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STANDARDIZED AND WELL STRUCTURED GMP CHECKLIST AS A VALUABLE TOOL FOR CONSISTENT AND SUCCESSFUL INTERNAL AUDIT

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Abstract

Audit planning in the pharmaceutical industry, is the most crucial phase of the audit process, therefore it is imperative for the auditor to gain as much information in advance of this process, that should help him design tools useful in achieving the desired results. A GMP audit checklist is considered to be an invaluable and an effective tool in the implementation of an audit process. A well-prepared checklist comprises of a carefully structured series of questions that may be asked when verifying strengths and weaknesses within the organization's control system. Therefore, this review outlines the most important sections recommended to be, at the very least, included in the GMP audit checklist. A bibliographic-research consists on analysis of review articles, original articles, guidelines, standards using the databases of PubMed, EBSCO, Scopus, Sage, Science Direct and Google Scholar. Based on the fact that GMP includes all parts of production starting from materials, equipment, documentation, storage to personnel training and hygiene, there are several sections recommended to be included in the audit checklist, such as Quality management, Personnel, Facility and Equipment System, Documentation, Production System, Packaging and Labelling System, Storage System, and Laboratory Control System. A well designed and structured checklist should enable assessment and identification of the problematic areas and possible problems, and can ensure beneficial, consistent and successful audit process and reports.

Keywords: Internal audit, GMP audit checklists, pharmaceutical industry, quality management system.

1. Introduction

In recent years, companies have been confronted with a multitude of new challenges, such as increasing economic complexity, extended regulatory requirements, and technological advances (Eulerich M., & Eulerich A., 2020). To occupy competitive positions on the international market, organizations are beginning to use a new management tool – internal audit (Nedelcheva, 2014). Building internal control systems is one of the very important measures since they help prevent and detect mistakes and weaknesses in order to minimize losses and improve efficiency to help the organization achieve its goals (Thieu Nguyen, 2021).

According to regional legislations, the internal audit is defined for EU members as "self-inspection" (European Commission, 2013) and as "measurement, analysis and improvement" according to ISO 9000:2000 (Mc Cormick, K, 2002). The activities of First-Party Audit or self-audit as it is also called this type of audit, are defined by the Institute of Internal Auditors' (IIA) as assurance and audit services, which aim to create value and improve an organization's operations. (IIA 2020). Self-inspection provides a number of advantages among which the possibility you can play with an open hand and as well the immediate correction of any identified deficiencies. A disadvantage of this type of audit is that the internal auditor is generally too familiar with the individual processes and only uses internal terminology (Oechslein, Gotter & Lazar, 2016).

Audit planning is the most crucial phase of the audit process, therefore it is imperative for the auditor to gain as much information in advance of this process.

A GMP audit checklist is considered to be an invaluable and an effective tool in the implementation of an audit process. A well-prepared checklist comprises of a carefully structured series of questions that may be asked when verifying strengths and weaknesses within the organization's control system. It must include comprehensive organization's terminology and ensures that staff understand the requirements.

A well-designed audit checklist has several advantages:

- Ensures consistency among the auditors. If all the auditors use the same checklist, it will result in more accurate and effective audited process.
- Ensures thorough coverage of QMS requirements
- Provides space for recording conformances and non-conformances during the audit
- Saves time in preparing for the audit, makes the internal auditor's job easier and more effective.

The use of checklist during the audit can be useful but the focus should not be only on regulatory compliance, but the potential business risks and leadership issues should be covered as well (Barsky, Grunbaum (2007) & Borkar, 2006). However, as demonstrated by Oechslein, Lazar, Halfmann & Kutsch (2009), when using checklists to prepare for an audit, several points are of importance:

- Completing these lists may provide an initial overview, however, it does not replace the intensive challenge of the individual Quality System in place.
- Due to the diversity of companies in terms of organizational differences, various product ranges and different equipment pools, checklists can never be comprehensive, exhaustive or specific enough to do justice to the situation in each company (pharmaceutical, supplier, packaging, etc.).
- Specific national legal requirements may have to be considered in addition.
- Therefore, this review aims to outline the most important sections recommended to be, at the very least, included in the GMP audit checklist in the pharmaceutical industry.

2. Materials and methods

The study methodology is based on the conceptual and critical analysis of review articles, original articles, guidelines and standards. We searched the databases of PubMed, EBSCO, Scopus, Sage, Science Direct and Google Scholar and only articles in English language are selected. Keywords "internal audit", "GMP audit checklists", "pharmaceutical industry", "quality management system" were used in our search . Media articles with no appropiate certified references are excluded.

3. Guide to the audit checklist

In pharmaceutical industry internal audit, there are several sections recommended to be, at the very least, included in the GMP audit checklist:

- Quality management
- Personnel
- Facility and Equipment System
- Documentation
- Production System
- Packaging and Labelling System
- Storage System
- Laboratory Control System

Quality management

A quality management system (QMS) is a formalized collection of processes, procedures, and documented policies for improving organization's effectiveness and efficiency on a continuous basis. The auditor looks to find out if the system complies with GMP requirements. This is to review management control, investigations and reporting of deviations, validation, applications of risk management, recall systems, complaint management, as well as to ensure the performance of internal audit programme.
According to GMP regulations, there should be a Quality unit, responsible for ensuring that all the Quality Control arrangements are effectively and reliably carried out. Therefore, an internal audit checklist should verify the main responsibilities of a quality unit including:

- Establishing, validating and implementing all quality control procedures
- Approving and rejecting incoming materials and products, packaging materials and labelling.
- Reviewing and approving/rejecting any document that gives work instructions, procedures, protocols, and specifications.
- Maintaining adequate laboratory facilities.
- Having a complete procedure describing responsibilities in writing and follow the procedure.

Personnel

A GMP audit checklist should cover all the necessary procedures to ensure that the organization's hiring and supervising practices are fulfilling GMP requirements. Most often, the selection of the group of trained auditors depends on the size of the organization. Elimination of conflicts of interest is an important segment of the audit process. If there is an indication of any conflict of interest the auditor may have, it is essential to reveal it promptly and avoid it by changing the auditors.
The internal GMP auditor should maintain a good working relationship with the auditees and by ensuring that the GMP quality requirements are fulfilled, it helps the organization to remain respected and profitable. Therefore, the personnel must:

- Be competent, have a background of education and relevant qualifications, have knowledge for compliance with GMP requirements and ways of contribution to improvement.
- Possess continual GMP training for higher understanding of law and regulations and special training in particular manufacturing, design or safety operations for which the employee is engaged. The trainings should be properly documented.
- Wear special clothing and hair coverings in the various manufacturing, packaging, and testing areas to prevent contamination.
- Practice good personal hygiene and health habits

Job descriptions of all personnel engaged in the manufacturing should be specified in writing and be reviewed regularly.

Documentation

Documentation is the basis for confirming compliance with GMP requirements, ensuring traceability of all development, manufacturing and testing activities.
Common documents verified by the auditor that should be stored and recorded and include:

- Site Master File
- Instructions (directions, or requirements)
    - Specifications
    - Manufacturing Formulae, Processing, Packaging and Testing Instructions

    - Procedures (Standard Operating Procedures, or SOPs)
    - Protocols
    - Technical Agreements (Orlando, 2015).
- Record/Report
    - Records
    - Certificates of Analysis
    - Reports

Facility and Equipment System

GMP requirement include the design, construction, and purchasing of a facility as a direct impact in processing, packing and efficiency of the organization. The auditors review the layout, construction, size, location of the facility and main areas such as production area, storage, and laboratory.
Several facility requirements need to be included in GMP checklist:

- Adequate lighting for the intended operation and staff comfort
- Ventilation to minimize odors, dust, control equipment for temperature, air pressure, humidity and microbiological control.
- Water supply and water purity
- Smooth and free from cracks walls, floors, and ceilings
- Cleaning and sanitation,
- Washing and toilet facilities

Equipment used in the manufacture must be adequate for its intended purpose, must be correctly installed, operated in accordance with written instructions, maintained and cleaned.
Each item of equipment used in manufacture or for quality control purposes should be routinely calibrated, inspected or checked to ensure proper performance at defined intervals, in accordance with a written procedure. In this manner, the auditor should also conduct system and equipment qualification.
The GMP checklist should as well, address equipment's cleaning and maintenance validation, in a manner to protect them from dust, splash or to avoid cross-contamination issues.

Production System

The production and process audit checklist is used to assess organization's various stages of manufacturing to ensure products meet ISO 9001 requirements.
The GMP audit checklist should include:

- Raw materials. Written procedures of weighing or measuring of raw materials should be followed to ensure their suitability for use and to avoid cross contamination, mix-up or decomposition. If a deviation is noted at any time during the processing steps it should be documented.
- Time limits. If time limits for intermediates held for further processing are specifically defined, they should be met to ensure that appropriate storage conditions guarantee their quality. Any deviation should be documented.
- In-Process sampling and controls. There should be written and approved procedures for monitoring and controlling of the processing steps and the approved acceptance criteria of critical in-process controls. Scientifically based procedures of sampling methods and plans should be defined and written to ensure truly representatives of samples.
- Blending batches of intermediates or active pharmaceutical ingredient (APIs). Each batch should be manufactured using a controlled and documented blending process and each individual batch should

be adequately documented and should conform to chemical and physical property specifications. The blending process should enable traceability of the material through the process.

- Contamination Control of intermediates or APIs. Production operations should be conducted on the basis of strict procedures to avoid either cross-contamination or contamination by microorganisms or other materials.

Process validation is considered an important quality management requirement of manufacturing in pharmaceutical industry. The auditor's role will be to examine executed validation protocols and reports, process work instructions and the Device Master Record, Maintenance records, Device History Record.

Packaging and Labeling System

Pharmaceutical products, packaging and labeling materials should be prevented from the risk of contamination, mix-ups and cross-contamination by handling and storing them in in adequately secure conditions. It is of particular importance the control of the security and quality of packaging.

Elements that relate to labeling such as documentation, storage of starting materials and finished products, packaging and labeling operations must be incorporated in the audit checklist in order to comply with the GMP requirements.

Labeling operations are controlled and include package and equipment labels, directions for use, etc. The same requirements apply to suppliers of packaging materials who play an important role in the quality assurance of the final product.

Errors that can happen during the packaging and labeling process are often reported.

Storage

A well-organized warehousing, storage area will mainly be concerned with checking the procedures that deal with the product storage system and needs to fulfill GMP requirements. Therefore, GMP checklist should include two main point:

- Quarantining of final products,
- Storing products under special storage conditions

Internal auditing of storage system should prevent occurrence of mix-ups, damage, physical, chemical or microbial contamination.

Laboratory Control System

The pharmaceutical control laboratory is an essential system of the pharmaceutical industry. As it is written in the Guide to inspections of pharmaceutical quality control laboratories (2014), laboratory records and logs represent a vital source of information that allows a complete overview of the technical ability of the staff and of overall quality control procedures. In this context, the auditor by using a well prepared checklist could review laboratory documentation and notebooks, standard operating procedures (SOPs), sampling plans, calibration records, all written in a current, readable, clear and complete manner. The auditor may choose to perform a general review of the laboratory or depending on past results may choose to focus on specific area.

All laboratory processes, including facilities, equipment, analytical methods, cleaning, and computer programs used in the analytical testing of pharmaceutical products must be validated (Vesper, 2000).

An adequate system, for controlling changes within the production process, should exist and needs to be described in an SOP. It includes review and approval of changes to processes, test methods, specifications, documents, and equipment.

4. Conclusions

A GMP checklist is considered a valuable and useful tool in the internal audit process. Checklists can be designed to serve as guidelines for evaluation of compliance to standards and documentation, as well as for the effectiveness of the audited process. A list of questions as a part of the checklist can guide the auditor through the preparation phase to ensure that all the important aspects are included and discussed. However, preparing an internal audit checklist is a challenge itself and not an effortless assignment. Structuring, formulating, and implementing an audit checklist can take a lot of time. Those in charge for designing a well-established checklist should have adequately educational qualification and ongoing GMP trainings as well.

A checklist, finally designed, should enable assessment and identification of the problematic areas and possible problems, and as well in response to that assign corrective actions followed by verification of completed corrective actions. From one audit to the next, the well-designed checklist may be used with the same approach. Standardizing and structuring the internal audit checklist can ensure beneficial, consistent and successful audit process and reports.

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