INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Review Article

AUDITING ON REGULATORY SIX SYSTEM IN PHARMACEUTICAL INDUSTRY: A REVIEW

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Article Received on: 22/11/19 Approved for publication: 29/12/19

DOI: 10.7897/2230-8407.11011

ABSTRACT

Inspection is a key to auditing. First, we want to check visually, and every system focuses on safety and effective manner. Each system fixes the quality of the drug product mainly self-inspection should be conducted before auditing, step by step, the process must inspect from starting material to the finished, approved product. Labels, equipments, materials to be checked as per GMP guidelines. The Principles of quality management system was demonstrated by good manufacturing practices. The inspector follows the guidelines accurately in the system; we want to check the personnel, hygiene, quality, scale-up activity and overall quality functions. In production system guidelines demonstrate the critical manufacturing test area check properly by the inspector in the field weighing, sieving, are performed in the system IPQC and FPQC conducted test to be check properly it follow as per GMP guidelines. In the facility and equipment system not, only equipment also inspects manufacturing, processing and production activity. In the laboratory and control system, check the stability test area and quality control area. The material systems order to monitor the component status accurately. In the packaging and labeling system, check the labels, storage control and mix-up area study properly. Finally, the regulatory inspector submits the report to PIC/S. This article focuses on six system auditing models and the guidelines for regulatory inspectors.

Keywords: Regulatory inspector, quality system, verification, record, method, document, sample, quality, accuracy, stability, sterility, auditing, inspection.

INTRODUCTION

Six system auditing models mainly carryout for avoiding substandard medicines in the market; there are many steps to avoiding substandard medication by using the tool of auditing. The regulatory inspector conducts auditing. During the verification, the inspector performs an incorrect manner to prevent substandard medicines. In the review paper, in what way we inspect all six systems.[1] Audits should be conducted to ascertain the validity and reliability of the information; also, to provide an assessment of the internal control of the order. It provides management with information on the efficiency with which the pharmaceutical company controls and maintains the quality of the products.[2]

The audit, in simple terms, was explained as the inspection of a process or a system to ensure that it meets the requirements of it intended us.[3]

Six systems

The six-system auditing is a lengthy process, and it should carry out step by step process. Flow of quality management system to package and labeling system are helps to satisfy the quality.[4] The six systems have given below.

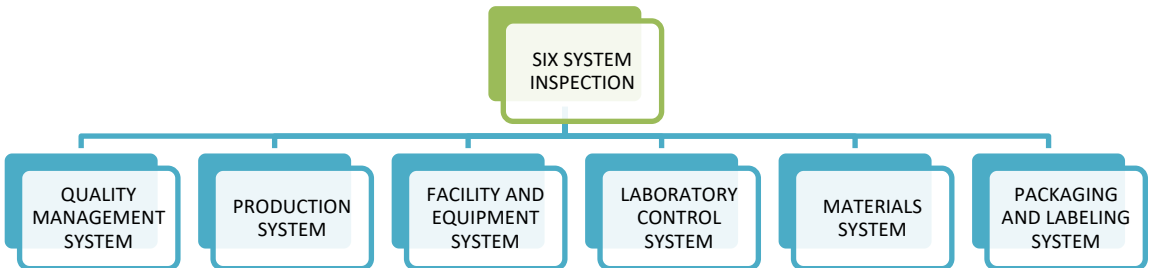

Figure 1: Six system auditing

Quality Management System

It is a structured collection of process, procedures and documented policies and evidence are constructed to upgrade the system. CAPA (corrective and preventive action) plays the primary role to know the defectiveness of the product and helps to improve quality and safety. The regulatory inspector is looking for weak spots in a firm's manufacturing operation.[5]

Inspector normally focuses on management control, production/process controls and corrective/preventive actions. The inspector review management procedures/high-level quality system procedures. Quality manual, quality plan and designing

documents must to view and preview before the auditing. In the inspector's review of any section, he does an overall view of subsystems and understanding the subsystems. The inspector must view if the system complies with GMP. To ensure the quality system (product development system) is functioning correctly. The inspector verifies quality policy, management review, quality manual and quality audit procedures, quality plan and system procedures and instructions have been defined, tested and documented.[6]

He also determines whether management reviews, including review of the suitability, safety, preventive measures and effectiveness to check the contractor and the product details of the certified contractor and the tender details, check the regular meeting details and the topics on the meeting, verification on quality improvement activities, check scale-up events and also check the manufacturing control and quality system.[7]

Figure 2: Quality management system

Production System

Critical manufacturing steps

Critical manufacturing steps are selection, weighing, measuring, identifying and addition of components during processing. From batch records, mixing time, sieving time and testing, the in-process material deviation should be recorded. The inspector determines whether such critical steps are being done by a responsible Individual after the finishing second responsible individual must check it properly. The processing by controlled by manual, automatic, mechanical, or electrical equipment performance verified. The record should be verified incorrect manner. To check the signature of the test performed person and cross-check them.[8]

Equipment identification

The inspector determines all type of containers and equipment are used to manufacture a drug product. Identifying the label content including batch number and stage processing and verify the batch production and stored to prevent mix-ups or contamination. All of the activities should record on the BMR or MMR.[9]

In-process testing

To check the weights, dissolution, and disintegration time of tablets, filling with liquids, adequacy of mixing, homogeneity of suspension, clarity of solution. The inspector alert to verify pre-recording of test result such as tablet weight determination. The inspector must visit an ongoing test procedure and verify which type of specifications followed for the test.[10]

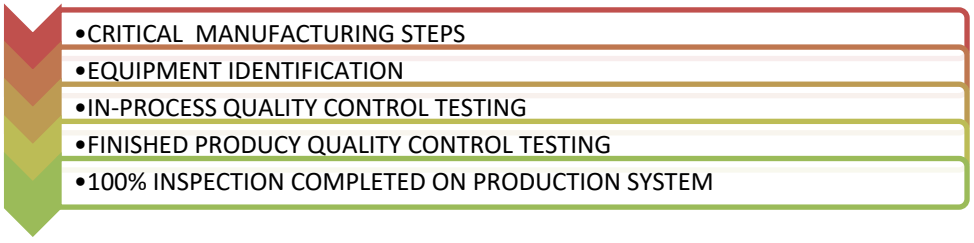

Figure 3: Production System Auditing

Finished product testing

To check the product from the production area, equipment and apparatus for FPQC should check properly and to evaluate the method of the process done the FPQC test.

Facility and Equipment System

Building and facility

The inspector typically reviews the layout, exit poll, construction, size, structure and location of the plant. He would be looking out for adequate lighting, sanitation, ventilation, screening and all physical barriers like dust, temperature, humidity and microbiological control. To check they followed SOPs or not, monitor the pest control activity and inspect the water purity,

HEPA filters, HVAC system, and compressed air system must be at hand for review by the inspector. He also looks at an adequate locker, toilet and hand washing facilities.

To prevent contamination, need to following procedure.

- Receiving, sampling, and storage of raw materials
- Manufacturing, primary and secondary packaging, and product and final labeling.
- Room for the container, primary and secondary packaging materials, product and final labeling, and finished products.
- Drug product Production and control of laboratories.[11]

Equipment

The inspector reviews the design of the instrument, the capacity of the machine, construction of the device and the location of material used in the production field, flow line for the manufacturing process is in given below.

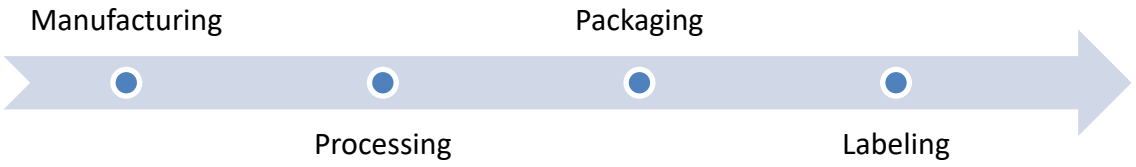

Figure 4: Manufacturing Flow Diagram

He checks the equipment to protect the identity (visual examination), content capacity, quantity, strength (flexibility), assured the quality or purity of the drug. Check the validation report, quality unit, FAT and SAT installation.

Inspector specifically looking for

- Equipment installed in the perfect place, and it is suitable for easy cleaning, maintenance and adjustment
- To prevent contamination from other formulation or disease from others (previous formulation)
- Equipment cleaning and maintenance status usually documented in a logbook (evidence purpose) with calibration details

Laboratory Control System

It covers all components like in-process and finished products and should include specifications. They confirm appropriate standard of identity of the instrument, the strength of the system, quality and purity, and evaluate all records.

Inspector determines the specification

The raw materials used in drug product manufacturing, sample procedure, sample content or sample size, no of containers to be sampled all details included in the master file. Received raw material should verify as per the protocol, from the supplier to manufacturer (he is responsible for conducting a test to receiving the material) Raw material specifications should include approved suppliers. In-process product and a finished product of natural materials testing under IPQC and FPQC that claim drug Product send for the test during processing and representative sample is collected from various steps of processing. Description of laboratory testing procedures for starting and finished products should determine. Method for checking the drug product or API means to identity and strength of active ingredients, including the pyrogen, content uniformity, and sterility testing. Many laboratory animals and overlooked –the type of care is provided to these animals on weekends and holidays.[12,13]

Inspectors primarily look for Sterility testing procedure

The physical condition of testing room and sterility testing used for finished products

- How to handle sterile products?
- How to Use of UV lights?

To know the number of units tested per batch, identifying test media to know microbial growth with specific quantities to evaluate the length of the incubation period, Procedure for diluting products (without the effect of bacteriostatic agents). The test made outside the laboratories and the inspector requires the name of the laboratories. The test if they have precautions to ensure work done correctly. Analytical method validation used to check all requirements. Validation and calibration required documents for the purpose. How they fix criteria for final acceptance or rejection of raw material. The inspector evaluates the reserve sample program. Storage containers must maintain the stability of the product.[14]

Stability tests for

- Drug product and substance in the closed container and different closure systems in which marketed.
- For solutions, we determine if shelf life dates, based on an appropriate confirmatory test, are placed on labels.
- If penicillin and non-penicillin products manufactured like the same, but some special requirements needed.[15]
- Whether non-penicillin products mostly contaminated during production, so before production, we want to test for penicillin contamination.
- NOTE: The inspector retains copies of laboratory records, batch manufacturing records, master manufacturing records and any other documents that show errors or other deficiencies.[16]

Materials System

The inspector inspects the warehouse or storage area, to know how they handled the product. What are the criteria follow to approved and reject the product, How they permit the API, How they prepare to export the product. The inspector may challenge the system to decide if it functions correctly. Handling and

storage of components under systemic accessing way so he must check program validation records. Components status is Quarantine, approved, or rejected.

The criterion for extracting components from quarantine is the critical step and to make them approved. Records are maintained in the different storage areas to evidence the movement of the product to other cities and also how the industry handles the rejected components.

Table 1: Component Status in Pharmaceutical Company

S. No.	Components status	Colors to be used	Send to
1	Quarantine	Orange	Further testing
2	Approved	Green	Ready to deliver
3	Rejected	Red	Prepared to waste disposal

The inspector ensures that the receiving record provides traceability amount to the component manufacturer of the product and supplier of the product. The receiving records for drug substance, additives, excipients or chemicals and also show the details of Name of the materials, receiver or manufacturer, Supplier and Carrier. It should include receiving date of the product, manufacturer's lot number (it changes batch to batch), quantity received from a wholesaler and control number of the product. To check sanitation in the storage area, as per norms perform stock rotation practices and storage conditions. The inspector is primarily looking for components, colors, and food additives. He investigates drug labels and he observe an unusually high quantity of any material. The inspector must check inventory records (comparing the performed results against the quantity remaining).

Packaging and Labeling System

The inspector reviews the label to prevent drug and label mixtures.[17] He determines to assure that all the content in labels is correct. Labeling and packaging areas have adequate physical separation from the manufacturing process. Do not allow without the Labels are checked manually against the master label content before released to the product. The inspector determines the responsible person for the label review.[17] Storage area is separated from one another to avoid mix-ups Inventory of label stocks. The eligible individuals are responsible for the labels and he issues all the labels under his knowledge. Receipt of these departments, the record should be showing the number of labels needed for a single batch. Adequate controls of the quantity of labeling issued, labeled, and remaining are returned (excess labels place in a separate place with documented evidence). Mistaken labels must utterly destroy without any missing. As per the specification, Inspector visits the labeling section correctly to ensure that all previously used labels destroyed or not. To assure that all production batches well monitored during packaging. Under controlled conditions to follow packaging necessary for drug packaged and no labeling should be issued. To prevent cross-contamination and the labels mix-up also stopped. What is the way to know similar labels should follow and labeled containers to prevent mix-up? Quarantine finished packaged products to be tested for examination or testing of a representative sample to be safely tested and shift into approved one incorrect manner.[18] An outside contract packer is distributing labels and control all the labeling content; it is a qualified label or not. He requires an explanation of how the finished package control number relates and how it is used to find the identity of the original batch.[19] He may also like to ensure that the label batch number is the same as the control number on the finished package.

Internal Audits

- To verify compliance with its principles of Good Manufacturing Practice for APIs, it is the first unique step in the self-inspection.
- And it should be performed under an approved schedule.
- Audit findings and CAPA it should be documented, and the management is responsible for all type of problems
- Agreed CAPA should completion time
- Action should be a safe and effective manner.

How PIC/S React for the Auditing Report

The regulatory inspector submits the report to PIC/S.

- If the system may follow as per the guidelines instruction the commission accepts the company product to marketing.
- If the system may be failed to follow the guidelines, the PIC/S action against the company.

CONCLUSION

The auditing should be held in a planned way unless we get confused; each step fixes the quality of the product. The quality was not satisfied it is not good. The auditing helps to know our self-quality and it is the beginning of the audit. The product quality was depending upon the way of selection of raw material, manufacturing, packaging. Each step to be crucial, it only assures the quality. By way of auditing, we know the quality level of the product. The product marketing is depending on PIC/S approval.

Abbreviations

GMP----Good Manufacturing Practices
PIC/S---Pharmaceutical Inspection Co-operation Scheme
BMR----Batch Manufacturing Record
MMR---Master Manufacturing Record
FPQC---Finished Product Quality Control
IPQC---In-process Product Quality Control
HEPA--- High-Efficiency Particulate Air
HVAC--- Heating, Ventilation and Air Conditioning system
CAPA---Corrective and Preventive Action
UV-------Ultraviolet
API------Active Pharmaceutical Ingredient
FAT-----Factory Acceptance Test
SAT-----Site Acceptance Test

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Cite this article as:

P. Shanmugapriya and R. Sanilkumar. Auditing on regulatory six system in Pharmaceutical Industry- A Review. Int. Res. J. Pharm. 2020;11(1):1-5 http://dx.doi.org/10.7897/2230-8407.11011

Source of support: Nil, Conflict of interest: None Declared