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A Case Study on The Retrospective Audit of BA/BE Studies

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ABSTRACT

In this paper, a retrospective audit of the study data including trial master file, raw data, CRFs of BA/BE studies has been carried out. A retrospective audit of the study data of BA/BE studies was undertaken to identify problems, reduce costs, assess personnel competency, review equipment maintenance programs, provide visible management support, ensure adherence to process standards, determine system effectiveness, and identify system inefficiencies. An audit plan was prepared as per the template of 'Audit Plan' by identifying the critical phases of the BA/BE study before conducting the audit which is approved by the Head QA/Designee.

INTRODUCTION

An audit is a "systematic, independent and documented process for obtaining audit evidence [records, statements of fact or other information which are relevant and verifiable] and evaluating it objectively to determine the extent to which the audit criteria [set of policies, procedures or requirements] are fulfilled [1]. Auditing is a critical function within a pharmaceutical company. It provides management with information about how effectively the company controls the quality of its processes and products. The audit process is one means of reviewing pharmacy programs; it ensures that procedures and reimbursement mechanisms are consistent with contractual and regulatory requirements [2]. The general definition of an audit is an evaluation of a person, organization, system, process, enterprise, project, or product. Internal Audit Standard Board (ICAB) defines auditing as the independent examination of financial information of any entity, whether profit-oriented or not, and irrespective of its size or legal form, when such an examination is conducted to express an opinion thereon." Internal auditing is fundamental to any quality improvement initiative. In particular, the FDA cGMP's for pharmaceutical products require that an organization conduct an internal quality audit to determine the effectiveness of its quality system. Auditors are a typical part of the Quality Assurance (QA) or Regulatory Compliance function for examining the data trial to determine whether company policies and procedures are followed[3]. Depending upon key focus areas, audits are divided into two main groups which are Internal and Statutory/ Regulatory or External. Internal auditors are appointed by the management of the organization, whereas statuary auditors are appointed by different authorities such as US-FDA, CDSCO, etc. The scope of internal audit is limited to people and processes of an organization while the scope of regulatory audits is much bigger keeping public health in mind. Internal audit report findings are only submitted to the management of the organization, whereas statutory audit report is shared with the shareholders[1, 2]. Auditing has become one of the important keys to the success of a pharmaceutical company. Regulatory agencies play a very important role in pharmaceutical companies by assuring good quality so that safe and effective products should be delivered to the public. Quality is determined by whether the firm complies with GMP requirements and makes scientifically justified decisions[4-6]. Pharmaceutical companies are now taking a proactive stance with the new GMP Systems approach, more effective internal auditing, and increased regulatory awareness throughout the company. Auditing in a pharmaceutical company is very important to ensure delivery of high-quality medicinal products, to establish and implement an effective

pharmaceutical QA system, to assess the effectiveness of the QA system and its compliance with GMP, etc.

The goal of an audit is to express an opinion on the person, organization, system, etc. in question, under evaluation based on work done on a test basis. Audits are performed to ascertain the validity and reliability of information; also to provide an assessment of a system's internal control. A company that makes medications today must be able to prove that it does so with absolute reliability, under optimal secure conditions, and with extreme uniformity to allow for exact reproduction. An effective audit leads to improvements in a company's Quality System as well as its basic management practices. There are three discrete types of audits which are product, process, and system audit. Product audit is an examination of a particular product or service (hardware, processed material, software) to evaluate whether it conforms to requirements (that is, specifications, performance standards, and customer requirements). The process audit is a verification that processes are working within established limits. It evaluates an operation or method against predetermined instructions or standards to measure conformance to these standards and the effectiveness of the instructions. System audit is an audit conducted on a management system. It can be described as a documented activity performed to verify, by examination and evaluation of objective evidence, that applicable elements of the system are appropriate and effective and have been developed, documented, and implemented in accordance and conjunction with specified requirements. Eg. Quality management system audit, environmental system audit, food safety system audit, safety system audits.

The quality audit system is of three different categories which are internal audits, external audits, and regulatory audits. The internal audit also called a first-party audit or self-audit which is performed within an organization to measure its strengths and weaknesses against its procedures or methods and/or against external standards adopted by (voluntary) or imposed on (mandatory) the organization. External auditing also known as the second-party audit is an audit that is performed on supplier or contractor by customer. The regulatory audit also called a third party involves a regulatory or independent body to conduct an audit[7].

Risk-based internal auditing (RBIA) is a methodology that links internal auditing to an organization's overall risk management framework. Risk-based auditing is a proactive approach to detect possible issues before they occur, with all best intentions that they may occur is implemented in the organization. Each potential risk that may occur during the

process is prioritized to enable the QA team to focus their efforts on particular parts of the processes[3].

Before conducting an audit, there should be a proper audit team who must be trained in an audit procedure, knowledge of the processes and products to be audited, cGMPs, quality system requirements, communication skills, and human relations and interactions during audits[8]. A past audit and its results must be reviewed in preparation for an audit. An audit agenda should be prepared to provide a timeframe to all parties involved in an audit. While conducting an audit the auditor must follow the rules and regulations of the operation like hair covering and also there should not be any interference to operation by the audit team. After auditing, there is a close-out meeting to discuss observation. A timeframe should be provided for both audit reports and corrective actions to be taken for observations[8]. Collectively, audit planning consists of audit preparation, audit performance, audit reporting, and finally follow-up and closure with audit certification. (5) During the development of the audit plan a meeting with the auditors is held to discuss the objectives and the details of the audit is planned. Auditors must review the reference documents that will be used to audit against as well as any applicable SOPs for the areas being audited. The team must identify the appropriate and meaningful elements to be included in the audit. Once the areas of focus have been identified, area-specific checklists can be prepared to guide the auditor through the items to be checked. The checklists that are created should be used as a guide only, and the audit should not be limited to only those items shown on the checklist. It is recommended that the auditor share the checklist with the department or functional area being audited to help them prepare for the audit.

Most commonly, observations in the audit are separated into two levels of significance which are minor and major. Minor observations are those which would not hamper the quality of the finished medicinal product or may not have any impact on the management system. While major observations are those which would affect one or more quality systems that may adversely affect the finished product or management system[9].

A retrospective audit is an audit in which already available data stored in an electronic database is used for the audit process[10, 11].and done to make sure that all the audit plans should be prepared as per the template of the audit plan and available before the audit begun to identify the critical phases of the study. The prepared audit plans should be approved by the concerned QA head/ Designee before implementation.

The main objective of this audit is to determine the conformity or non-conformity of the quality system in meeting the specified requirements, to determine the effectiveness of the implemented quality in meeting the specified Quality objectives, to provide the Audit team with an opportunity to improve the Quality system. to meet the regulatory requirement, to permit the listing of the audited organizations Quality systems in a register.

All quality management processes are dynamic. Thus, continuous improvement is only ensured, when quality management processes are constantly adapted by collecting and using the information on an ongoing basis, and when changes are routinely evaluated to make sure they are effective. It is an essential part of the risk-based quality management system that review takes place as additional information becomes available. The results of risk assessment can then be used to determine audit priorities and help judge how often each of the areas needs to be audited.

MATERIALS AND METHODS

The prerequisites required before conducting an audit are essential documents, informed consent documents, medical screening records, study source records, registration files of the subjects involve in the study, checklist for retrospective audit.

METHODOLOGY

The retrospective audit is performed of the study conducted in BA/BE study business unit by the QA department. The study source documents, Informed consent documents, trial master file, registration files, and all the study related documents are audited. The Clinical Study Report of the study is also audited concerning source records. Then an audit report is released compiling all the relevant observations found during the audit. Thereafter appropriate responses shall be provided by the operational department with the corrective actions taken within the due date of response. The response is verified by the QA department. Follow-up to the observations is also taken if any. After verifying all the responses to the observations Closure is done by QA personnel. Finally, a QA certificate is released.

OBSERVATIONS

The observations like documentation errors, transcribing errors, reporting errors and inadequate documents were reported in an audit report found during the audit. The corrective actions against the observations were taken by the concerned operational department within

the due date of response. The response is verified by the QA department. The follow-up to the observations was also taken if any. An audit report after verifying all the responses to the observations, closed by QA personnel with a final QA certificate.

Escalation Plan

In this plan, the criticality and seriousness of the quality issue are identified. The audit percentage may escalate to 20% or higher if quality issues are critical and serious which were to be informed to the concerned department by the Head QA/designee for thorough review and corrections. The concerned department has to review and revise the audit plan depending on the increased audit percentage. Once all the corrections are implemented and a thorough review is completed by the department, the data will again be provided to the QA department.

EXPERIMENTAL WORK

An audit plan was prepared as per the template of "Audit Plan by identifying the critical phases of the study before conducting the audit which is approved by the Head QA/Designee are given below:

Before the beginning of the audit, approved Protocol and Amendments, Case Report Form (CRF) of subject diaries if applicable, etc., were reviewed to become familiar with the requirements of the study/project Checklists were prepared for all types of audits.

Template 1: Audit plan

AUDIT PLAN

Version#:

MV No. / Protocol No. / Study No.: Date:

☐ BA/BE Study ☐ Method Validation ☐ Others, Specify_____

In-process Audit	
	Activities to be performed
Clinical Pharmacology	
Bioanalytical	
PK and Biostatistics	
Clinical Laboratory	
Others	
Retrospective Audit	
Remarks:	

Prepared by: _____ Approved by: _____

(Name) (Name)

Signature & Date: _____ Signature & Date: _____

Template 2: Checklist of Study

Serial No.	Items	Y/N/NA
1.0	Protocol	
1.1	Is the protocol reviewed and approved by IEC/ IRB	
1.2	Are there any amendments to the protocol?	
1.3	Were the amendments approved by ethics committee?	
1.4	Were the personnel involved in the study activities trained on the protocol?	
1.5	Were the personnel involved in study delegated appropriate study related activities?	
Comments		
2.0	Informed Consent Forms	
2.1	Are informed consent forms of all the subjects in the study available duly signed and dated by the subjects?	
2.2	Are details available in informed consent forms complete?	
Comments		
3.0	Raw Data	
3.1	Are the forms complete and reviewed?	
3.2	Were good documentation practices followed while recording the data?	
3.3	Is the data recorded in a consistent manner?	
3.4	Is the information provided traceable between different activities performed?	
3.5	Are the dispensing records available and complete?	
3.6	Is the accountability of investigational products available and accurate?	
3.7	Are there any adverse events or serious adverse events in the study?	
3.8	If yes, were they documented in the relevant forms?	
3.9	Were these events informed to IEC/ IRB and sponsor?	
3.10	Were these events followed up timely and necessary actions taken?	
3.11	If yes, were they documented and record available?	
Comments		
4.0	Report	
4.1	Are the contents of the report consistent?	
4.2	Is the page numbering given correctly?	
4.3	Is the table of contents matching with different sections of the report?	
4.4	Is the report format complying with applicable regulatory guidelines?	
4.5	Is the report reflecting the raw data accurately?	
4.6	Are the deviations (if applicable) mentioned under specific sections of the report?	
4.7	Are note to file (if applicable) mentioned under specific sections of the report?	
Comments		

- A number was assigned to the checklist which was approved by the Head QA/Designee.
- The format for numbering the checklist is A-B-VXX

Where,

A = Department name

B = Type of audit (Inp = In process, Ret = Retrospective)

V = Version

XX = Version Number starting from 00 for each kind of checklist

- At least 10% of the total number of subjects that participated in the bio-study were audited.

Following are the documents that were audited during a Retrospective audit:

- Essential documents
- Informed consent documents
- Medical screening records
- Study source records
- Registration files of the subjects involved in the study

Essential Study documents

Essential Study documents are those documents that individually and collectively permit evaluation of the conduct of the study and the quality of the data produced. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated:

- before the clinical phase of the trial commences
- during the clinical conduct of the trial, and
- After completion or termination of the trial

All documents compiled in the Trial Master File should be available for audit by the sponsor's auditor and inspection by the regulatory authority/(ies).

Informed Consent document

A process by which a volunteer/subject voluntarily confirms his or her willingness to participate in a particular Clinical trial/Clinical Study, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate.

Informed consent is documented utilizing a written, signed, and dated informed consent form.

Medical screening

A volunteer(s) must undergo the process of screening to ascertain his/her eligibility for participation in a clinical study.

The screening process usually includes:

- demographic information
- medical history
- history of allergies
- clinical examination
- laboratory investigations
- ECG and radiology investigations (as applicable).

Study Source Record

A printed, optical, or electronic document designed to record the protocol-required information to be reported to the sponsor on each trial subject.

Study Source Record/CRF shall contain the following sections:

- Eligibility check on admission day
- Assessment of Volunteer's Eligibility for study participation
- Drug administration details

- Blood sample collection details
- Vital signs recording and health status
- Clinical evaluation at admission and on discharge
- Post-study safety assessment and review
- Subject withdrawal/Dropout information

The final study audit report was reviewed to confirm the following, but not limited to:

- Methods, procedures, and observations are accurately and completely described.
- The study is by the protocol and any subsequent amendments, applicable SOPs, and regulatory requirements.
- Raw data/Source documents, whether it is computer-generated or manually recorded, is completely and accurately reflected in the report.
- Consistency of the report.

Template 3: Response for audit report

RESPONSE TO AUDIT REPORT

Audit Report No.	Study No./ Protocol No./ MV No.:
Data Audited:	Audit Report Date:
Auditee(s):	Auditor(s):
Due Date for Response:	Response Date:

S. No.	Observations and/ or Recommendations	Root Cause	Response	Date of completion

Compiled by: _____
(Name)
Signature & Date: _____

Approved by: _____
(Name)
Signature & Date: _____

	Received by QA
Signature	
Date	

Follow up (if any) and closeout of observations by QA:	
Signature	
Date	

Reporting of Audit

- All of the audit observations were compiled in the audit report after conducting the audit.
- A number was assigned to the Audit Report as explained below:

Study No./Protocol No./MV No./Project No.-XXX-YY

Where,

XXX - Serial No. in continuation from 001 for studies/projects audit conducted in a year

YY – Year

Categorization of observation

The observation was classified into three classes-Minor, Major, and Critical. The rationale for the classification is explained below-

- **Critical** - A confirmed deficiency or non-compliance that is considered to be significant and has a negative impact on the study, product, deliverable, service, or contractual obligation. Repeated minor observations may also constitute a critical observation, particularly when they indicate a more significant or systemic problem. Critical observations include those that:

➢ Pose a threat against the life, health, or rights of clinical study patients.

➢ Jeopardize the integrity of clinical study data.

➢ Pose a threat to the safety of employees.

➢ Substantially reduce process quality and impede deliverable(s)/outcome(s);

➢ Could result in the closure of a clinical study.

➢ Indicate the absence or breakdown of an element in the quality system.

- **Major** - Nature and/or scope of the audit observations represent significant or potentially significant issues. Observations may adversely affect the rights, safety, or well-being of the subject and/or data integrity/quality.

- **Minor** - When the nature and/or scope of the audit observations appear to be routine. Observations, when noted, may represent departures from the protocol or regulatory requirements, but would not be expected to adversely affect the rights, safety, or well-being of the subject nor the quality/integrity of the data.

The audit report was completed by providing a maximum of 15 working days for the auditee to respond to the audit report.

QA Certificate

A QA certificate was issued to the concerned department after all the responses have been closed by the QA personnel after verifying the same.

Template 4: QA Certificate

QA CERTIFICATE

Study No.: **Version No.:**

The conduct of the study was subjected to periodic audits of different types as specified below:

Dates of Audit	Phase of Audits	Report Date

It is hereby certified that the study was conducted in accordance with the approved protocol (No. _Version __), applicable in-house SOPs, GCP, GLP and other applicable Regulatory Guidelines. All of the information presented completely and accurately reflects the raw data and the results obtained during the study.

_____ _____

(Name) (Signature & Date)

_____

(Title)

RESULTS AND DISCUSSION

The retrospective audit was done by the QA department by evaluating and auditing different documents like essential study documents, Informed consent documents, Medical screening records, Study source records, and Registration files of the subjects involved in the study.

Also, different templates like audit plan, template for the checklist, for audit report, and QA certificate were prepared before the audit process with the approval of the QA head. Observations were made as per the criticality of a quality issue as critical, major, and minor. All the activities were documented and all the observations were resolved by taking corrective actions by the department. Then an audit report was closed by the QA department and a QA certificate was provided to the specific study by the QA department.

CONCLUSION

A retrospective audit of the trial master of BA/BE study was successfully conducted with the preparation of different templates for audit plan, checklist, audit report, QA certificate. An evaluation and checking of documents like Essential documents, Informed consent documents, Medical screening records, Study source records, and Registration files of the subjects involved in the study were done by the QA department. After reviewing all the documents, observations were done and quality issues were resolved by the concerned department if any and finally all the corrections were implemented, QA department closed the audit report after providing a QA certificate to the specific study.

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