Regulatory Auditing of Medical Devices

Ms. Devanshi Brahmbhatt[1], Mr. Devang Tandel[2]
[1,2]*Assistant Professor, Department of Pharmaceutical Quality Assurance, Anand Pharmacy College, Opposite to town hall, Anand 388001, Gujarat, India*

Abstract **- Medical devices are a crucial part of the healthcare sector, as they are used to save lives. That is why it is so important to keep them safe. Patients expect the gadgets they are using to enhance their quality of life, thus demonstrating regulatory compliance is crucial. Each medical device producer goes through thorough quality audits conducted by the regulatory organizations as part of the auditing process. They ensure that the producers are producing high-quality goods following the set standards. Even the approved auditing bodies and the organization being audited must possess a high level of training, expertise, and adherence to several rules and obligations. Various types and methods are mentioned in this article, which covers every part of the auditing requirements.**

Index Terms **- Audit, Auditing phases, Clinical trials, Medical devices, Regulatory audits.**

INTRODUCTION

An audit is a methodical, independent, and documented way to gather evidence and evaluate it objectively to determine whether predetermined criteria are met. There are several requirements that a medical device maker must meet in order for an approval audit to be successful. An audit of a manufacturer of medical devices can evaluate the standard management system for compliance with the quality management system and restriction requirements, and consequently the manufacturer's established procedures. The acceptable quality management system standards or regulations support the standard management system. The audit should be process-oriented and, preferably, follow the manufacturer of the medical device's development procedures.

The audit is risk-based with a spotlight on key processes of the standard management system necessary to Manufacture the medical devices lined by the audit. The auditor ought to consider factors that are presumably to have an effect on safety of the medical devices whereas at a similar time guaranteeing adequate coverage of all categories of medical devices inside the scope of the audit. Rather than that specialize in individual necessities, associate audit ought to specialize in the general effectiveness of the standard management system. Subsystems are known to interrupt the audit into a lot of manageable elements [1].

For instance, when auditing the following categories of manufacturers:

- A manufacturer who purchases the finished medical device, or
- Who outsources crucial tasks, such design and development, manufacturing, sterilizing, etc.?
- Who buys essential parts and subassemblies?

Fig 1: Audit Cycle

REGULATORY AUDIT

The examination of a quality management system to show compliance with the standards for the system for legal reasons .A medical device is what the FDA (Food and Drug Administration) describes as:

An instrument, apparatus, tool, machine, devise, implant, in vitro reagent, or other similar or related

object, including a part or accessory that is recognized in the official National Formulary or the United States Pharmacopoeia, or any addition to them, designed for use in the diagnosis of illness or other problems, or in the treatment, mitigation, or prevention of illness in humans or other animals, not dependent upon being metabolized for the accomplishment of any of its primary intended purposes, intended to affect the structure or any function of the body of a man or other animal, and which does not achieve its primary intended purposes through chemical action within or on the body of a man or other animal. A manufacturer is a person or business that transforms raw materials into finished products utilizing a range of machinery, procedures, and tools before offering those products for sale to customers. A manufacturer is a person or business that creates or makes a finished good or a medical device from raw materials using a variety of tools, machinery, and procedures. [2-3]

Audit Principle

1. Fair presentation
2. Due professional care
3. Confidentiality
4. Independence
5. Evidence-based approach

The foundation of professionalism is integrity. As a result, specific ethical standards must be followed by the Auditor and everyone else who is directly involved in the audit. This requires adherence to legal requirements, proof of appropriate, fair, and impartial competence, honesty, diligence, and a feeling of responsibility at work. The audit findings, conclusions, and reports must accurately reflect the audit activities. It is required to report all records honestly and accurately. The communication must also be accurate, timely, concise, and thorough. Dissenting factors or viewpoints throughout the examination should not be hidden, and all audit results must be factual. To reconstruct the examination later, evidence or similar papers must be pretty accurate. Making informed decisions requires attention to detail and consideration of the task's importance. To fulfill his duty of care and apply his logical reasoning for a fair assessment and analysis, the auditor must possess sufficient qualifications for the audited area. It is necessary to guarantee the security of the data utilized and acquired during the audit. Therefore, audit data shouldn't be used for the auditor's or the organization's improper personal gain. The cornerstone for the impartiality of the audit and the objectivity of the audit evidence is the proper management of sensitive and confidential information. The audited activity must not be related to the auditor, and the auditor must always perform impartially and without conflict of interest. The auditors for internal audits must be separate from the individual in charge of the area of activity being audited. As a result, objectivity must be maintained at all times during the audit process. In a systematic audit process, a rational approach should be employed along with the strategy to reach credible and understandable audit conclusions. Therefore, audit evidence ought to be corroborated. [4]

OBJECTIVE

- The results of the audit are consistent regardless of which auditing organization or individual auditors conduct the audit.
- The effectiveness of the manufacturer's quality management system, including the fulfillment of regulatory requirements, is assessed systematically and effectively within a reasonable time.
- The audit determines how issues related to a medical device or the quality management system are identified and resolved.
- The audit is transparent to the auditee. The ultimate goal is for harmonization and mutual recognition of audit results.

AUDITING APPROACHES

An effective quality management system is a control mechanism that can prevent and recognize deviations and identify the causes. It ensures that corrective or preventive measures are identified, implemented, and effective. The auditor should assess whether the functional subsystems and processes of the quality management system are structured and effective as automated control processes. There are different approaches to conducting an audit. They are Top-Down, Bottom-Up, Combination, and Product.

Top-Down

It performs an audit starts with an assessment of the management, design, and development, product documentation, production and process controls, and

corrective and preventive actions subsystems of the quality management system. Selected subsystems are examined to see if the manufacturer has met the fundamental needs by defining, documenting, and putting in place the necessary procedures. Using a PDCA (plan-do-check-act) cycle, for example, is a good way to ensure that a process approach is used throughout the quality management system and in each subsystem. The auditor will confirm that the manufacturer has implemented acceptable procedures and policies using the "top-down" approach. To determine if the manufacturer has properly implemented the procedures and policies and if the quality management system is compliant with regulatory requirements, the auditor will examine the evidence, including documents. For the authorities, auditing organizations, and the manufacturer, this is a unified strategy for a methodical and transparent audit procedure. This method, however, does not make it easier to concentrate on the evaluation of a particular product.

Bottom-Down

A quality issue, such as a medical device report of an adverse event or a nonconforming product, might serve as the beginning point for an audit using the "bottom-up" methodology. As a result, the auditor begins at the bottom and moves up the manufacturer's quality management system until he reaches the management responsibility. It gives a quick insight into both the standard quality drawback's cause(s) and the efficacy of the selected subsystems and processes that are affected by it. Once employing this strategy, it is more difficult to assess the standard management system's overall effectiveness.

Combination

A "combination" of the two strategies could represent a third variation. The auditor reviews the topmost layer of the standard management system in the beginning (top- down), then audits some parts of the system's implementation (such as the assembly process), and finally, the auditor confirms that the pertinent processes are being followed (bottom-up). The combination technique is typically more cost-effective than using either the top-down or bottom-up strategy. Additionally, it provides more freedom for examining particular problems while gauging the efficiency of the standard management system.

Product

In this approach the auditor selects a single medical device, batch, or lot and follows the history of this sample through the various processes of the quality management system (planning, design and development, purchasing, production, packaging, distribution, etc.) This can be done either forward from planning, or backward from distribution. Additionally, by selecting a sample with a known problem, the auditor can also include the CAPA subsystem in his audit trail. [5]

PROCESS BASED AUDITING

An effective quality management system is a control mechanism that can prevent and recognize deviations and identify the causes of such deviations. An effective quality management system should ensure that corrective or preventive measures are identified, implemented, and effective. The auditor should evaluate whether the functional subsystems and processes of the quality management system are structured and effective as self- regulating control processes. For example, ISO 13485:2003 facilitates generic questions that can be asked throughout the audit.

Plan: Has the manufacturer established the objectives and processes to enable the quality management system to deliver results following regulatory requirements?

Do: Is the manufacturer following the quality management system?

Check: Does the manufacturer regularly evaluate quality management system processes and measurement results against objectives and regulatory requirements? Does the manufacturer evaluate the effectiveness of the quality management system at planned intervals through internal audits, management reviews, etc.?

Act: Has the manufacturer implemented effective corrective and preventive actions for providing high-quality medical devices and for conforming to applicable laws and regulations? [6]

Fig 2: PDCA Cycle

GUIDANCE FOR LOGISTICS DURING AUDITING

- Modifications made by the manufacturer that are presented at the opening meeting differ from those that were previously provided to the auditing organization (e.g., organization, quality management system, facilities, processes, goods).
- When it comes to scheduling and the amount of time spent monitoring management responsibilities, efforts should be taken to satisfy executive management.
- As soon as practicable, follow up on any nonconformities from the previous audit to see if the manufacturer has successfully implemented corrective measures.
- Starting an audit with an audit of the warehouse enables the selection of samples that may be followed up later (e.g., nonconforming material, batch records, etc.)
- Surveillance audits focus on either design or production and their related activities, taking into account factors like the range of products and/or scope of the certificate.
- Auditing traceability at an early stage of the audit allows the traceability path to be followed either forward (e.g., simulated recall) or backward, and gives the manufacturer sufficient time to access relevant information (s)
- Every audit includes a discussion of internal audits, complaints, CAPA, and management reviews.
- Evaluating the internal audit system towards the end of the audit avoids biasing the audit team.
- Reviewing documentation and training at the end of an audit provides for better follow-up of the examples picked up during the audit.
- To prevent wasting time, it is important to take into account how the local context may affect the audit's order. [7]

AUDITING SUB SYSTEMS

When studying each subsystem, a certain objective is in mind. Each subsystem testing strategy should be process-based and enable the accomplishment of the objective. Verification of compliance with the requirements addressed by each subsystem should be part of this process. To detect and address safety concerns, risk management concepts should be employed. These standards apply throughout the product realization process of a medical device for regulatory auditing purposes. Along with the appropriate subsystems, risk management practices should be audited. To make sure that adequate and effective risk management has been established and maintained throughout the product realization process, the risk management process is audited.

Management Objective

The purpose of the management subsystem audit is to verify that the top management ensures that an adequate and effective quality management system has been established and maintained. Major Steps involved as a guide in the audit of the Management subsystem:

- Confirm that the quality management system procedures and instructions, quality plan, management review, quality audit procedures, and quality manual have been defined and documented.
- Confirm that a quality policy and objectives have been established, documented, and followed up on.
- Confirm that risk management planning and continuing evaluation of the efficacy of risk management activities are incorporated into the product realization process. This will ensure that policies, procedures, and practices are formed for analyzing, evaluating, and controlling risk.

- Examine the organizational structure and related papers of the manufacturer to ensure that they have provisions for roles, powers (such as management representative), resources, competencies, and training.
- Confirm that management reviews are being carried out and that they examine the efficacy and applicability of the quality management system.
- Ensure that the quality management system's internal audits are carried out and that they involve the verification of corrective and preventative measures
- The management subsystem is the starting point and the finishing point of the audit; however, the other subsystems are audited in between.
- Whether senior management has taken the necessary actions to guarantee an acceptable and An effective quality management system must be determined at the end of the audit. [8]

Types of Audits

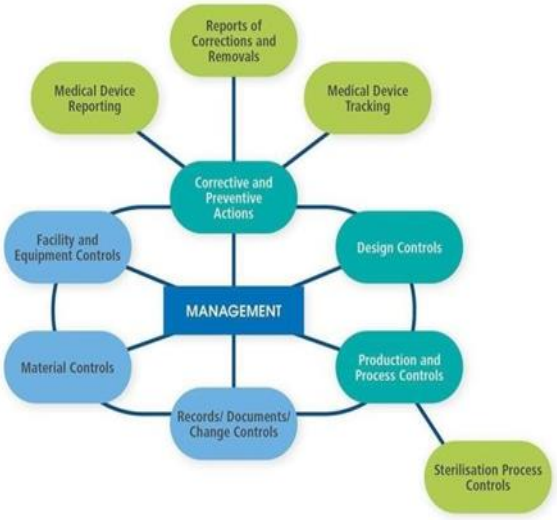

Fig 3: Management Subsystem

Internal audits: It is referred to as "first-party audit". They are carried outby the company itself or on its behalf for management assessment or other purposes.

Table 1. Requirements for internal audits

Determining the procedure	The documented procedure with responsibilities for planning, implementation, reports, records Objectivity and impartiality of the audit process
Auditors	Auditors are not allowed to audit their own activities
Audit objective	Determining the effectiveness of the QM system in regarding to the applicable legal and standard requirements as well as self-defined requirements of the organization
Audit planning and preparation	Perform internal audits in planned intervals. Planning of an audit program - usually as an annual program- considering the status and significance of the areas and processes that are audited and the results of previous audits; Determine: • Audit criteria • Audit scope • Audit frequency • Audit method Determining a schedule for every audit
Audit performance	Performance of the audit must assure objectivity and impartiality of the audit process
Audit result	Record keeping

External audits

It is referred to as "second- or third-party audits". Second-party audits are carried out by parties that have an interest in the audited company. This includes customer and supplier audits. Third-party audits are done by external independent organizations, such as certifiers, notified bodies, or authorities.

Supplier Audit

In the course of the MDR reorganization of the Medical Device Ordinance, supplier audits have a new status, because manufacturers are now responsible for the entire life cycle of a medical device. This type of audit is an essential tool to verify supplier follow-up because the manufacturer must ensure that the quality, performance, and safety meet the respective requirements. For this, special criteria should be specified in the audit program and the audit should be carried out at regular intervals.

Unannounced audits by notified bodies

It has currently become necessary that audits by notified body's square measure to be performed unheralded. This truly suggests that the corporation's square measure was audited with no specific previous "warning". The EU laws offer the legal framework for it. There square measure bound obligatory components, that square measure examined throughout associate degree unheralded audit. This includes among others the review of the technical documentation following the merchandise, the system for traceability, and compliance with legal laws. In most cases, this sort of audit refers to a particular product. [9]

CLASSIFICATION OF MEDICAL DEVICES

A medical device is an article, instrument, apparatus, or machine that is used in the prevention, diagnosis, or treatment of illness or disease, or for detecting, measuring, restoring, correcting, or altering the structure or function of the body for some health purpose," according to the definition of a Medical device (World Health Organization). Examples include a Bandage, prosthetic body parts, surgical, diagnostic, or monitoring tools, as well as sophisticated implanted devices like pacemakers and neurostimulators. Medical devices are classified based on their intended use, invasiveness, duration of use, and the risks and potential harms associated with their use. [10]

Medical Device Single Audit Program (MDSAP)

The goal of the Medical Device Single Audit Program (MDSAP), which focuses on the QMS and regulatory requirements of medical device manufacturers, is to pool regulatory resources to run an efficient, effective, and long-lasting single audit program. These standards are based on the specific needs of the medical device regulations of the relevant approval authorities, as well as the requirements of the ISO 13485 medical device quality management systems for regulatory reasons. Recognized audit companies can undertake a single regulatory audit program of a medical device producer using MDSAP if it satisfies the necessary criteria for the cooperating regulator.

Therapeutic Goods Administration's (TGA) Role in MDSAP

TGA is Australia's regulatory authority for therapeutic goods. They execute a range of assessment and monitoring activities to ensure therapeutic goods available in Australia are of an acceptable standard to ensure that the Australian community has access, within a reasonable time, to therapeutic advances. Since it was proposed as a work item for the International Medical Device Regulators Forum (IMDRF) is 2012, the TGA has been an active participant in the MDSAP collaboration. Unless the medical device is exempt or exempt from these requirements, or if current guidelines require the use of MDSAP audit reports, the TGA currently uses MDSAP audit reports and certificates as part of the evidence that is verified to verify compliance with medical device conformity assessment procedures and market approval requirements. Our regulatory architecture still permits the TGA to investigate production facilities regardless of the existence of MDSAP evidence, even though manufacturers who have undergone MDSAP audits may occasionally be exempt from routine TGA inspections. When a foreign regulatory authority is satisfied that the device manufacturer has applied requirements to a medical device that are similar to Australian conformity assessment procedures, the foreign regulatory authority will issue an MDSAP certificate, a type of conformity assessment document for foreign regulatory authorities. The Therapeutic Goods (Medical Devices) Regulations 2002 must have been covered in the audit(s) for MDSAP certificates and audit reports to be taken into consideration by the TGA. Certificates* must also demonstrate that the manufacturer has been evaluated and found to comply with the pertinent provisions of the Regulations. [11]

Importance of Medical Device Design

The two most crucial stages of your TPLC are the design and development of an MD because, in the unlikely event that this is not the case, compliance with the Essential Requirements (ER) will be compromised if the intended safe performance is not guaranteed. A poorly designed device will not be able to enter the market through regulatory compliance. There is undoubtedly some danger involved in using any MD, and how much risk is acceptable depends often on the stakeholders' risk perceptions, cultural variety, academic proficiency, and patient profiles. Therefore, it is crucial for style to comprehend how users can move with the MD depending on their environment. As a result, during the look stage, the first-rate management of an Associate in Nursing MD is enforced following the requirements of the Quality Management System (QMS). In addition to the aforementioned, MD design is a crucial component of the device's TPLC since it specifies both the functional safety and usability of the device, allowing error-prone procedures to be contained. An MD will find it easier to utilize and less likely to make mistakes using a product with good usability. [12-13]

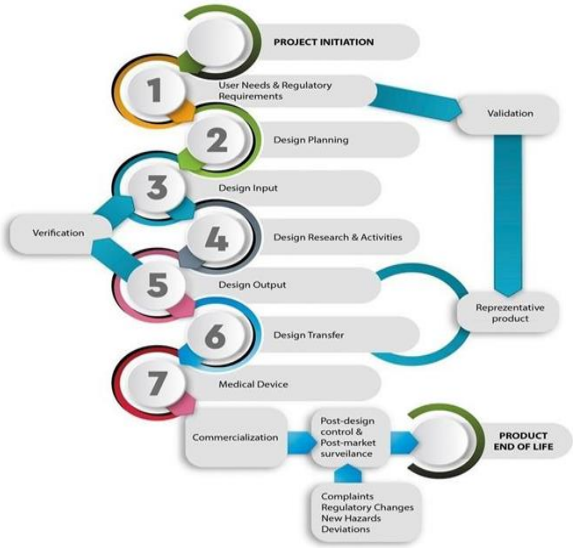

Fig 4: Design impact on Medical Devices

When do Medical Devices Require Clinical Trials?

Before they can be cleared for market introduction, not all medical devices need to undergo clinical studies. Clinical investigations are not necessary because the risk associated with Class I devices is so low. But in Australia, regardless of class, all medical devices must adhere to the Australian Regulatory Guidelines for Medical Devices (ARGMD), which include specifications for product design and manufacture, benefits outweighing hazards, risk minimization, and other regulations. They must also be registered with the Australian Therapeutic Goods Register, except for Class I devices (ARTG). An audit and clinical data or evidence may be needed for the approval process. A product's class, whether it is significantly comparable to or based on an already-approved product, and whether or not important clinical data supporting the new product have already been published in the medical literature all determine whether it should go through clinical testing. [14]

Fig 5: Clinical Trials for Medical Devices

REGULATORY AND ETHICS REVIEW

Before a clinical trial of a new product (or drug) can begin, the proposed study and product must undergo a review and reporting process to ensure the safety of study participants:

- A Human Research Ethics Committee (HREC) or an Institutional Examine Board (IRB) in the United States must review and approve the study's protocol, consent form, and other study materials. They'll keep an eye on the study as well.
- To determine if the study is appropriate for the site to undertake (for example, in light of the site's policies, capabilities, etc.), the site(s) at which the trial is scheduled to take place will perform a Site

Assessment or a Research Governance review.

Before clinical trials may be carried out, the sponsor (often the firm behind the new device) must notify the TGA or submit a request (CTN / CTX scheme) (Australia) if the device is new (unapproved) or is to be tested for an unapproved application. There is none necessary if the equipment has already received approval and is being used as intended. The suitability of the CTN or CTX scheme mostly depends on the availability and the caliber of the device's preclinical safety data.

The CTN (Clinical Trials Notification) Scheme entails informing the TGA of your intention to use the new gadget (through an online form) and paying a fee. Preclinical data, trial design, risks vs. harms, etc. are not assessed by the TGA; the HREC is responsible for doing so. Before employing the device, an application must be submitted to the TGA along with a fee, as part of the CTX (Clinical Trials Exemption) Scheme. The HREC will take care of the remaining tasks after the TGA has reviewed all technical device information and any preclinical or early clinical evidence. In general, this system is necessary for high-risk devices or novel technology for which there is scant or no safety information. Once approved, the device can go through as many clinical studies as necessary without another TGA evaluation being required. [15-17]

Pharmaceuticals			Medical Devices		
Phase	Subjects	Purpose	Stage	Subjects	Purpose
0 Pilot / Exploratory	10 - 15	• Test a very small (subtherapeutic) dose of a new drug to study its effects & how it works in the human body. • Not all drugs will undergo this phase.	Pilot / Early Feasibility / First-in-Human	10 - 30	• Small study to collect preliminary safety & device performance data in humans. • Guides device modifications &/or future study design.
I Safety & Toxicity	10 - 100	• True first-in-human study to test safety & toxicity, usually in healthy humans.	Traditional Feasibility	20 - 30	• Assess safety & efficacy of the near-final or final device design in patients. • Guides the design of the pivotal study.
II Safety & Efficacy	100's	• Assess efficacy & safety in patients.			
III Clinical Effectiveness	100's – 1000's	• Confirm clinical efficacy, safety & adverse events. • Compare the new drug to standard care or a commonly used drug.	Pivotal	100's	• Large study to confirm clinical efficacy, safety & risks. • Statistically driven.
IV Post-Market / Surveillance	1000's	• Monitor long term effectiveness & safety in the general population.	Post-Market	1000's	• Monitor long term effectiveness, safety & usage in the general population.

Fig 6: Phases vs. Stages

CONCLUSION

From the above information, the significance of the audit is clearly understood. Auditing any sort of system or medical device not only improves the customer s satisfaction but also leads to the quality of the product and ensures an errorless system. From time-to-time auditing of the devices ensures the acceptance as per cGMP guidelines. Maintenance of the auditing cycle is mandatory for the assurance of quality. It is the responsibility of the institute to ensure, that auditing principles are followed. Various types of auditing systems are mentioned in the above review article and based on the necessity and requirements; the auditing is to be done. Guidelines for Auditing changes as per the different requirements of the different countries and regulatory authorities have to work accordingly, for every medical device and so the importance of medical design has to be explained to every person working in a department. Clinical trials for the newly approved devices are suggested if found risky and that should be properly conducted and then only after it should be introduced in the market. Auditing in an organized way is the journey towards Total Quality Management.

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