possible that a validated procedure exempting identity testing of each incoming container of starting material could be accepted for: <ul style="list-style-type: none"> • starting materials coming from a single product manufacturer or plant; • starting materials coming directly from a manufacturer or in the manufacturer's sealed container where there is a history of reliability and regular audits of the manufacturer's Quality Assurance system are conducted by the purchaser (the manufacturer of the medicinal product) or by an officially accredited body.
Directive 2004/27/EC	(19) The quality of medicinal products for human use manufactured or available in the Community should be guaranteed by requiring that the active substances used in their composition comply with the principles of good manufacturing practice in relation to those medicinal products. It has proved necessary to reinforce the Community provisions on inspections and to compile a Community register of the results of those inspections.
Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use as amended by Directive 2004/27/EC	(33) in Article 46, point (f) shall be replaced by the following: '(f) to comply with the principles and guidelines of good manufacturing practice for medicinal products and to use as starting materials only active substances, which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials. This point shall also be applicable to certain excipients, the list of which as well as the specific conditions of application shall be established by a Directive adopted by the Commission in accordance with the procedure referred to in Article 121(2).
C.02.017(1)(b) Interpretation 1.2	1.2 In lieu of a contract, an on-site audit of the vendor's facilities and controls by qualified personnel is acceptable. The audit ensures that all criteria described under Interpretation 1.1 are verified. These audits are performed at an appropriate frequency, and the results are documented.

The criteria to be used for evaluation of audit observations should be addressed in the procedure. The GMPs can serve as a basic checklist, but more detailed checklists or criteria should be developed that are specific to the operation being audited. For example, if a laboratory is being audited, evaluation criteria might include such items as instrument calibration and maintenance, reagents and reference standards preparation and storage, sample handling, documentation, out-of-specifications (OOS), and analyst training. Of course each of these topics can be further broken down to more detailed criteria. Care should be taken when using checklists that items are not overlooked during the audit because they were not included on the checklist.

Often rating criteria are applied to assign a score to audit observations. If such rating systems are used, they

should be defined in the audit procedure. Rating systems may be quantitative, such as 1 to 5 with 1 being full compliance and 5 being out of compliance, or qualitative, such as critical, major, minor, or recommendation to note the severity of an observation.

AUDITORS

An audit is only as good as the audit team members' experiences and knowledge; therefore for a successful audit operation, audit team members should be chosen carefully and be properly trained.

Auditor training should include training in the audit procedure, knowledge of the processes and products to be audited, CGMPs, quality system requirements, communication skills, and human relations and interactions during audits.

Audits tend to be stressful for both the audit team members and the principals being audited, so understanding the importance of diplomacy and appropriate behavior and interactive skills can be essential to a successful audit. As an auditor it is important to remember that the auditor is really a guest, even when conducting an internal audit, and should act accordingly. For those being audited, it is essential to keep in mind that the audit team is there to help improve operations and not to attack or belittle operations. Although it is often difficult to do, audit findings should not be taken personally and neither the auditor nor those being audited should ever be personally denigrated. A level of trust and open communications are critical to a successful audit.

An audit does not need to focus on the negative findings. If positive observations are made, such as improvements in facilities or documentation due to a change in how tasks are completed, such positive observations should be noted.

AUDIT PREPARATION

In preparation for an audit, the audit team should review past audit results or histories. If an audit is being planned for an outsourcing operation or supplier, the audit team should review any regulatory inspection reports that are available and any quality agreements that are in place. When preparing for an internal audit, relevant policies and procedures should be reviewed. Time should not be wasted during the audit reading procedures that can be obtained and reviewed in advance. If audit checklists are used, specific checklist items should be prepared that are focused on the specific operations to be audited.

It is useful to prepare an audit agenda, which provides a relative timeframe for all parties involved in the audit. Such an agenda helps ensure availability of personnel, facilities, and documentation at the appropriate times. Often it is helpful to start the audit with a pre-planning meeting to review and agree on the proposed agenda. The agenda should be structured to allow time at the conclusion of the audit to discuss observations and potential corrective and preventive actions.

AUDIT CONDUCT

As previously mentioned, the audit team is a guest and therefore should abide by the rules of the operation that

is being audited. If specific gowning or hair-covering requirements are in force in an area then the audit team should comply with the requirements. Safety requirements should always be followed.

When conducting audits of outsourcing operations, it is essential to respect the confidentiality of other potential customers of the outsourcing company. Logbooks and other records may include identification of other customers and should only be reviewed by the audit team after the materials have been reviewed and cleared by the outsourcing representatives.

The audit team should not interfere with operations when conducting an audit. Audits tend to be disruptive to operations; therefore, every attempt should be made to minimize the disruptions including interfering with or distracting personnel trying to do their jobs.

Document specific observations when possible. For example, if materials are observed to be stored incorrectly the specific material including name and lot number should be recorded. Inquire about observations when the observations are made so that any explanations can be made in the context of the situation and not later when the exact details may not be available. Do not jump to conclusions when making observations. Although it is important that an auditor be experienced, it is also important that they do not let their experience bias their observations. There are often many ways to meet CGMP or quality system requirements, and the auditor should not consider the way in which he/she has always done it to be the only way.

AUDIT CLOSE-OUT AND FOLLOW-UP

At the conclusion of the audit, there should be a close-out meeting to discuss the observations. If management representatives are present, it may be possible to obtain commitments for corrective actions to be taken. Ensure that all parties have a clear understanding of the observations and any commitments to corrective actions. Timeframes should be provided for when the audit report will be made available and when responses to observations will be provided. Schedules for completing corrective actions should be developed.

Depending on the observations made and the commitments to corrective actions, a follow-up audit may be necessary. If a decision is made to not conduct a follow-up audit, the corrective actions should be reviewed in any future

audits. Documentation of the rationale for not conducting a follow-up audit can be useful for future audits; unless the audit procedure clearly defines when follow-up audits are or are not required.

Preventive as well as corrective actions should be taken to address unfavorable observations. Preventive actions are focused on improving the quality system so that the same unfavorable observations are not made again.

DOCUMENTATION AND COMMUNICATION

The audit results should be documented and communicated to management. The method of documentation and communication including the security and confidentiality of the audit reports should be defined in the procedure. It is important to remember that those responsible for the audited operation should always receive a copy of the report, including outsourcing management and supplier management. Such reports should clearly describe the audit team observations including specific examples when possible. If commitments have been made to implement corrective actions, such commitments should be included in the report. Security of audit reports should be strictly enforced and distribution of the report should be limited.

When providing audit reports to external sources such as outsourcing companies or suppliers, a subset of the internal report may be provided as long as the observations are included.

MANAGEMENT REVIEW

If the objective of the audit is to evaluate the effectiveness of the quality management system then it is imperative that management should view the results of audits as part of their periodic review of the quality system. Management should review internal and external audit results and act upon the findings as part of the continuous improvement process. Management is responsible for ensuring the effectiveness of the quality system and should be made aware of any observations that impact the quality system. ICH Q10 lists the following as potential outcomes of management reviews:

- “Improvements to the pharmaceutical quality system and related processes
- Allocation or reallocation of resources and/or personnel training
- Revisions to quality policy and quality objectives

- Documentation and timely and effective communication of the results of the management review and actions, including escalation of appropriate issues to senior management.”

ISO 9001 refers to a “Plan-Do-Check-Act” methodology for addressing processes in a quality management system. This methodology can be applied two ways in regards to audits. The audit itself may be considered a process in which one plans by developing an auditing procedure and audit schedule, does the audit, checks that the audit process worked properly, and then acts upon any observations of the audit process. Secondly, the auditing process can also be used as a part of the checking step in the Plan-Do-Check-Act methodology. The Act step is the corrective and preventive actions taken as part of a continuous improvement of the audited process.

Audits should not be viewed negatively as a means of finding weaknesses or problems, but in a positive light by looking for opportunities for continuous improvement in operations.

Of course audit results are only one piece of the total picture that management should consider when performing management reviews of operations, but they should serve as unbiased observations of opportunities for improvement.

OUTSOURCING OPERATIONS AND SUPPLIER EVALUATIONS

As mentioned previously, most regulatory requirements only require that materials be obtained from approved suppliers and that outsourced operations are evaluated. Audits are one means of evaluating both suppliers and outsourced operations. A key point to remember is that the pharmaceutical company is ultimately responsible for their product so decisions regarding the method of evaluation can be critical to the quality of suppliers and outsourcing operations used. If a supplier provides bad materials and the materials are used and the drug product is released to the market, it is the responsibility of the pharmaceutical company that made the product. To emphasize this point there are a number of discussions within the industry today regarding the need for a complete pedigree for the product to enable complete traceability of all ingoing materials.

Quality cannot be tested into the product or the materials supplied; therefore, it is important that additional measures be taken to ensure the quality of the supplies received. Ensuring that the supplier or outsourcing operation has an effective quality management system in place adds to the confidence that the materials supplied will meet their defined characteristics.

ICH Q10 provides the following guidance in regards to use of outsourced operations:

- Assess, prior to outsourcing operations or selecting material suppliers, the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (e.g., audits, material evaluations, qualification)
- Define responsibilities and communication processes for quality-related activities of the involved parties in a written agreement
- Monitor and review of the performance of the contract acceptor or the quality of the material from the provider, and the identification and implementation of any needed improvements
- Monitor incoming ingredients and materials to ensure they are from approved sources using the agreed supply chain.

There are various ways of evaluating or assessing a supplier or an outsourced operation. The method selected should be defined in a written procedure. The procedure should clearly define when an audit is required or when other evaluation methods are acceptable. The key requirement for evaluation is to ensure that the supplier or outsourced operation can provide the material or products meeting their quality specifications and requirements.

Risk assessments (see ICH Q9) may be performed as a means of determining the type of evaluation to be used. For example, an outsourcing operation for filling a parenteral product might be considered a higher risk than outsourcing a secondary packaging operation and, therefore, require an audit to be conducted while the packaging operation may be evaluated by testing sample packages from different lots.

Another method of evaluating or qualifying suppliers of a material, especially APIs, is to obtain samples from different batches and test the samples against the specifications. If they pass the specifications, experimental batches

of product may be made to test the material functionally within the process (e.g., with the equipment) and placed on accelerated stability to see if the product made with the material is stable.

If a decision is made to audit an outsourced operation or supplier, many of the same principles addressed above for internal audits apply. The key focus of an audit of a supplier or outsourced operation should be whether the supplier or outsourcing operation has a quality system in place and the effectiveness of the quality system. Often audits of external resources result in the pharmaceutical company dictating how they want the operations performed rather than looking at the external resource's quality system. If the external resource has an effective quality system in place and is complying with their quality system, the operations should be in a state of control and the quality of goods produced should be acceptable. An effective quality system will ensure that quality products are produced and delivered without the need for the pharmaceutical company to be present to observe the operations continuously. Although the external resource's quality management system should be consistent with the pharmaceutical company's quality management system there is no need for the two systems to be identical.

Once a supplier or outsourced operation is approved, it should continue to be monitored. The methods for continuous monitoring may vary depending on risk assessments and may include periodic testing, review of documentation, periodic audits, and monitoring of regulatory findings for the external resource.

Quality agreements should be in place for all outsourced operations that define responsibilities and lines of communication. An extremely important aspect to address in the quality agreement is change management and communications and responsibilities associated with changes.

CONCLUSION

Although auditing may not always be required by regulations, a good audit program can play an integral role in product realization, process performance and quality monitoring, and continuous improvement within a quality management system as outlined in ICH Q10. Use of risk management practices as defined in ICH Q9 provides a useful tool for prioritizing audits.

Increasing use of suppliers from less developed countries and outsourcing operations is focusing more regulatory attention on API and excipient suppliers. Companies should examine their auditing programs to ensure that the key objectives described in ICH Q10 are being met. A strong audit program provides a key component to maintaining quality products and an effective quality management system.

The audit program should address both internal and external audits and such audits should be defined in written and approved procedures. The objectives of all audits should be to evaluate the effectiveness of the quality system with reports being fed back to management for use in continuous improvement of the quality management system.

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ARTICLE ACRONYM LISTING

APIs	Active Pharmaceutical Ingredients
CAPA	Corrective Actions and Preventive Actions
CGMP	Current Good Manufacturing Practice
EU	Europe
FDA	US Food and Drug Administration
FD&C	Food, Drug, and Cosmetic Act
GLP	Good Laboratory Practice
ICH	International Conference on Harmonisation
OOS	Out-Of-Specifications
QSR	Quality System Requirements

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