# UNIT-1
# PHARMACEUTICAL QUALITY AUDIT

# SYLLABUS

- INTRODUCTION
- OBJECTIVES
- MANAGMENT OF AUDIT
- RESPONSIBILITES
- PLANNING PROCESS
- INFORMATION GATHERING
- ADMINISTRATION
- CLASSIFICATION OF DEFICIENCIES

# INTRODUCTION

- International organization for standardization (ISO) defines the audits as "Systematic, independent and documented process for obtaining audit evidence and evaluating them objectively to determine the degree to which the verification criteria are met".
- In the pharmaceutical industry, audits are virtual means for assessing compliance with the established objectives defined in the quality system and thus paving the way for the continuous improvement program by providing feedback to management.

# INTRODUCTION…

- A company that produces drugs today must be able to demonstrate that it does so with absolute reliability, in optimal conditions and with extreme uniformity that allows accurate reproduction.
- Audits are conducted to ascertain the validity and reliability of the information; also to provide an assessment of the internal control of a system.
- It provides management with information on the efficiency with which the company controls the quality of its processes and products.
- The audit in simple terms could be defined as the inspection of a process or a system to ensure that it meets the requirements of its intended use.

# INTRODUCTION…

- Instead of considering the audit as an intrusive and potentially threatening review, pharmacies should consider the audit as a quality control mechanism.
- The results of the audit and the resulting corrective actions ensure all the involved parties that a program works in accordance with established rules of practice.
- Pharmaceutical audit experience includes the drafting and revision of validation policies, guidelines and standard operating procedures (SOP) from project qualification to performance evaluation phases.

# TYPES OF AUDITS

- Quality audits are performed to verify the effectiveness of a quality management system. The quality audit system mainly classified in three different categories:

  1.Internal Audits

  2.External Audits

  3.Regulatory Audits

- Regulatory authority for quality audits:

  ISO standards ,

  Code of federal regulations [CFR] ,

  ICH Q10,USFDA ,GMP

# INTERNAL AUDITS

- This type of audit is also known as First-Party Audit or self-audit. Those auditing and those being audited all belong to the same organization.
- Internal audit is a professional activity that consists of advising organizations on how to achieve their goals in a better way.
- The internal audit involves the use of a systematic methodology to analyze business processes or organizational problems and recommend solutions.

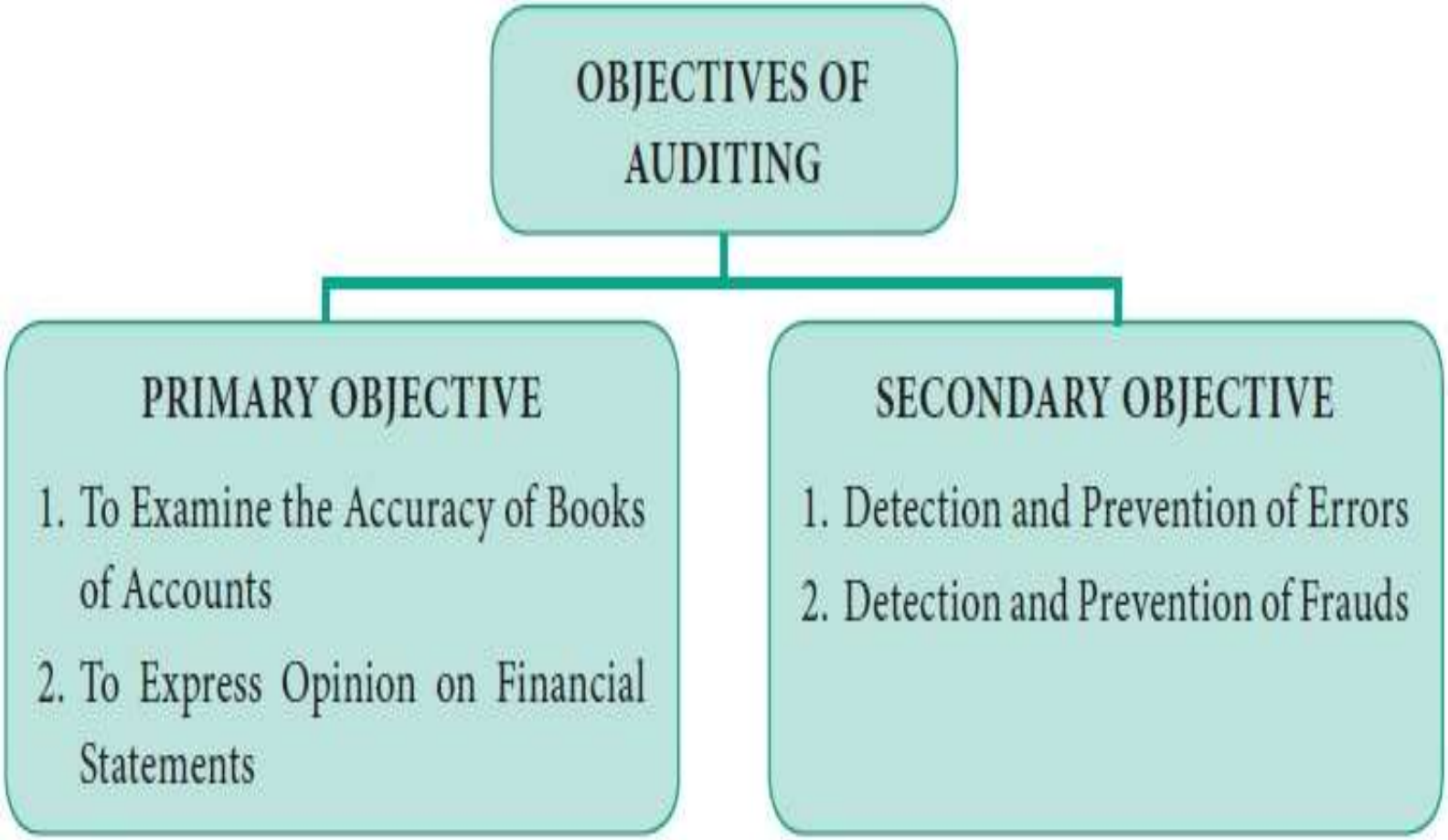
# EXTERNAL AUDITS

- This type of audit is also known as Second-Party Audit. It refers to a customer conducting an audit on a supplier or contractor.
- Although there are no strict legal requirements for this control.
- It is always advisable to evaluate the competence of the contractors in which we produce our products or carry out the analysis of our products or any other activity according to GMP.

# REGULATORY AUDITS

- This type of audit is also known as Third-Party Audit. Neither customer nor supplier conducts this type of audit. A regulatory agency or independent body conducts a third party audit for compliance or certification or registration purposes.
- International regulatory bodies such as MHRA,UK, USFDA, Therapeutic goods administration (TGA), Australia, Medicines control council (MCC), South Africa ,etc. are responsible for carrying out these checks.
- There is a team to perform the audit, it must be composed of audit inspectors and multidisciplinary company team.

# OBJECTIVES


OBJECTIVES OF AUDITING
PRIMARY OBJECTIVE
1. To Examine the Accuracy of Books of Accounts
2. To Express Opinion on Financial Statements
SECONDARY OBJECTIVE
1. Detection and Prevention of Errors
2. Detection and Prevention of Frauds

# OBJECTIVES…

- Evaluating conformity of requirements to ISO 9001.
- Evaluating conformity of documentation to ISO 9001.
- Judging conformity of implementation to documentation.
- Determining effectiveness in meeting requirements and objectives.
- Meeting any contractual or regulatory requirements for auditing.
- Providing an opportunity to improve the quality management system.
- Permitting registration and inclusion in a list of registered companies.

# OBJECTIVES…

- Qualifying potential suppliers.
- 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 listing of the audited organizations Quality systems in a register.

# Management of audit

- An audit program may include one or more audits, depending on the size, nature, and complexity of the organization to be audited.
- These audits may have a variety of objectives and may also include joint (multiple auditing organizations) or combined (Quality management and Environmental management systems) audits.
- Management of an audit program includes all the activities necessary for planning and organizing the types and number of audits, and for providing resources for conducting them effectively and efficiently within the specified time frames.

# MANAGEMENT OF AUDIT…

- The organization's top management should grant the authority for managing the audit program. Those assigned the responsibility for managing the audit program should:

  1.Plan, establish, implement, monitor, review and improve the audit program.

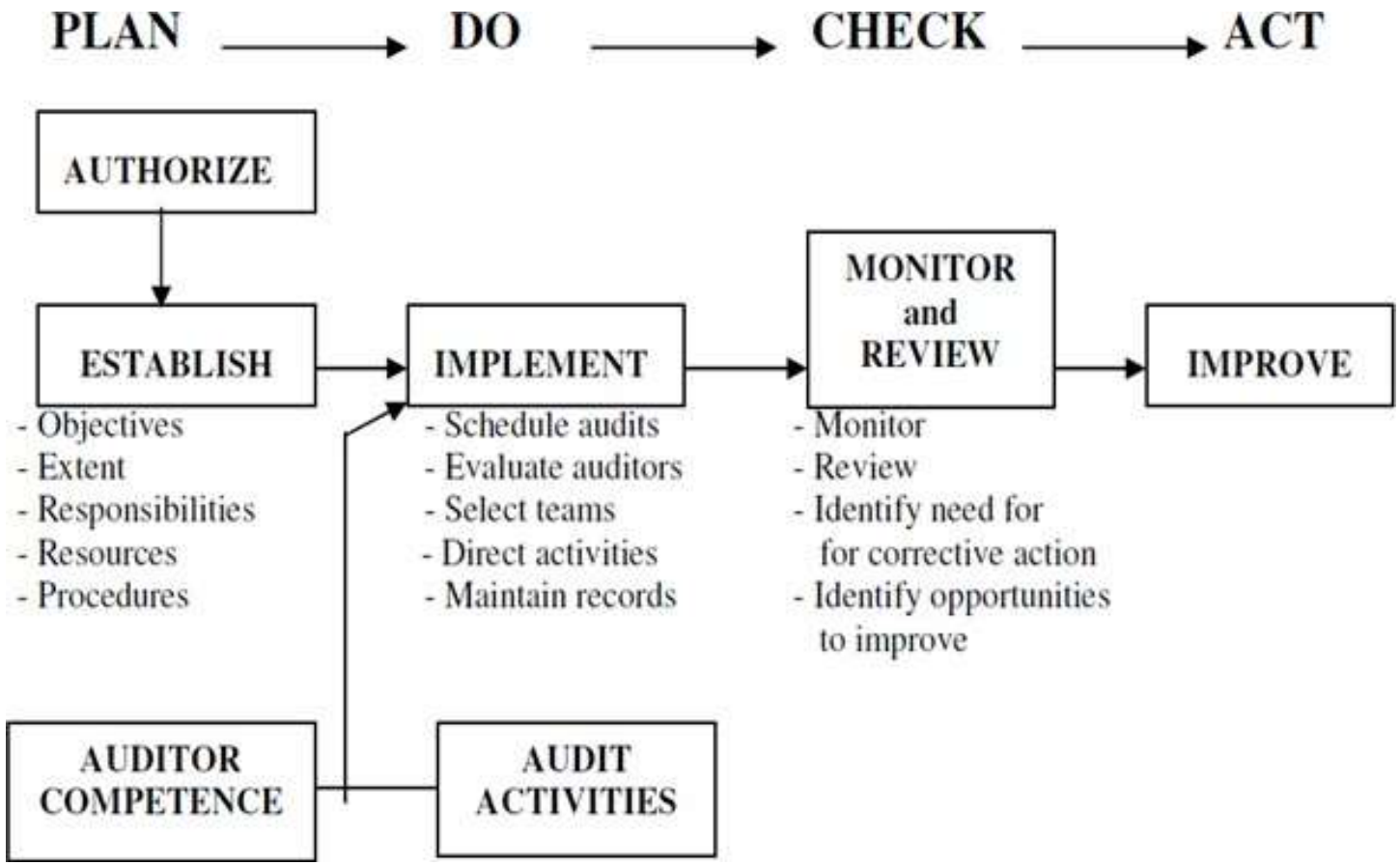
  2.Identify the necessary resources and ensure they are provided.

- The simple goal of this complex process is to evaluate existing activities and documentation and determine if they meet the established standards.

# RESPONSIBILITIES

- An audit will evaluate the strengths and weaknesses of quality control and quality assurance processes, the results of which will help us to improve processes and build a better system for the benefit of the company.
- Every product manufactured by a pharmaceutical company has characteristics that must be quantified or qualified by laboratory tests.
- Quality control and quality assurance are the necessary processes that play the role of control and balance system in pharmaceutical industry.

# MANAGEMENT OF AUDIT…



# RESPONSIBILITIES…

The auditor has the following responsibilities:

- Assist in the selection of the team and inform the team.
- Responsibility to plan and manage all phases of the audit.
- Represent the audit team with the auditee.
- Control conflicts and manage difficult situations.
- Direct and control all meetings with the team and the auditee.
- Make decisions about audit issues and the quality system.
- Report the results of the audit without delay.
- Report the main obstacles encountered.
- Report critical non-conformances immediately.
- Possesses effective communication skills.

# PLANNING PROCESS

- In order to conduct an audit effectively and efficiently, the work needs to be planned and controlled.
- The form and nature of the planning required for an audit will be affected by the size and complexity of the enterprise, the commercial environment in which it operates, the methods of processing transactions and the reporting requirements to which it is subjected.
- Audit planning is the formulation of the general strategy for audit which sets the direction for the audit, describes the expected scope and conduct of the audit and provides guidance for the development of the audit program.

# PLANNING PROCESS…

Adequate planning of an audit work aims at:

- Establishing the intended means of achieving the objectives of the audit.
- Assisting in the direction and control of the work.
- Helping to ensure that attention is devoted to critical aspects of the audit work.
- Ensuring that the work is completed expeditiously.
- Facilitating review of the audit work.
- Helping to assign the proper tasks to members of the audit team and coordinates outside experts.

# PLANNING PROCESS…

The **steps in planning** an audit include:

- **Basic discussions with the client** about the nature of the practices by sampling, reviewing the law and testing internal rules and practices for reasonableness.

  Engagement are performed first, and the auditor meets the key employees or new employees of a continuing client. The overall audit strategy or the timing of the audit may also be discussed.

- **Ask about recent developments** in the company such as mergers and new product lines which will cause the audit to differ from earlier years.

# PLANNING PROCESS…

- **Ask about recent developments** in the company such as mergers and new product lines which will cause the audit to differ from earlier years.
- **Interim financial statements** are analyzed to identify accounts and transactions that differ from expectations (based on factors such as budgets or prior periods).

  The performance of such analytical procedures is mandatory in the planning of an audit to identify accounts that may be misstated and that deserve special emphasis in the audit program.

# PLANNING PROCESS…

- **Timing** of the various audit procedures should be determined.
- **Outside assistance** needs should be determined, including the use of a specialist as required and the determination of the extent of involvement of the internal auditors of the client.
- **Pronouncements** on accounting principles and audit guides should be read or reviewed to assist in the development of complete audit programs fitting the unique needs of the industry.
- **Scheduling with the client** is needed to coordinate activities.

# PLANNING PROCESS…

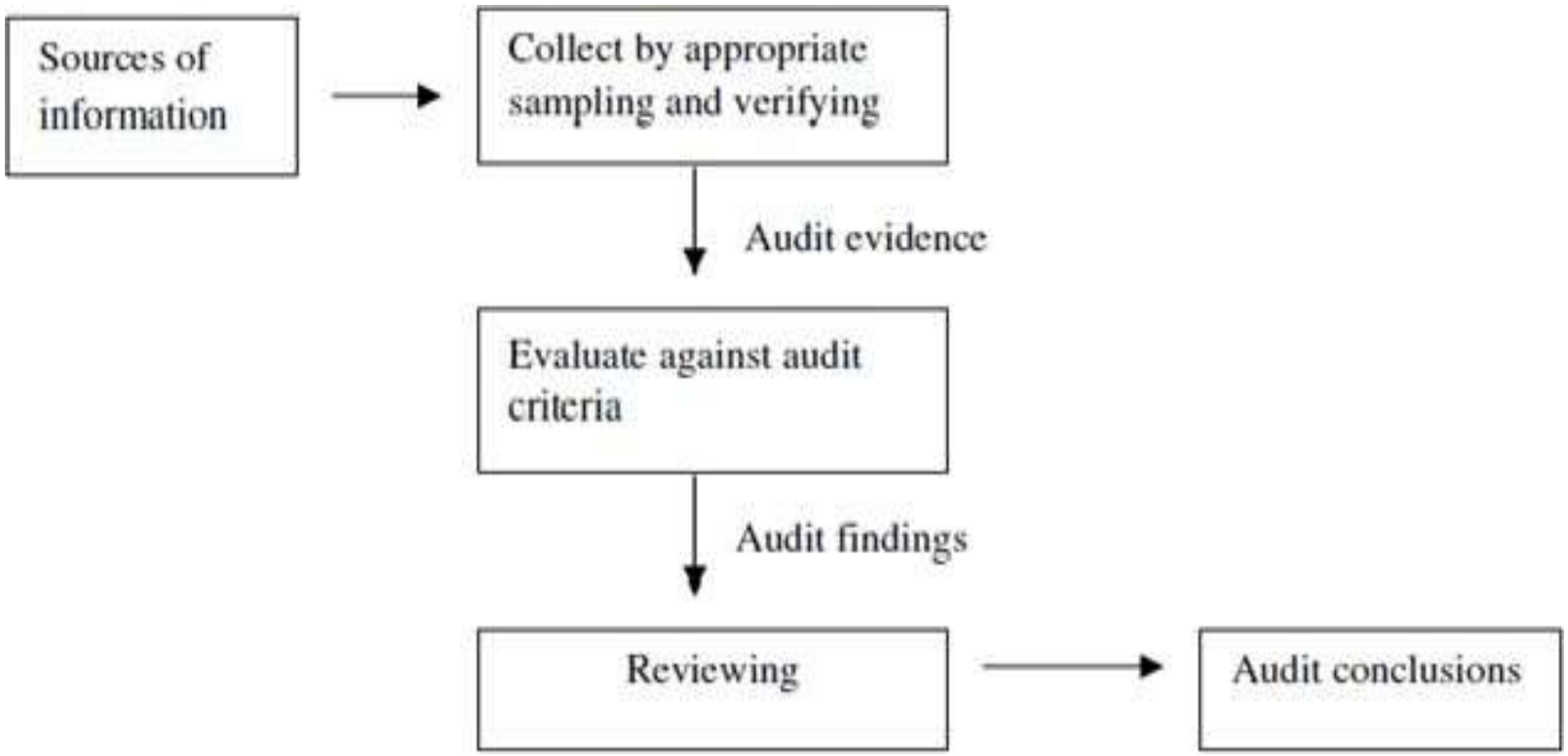
- **Non-audit personnel** of the accounting firm who have provided services (such as tax preparation) to the client should be identified and consulted to learn more about the client.
- **Staffing** for the audit should be determined and a meeting held to discuss the engagement.

  The purpose of all this is to ensure that the risk of performing a poor quality audit (and ultimately giving an inappropriate audit opinion) is reduced to an acceptable level.

# INFORMATION GATHERING

- Information is simply the facts or knowledge provided or learned. It can be tacit, in people's heads, or explicit, in documents-electronic or hard copy.
- During the audit, information relevant to the objectives, scope and criteria, including information on interfaces between functions, activities and processes, should be collected by appropriate sampling and should be verified.
- Only verifiable information can be audit evidence which must be recorded.

# INFORMATION GATHERING…



# INFORMATION GATHERING…

**Audit evidence:**

- It is any information used by the auditor to determine if the audited information is in accordance with the established criteria and to arrive at the conclusions on which the audit opinion is based. Internal Audit Evidence includes any data, information, process flows, vouchers, bills, memos, contracts or transactions.

**Methods of gathering audit information:**There are six basic methods of gathering information during an audit. Depending on the type of information that needs to be obtained, the Internal Auditor will need to determine which method, or combination of methods, should be used.

# INFORMATION GATHERING…

**Interviews:**

- Interviewing is a powerful data collection technique, which works well on its own and is often used to support other techniques, such as observation.
- The interviewee's insights can guide the Internal Auditor's decisions about what to observe.
- The most important thing to remember when interviewing is to always talk to the right person, as it can save a lot of time and confusion.

# INFORMATION GATHERING…

**Inspections:**

- When inspecting something, it is good practice to start with general observations and then proceeding to the more specific elements.
- First, the Internal Auditor will have a good overall look around the facility and then examine specific items more closely, noting anything that does not seem quite right.
- It is important to ask questions throughout the inspection. If a problem is found, the Internal Auditor must investigate (dig deeper) to explore the extent of the finding.

# INFORMATION GATHERING…

**Reviewing documents:**

- Documents should be clear regardless of who reads them. Details vary but, in general, every document should carry a title, an owner and a revision status. If any of this information is missing, the Internal Auditor should ask why.
- The revisions noted should be checked against the master record. Changes must be authorized, signed and dated by an authorized person.
- However, one sample taken in one given period of time is usually not enough to form accurate conclusions. Another important aspect of record keeping is clarity.

# INFORMATION GATHERING…

**Observations:**

- The simplest way to check how a process works is to observe it in action.
- Observing a routine activity for a couple of hours can give the Internal Auditor the opportunity to see how something is done under normal circumstances.
- He or she should ask questions about what they see, making sure at all times not to interfere with the processes they are observing, as that may cause the personnel not to carry out their tasks as they usually do.

# INFORMATION GATHERING…

**Vertical tracking:**

- This method is also referred to as “vertical auditing” and consists of following a specific development from the beginning until the end, simultaneously checking all the records that are produced in the process.
- Applying the vertical tracking technique can lead the Internal Auditor to areas that were not initially part of the scope, but it does facilitate a bigger picture view, as this allows the Internal Auditor to see how the various parts of a given program work together.

# INFORMATION GATHERING…

**Exercises:**

- The aim of an exercise is to test something that is usually done at the facility as part of the routine. However, the Internal Auditor gets to pick the time and the circumstances for the test.
- The subject of testing can be the personnel, the program, or the equipment. An Internal Auditor should not run an exercise without the knowledge and cooperation of the auditee.
- Doing so is likely to have negative consequences as unannounced actions may breach certain facility specific rules or regulations which the Internal Auditor is unaware of.

# ADMINISTRATION

**Administration:**

- The internal audit team must have the confidence and trust of the key stakeholders it works with and be seen as a credible source of assurance and advice.
- This confidence should not be assumed and can only be established and maintained by having an effective working relationship, by delivering high quality and timely advice and internal audit reports that are seen to be contributing directly to assisting the organisation to meet its responsibilities.

# ADMINISTRATION…

The key stakeholders of internal audit are:

1. Chief Executive
2. Board of Directors
3. Audit Committee
4. Senior management
5. External auditor
6. Other reviewers

# ADMINISTRATION…

**Chief executive:**

- While internal audit reports functionally to the Audit Committee, it is important that the Head of Internal Audit has direct access, as and when required, to the Chief Executive.
- Organisations today, recognize the advantages in making the Head of Internal Audit directly accountable to the Chief Executive. This not only sends a clear signal about the importance of the internal audit function, it also facilitates regular contact between the Chief Executive and internal audit.

# ADMINISTRATION…

- This contact should be used as an opportunity to gain insights into new and emerging risks and issues facing the organisation and to discuss the role the Chief Executive expects internal audit to fulfill in the company.

**Board of directors:**

- The Head of Internal Audit may formally report to the Board of Directors on the effectiveness of the internal audit function in order to exchange views and ideas.

# ADMINISTRATION…

- As the Audit Committee is usually a sub-committee of the Board, this responsibility is often delegated to the Audit Committee.
- As a minimum, it is important that the Head of Internal Audit has direct access to the Chair of the Board and the Chief Executive, as and when required.

**Audit committee:**

- Audit Committees play an integral role in the governance framework of organizations. It assists Chief Executives and Boards to understand whether key controls are appropriate and operating effectively.

# ADMINISTRATION…

- In this respect, the relationship between internal audit and the Audit Committee is crucial and has a number of dimensions which are mentioned below:

a. Advise the Chief Executive about the internal audit plans of the organisation.

b. Direct or coordinate work programs relating to internal and external audits.

c. Review the adequacy of responses to reports of internal and external audits.

d. Utilize the internal audit function to undertake secretariat compliance.

# ADMINISTRATION…

**Senior management:**

- To effectively fulfill its responsibilities, it is important that internal audit has a professional and constructive relationship with senior management of the organization.
- Internal auditors should interact on a regular basis with members of the senior management team, and through the delivery of practical, business-focused and useful reports and advice, build a relationship that is based on cooperation, collaboration and mutual respect.

# ADMINISTRATION…

- These meetings should also be used to obtain informal feedback about the performance of internal audit and to assist in identifying ways that internal audit can best assist organization management.

**External auditors:**

- External auditors too must help in developing internal audit strategy and internal audit work plan.
- Both audit teams need to address the key financial and business systems underpinning the company's financial statements and to avoid duplication of compliance and assurance.

# ADMINISTRATION…

- To avoid such duplication, the external auditor must evaluate the work of the internal audit function to determine its adequacy for external audit purposes.
- The Internal audit function can be made responsible for liaising with external auditor on behalf of the organization. Such a role can be a useful way for an internal audit team to be aware of planned and actual external audit coverage.
- Thus, a constructive relationship between both sets of auditors assists in the conduct of external audits.

# ADMINISTRATION…

- Such a role can only be fulfilled when there is healthy communication between teams which can be achieved by establish meetings to allow for a routine exchange of information.

**Other reviewers:**

- Internal audit is one of a number of internal and external review and assurance activities that exist as part of an organization's governance arrangements.
- The company shall benefit when all these activities, such as those performed by the Ombudsman and regulators, operate in a coordinated and complementary manner to the greatest extent possible.

# ADMINISTRATION…

- This requires regular formal and informal contact between review bodies to minimize duplication and overlap.
- Some organisations see a benefit in protocols being formalised for such activities: providing, for example, for the regular exchange of views and information and for the reporting of the results of work undertaken in a coordinated manner.
- Protocols can be particularly important in situations where internal audit needs to work closely with other entities as a result of inter-agency or other agreements.

# CLASSIFICATION OF DEFICIENCIES…

**Nonconformities or deficiencies:**

As the audit proceeds, there might arise some situations where the facts indicate there is a failure, either partially or wholly, of the quality management system, such a situation is called **nonconformity".**

**What is nonconformity?**

- a condition adverse to Quality.
- The non-fulfillment of a requirement.

The number of nonconformities that can arise during an audit can be numerous. Following types of defects are identified during an internal audit and these are helpful in regulatory compliance:

# Classification of deficiencies…

**Critical defect:**

- Critical defects have a high probability of resulting in a product recall or in an adverse physiological response by the consumer.
- Critical deficiencies found in internal audits that usually produce significant effects on the strength, identity, safety, and purity of the product that will be considered during regulatory compliance.The possible source of a critical defect are:
- Cross-contamination of materials of the product.
- Incorrect labeling.

# CLASSIFICATION OF DEFICIENCIES…

- Active ingredients outside of specifications.
- Product manufactured according to obsolete or unapproved procedures.
- Open sterile products located in a non-aseptic area.
- Untrained operators working in the sterile filling area.
- Contaminated purified water or water for injection system.

**Major defect**

Major defects found during the internal audit can reduce the usability or stability of a product, but without causing harm to the consumer.The possible source of a major defect are:

# Classification of deficiencies…

- Major equipment not calibrated or out of calibration.
- Inadequate segregation of quarantine components.
- Inadequate evaluation of production process outside of action levels.
- Process deviations not properly documented or investigated.
- Operator not trained in or familiar with the standard operating procedures.
- Preventive maintenance on a critical water system not conducted according to schedule.

# Classification of deficiencies…

- Lack of standard operating procedures for cleaning equipment.
- Audits of a contract manufacturer not conducted.

**Minor defect**

Minor defects have a low probability of affecting the quality or usability of the product which can help in regulatory compliance.Possible source of the minor defect are:

- Failure to complete all batch record entries.
- Warehouse not cleaned according to schedule

# Classification of deficiencies…

- Cracks in wall surfaces.
- Failures to correct documentation errors properly.
- Operator uniform not properly worn.
- Standard operating procedure review is overdue.
- Adhesive tape used on manufacturing equipment.
- Laboratory buffer solutions are obsolete.

# CONCLUSION

- Audits to be conducted at planned intervals to evaluate effective implementation and maintenance of the quality system and to determine if processes and products meet established parameters and specifications.
- An audit performed by a well trained and thoroughly prepared auditor can be highly beneficial by identifying areas for genuine improvement.
- Auditing in the pharmaceutical sector serves two different categories: regulatory compliance and business needs.

# REFERENCE


1.Review on“Pharmaceutical quality audits” by princy agarwal & amul misra , Nnovare;2018.

2. Vedanabhlata S, Gupta VN. “A review on audits and compliance management”. Asian J Pharm Clin Res 2013;6:43-5.

3. Kaur J. Quality audit: Introduction, types and procedure [Internet].Pharma Pathway; 2017. http://pharmapathway.com/quality-audit-introduction- types-and-procedure/.

4.Chartered Institute of Internal Auditors. How to gather and evaluate information;2017. https:/www.iia.org.uk/resources/delivering-internal-audit/how-/.

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# UNIT-2

# ROLE OF QUALITY SYSTEM AND AUDITS IN PHARMACEUTICAL" MANUFACTURING ENVIRONMENT

# ROLE

- This Chapter describes outlines and discusses the regulations applicable to the QA function and unit, structure, , charter, and application of the unit in the pharmaceutical manufacturing environment.
- By regulation
- Appropriate practice,
- Common sense,

# ROLE

- quality assurance (QA) is a critical function in the pharmaceutical manufacturing environment. The need for an independent unit to audit and comment on the appropriate application of standard operating procedures, master batch records, procedures approved in product applications,
- This helps assure that products are manufactured reliably, with adherence to approved specifications, and that current good manufacturing practices (cGMP) are maintained in conformance to regulation, both in the facility in general
  and the microenvironment of each product's manufacturing sequence.

# ROLE

- Quality assurance personnel must have the appropriate training, experience, familiarization with the manufacturing facility and products and the ability to review adherence to procedures, policies, This helps to provide both an environment and a manufactured product that can withstand Food and Drug Administration (FDA) inspection and support a firm's reputation for quality products.
- The cGMP regulations establish requirements that are intended to provide a high level of assurance that the pharmaceutical products produced satisfy the strength, purity, potency, and other quality requirements established for the finished product to assure that it is fit for its intended use.

# cGMP REGULATION

- The cGMP regulations for the manufacture of pharmaceutical products are contained in Parts 210 and 211 of Title 21 of the Code of Federal Regulations (CFR)
- Part 210 specifies the scope and applicability of the cGMP regulations and defines terms used in the regulations. Part 210 also indicates that the regulations establish "minimum" cGMP requirements and that products that are not manufactured under cGMP are adulterated. Adulterated products and the persons responsible for the adulteration are subject to regulatory action by the FDA.

# cGMP REGULATION

- Part 211 contains specific good manufacturing practice requirements for finished pharmaceuticals and is divided into Subparts A–K as follows:
- A. Scope
- B. Organization and Personnel
- C. Buildings and Facilities
- D. Equipment
- E. Control of Components and Drug Product Containers and Closures
- F. Production and Process Controls
- G. Packaging and Labeling Control
- H. Holding and Distribution
- I. Laboratory Controls
- J. Records and Reports
- K. Returned and Salvaged Drug Products

# cGMP REGULATION

- The cGMP regulations are written to address the primary potential sources of product variability.
- Subpart B establishes the quality control unit and the duties of that unit, establishes personnel requirements and addresses personnel practices (e.g. sanitation) intended to reduce the likelihood of product contamination.
- Sub- parts C and D establish requirements for buildings and facilities and equipment used in the manufacture, processing, packing, or holding of a drug product.
- Subparts E through H establish controls over the major processes associated with the production of a finished and packaged drug product that is ready to be shipped for distribution to users.

# cGMP REGULATION

- Subpart I requires the appropriate specifications, standards, sampling plans, and test procedures; requires instrument specifications and calibration
- Subpart J establishes documentation requirements including master and batch records,
- Subpart K addresses the control and disposition of returned drug products and places limitations on the salvage of drug products that have been subjected to improper storage conditions (e.g., smoke, heat, fire, moisture).

# Duties of Quality Control Unit under cGMPRegulations

- The cGMP regulations assign specific duties to the quality control unit. The unit is required to have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products
- The organization must assure that the quality control unit has adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products.
- In addition to duties associated with the approval of materials and finished products, the unit is also responsible for approving or rejecting all procedures or specifications for identity, strength, quality, and purity of the drug product.

# 2 Quality Assurance Function

- The term quality is used in many industries and in everyday life and can have various meanings depending on context.
- Quality mean the product requirements or attributes that have requirements.
- Quality assurance activities are those processes and activities conducted to assure that a product or service consistently satisfies its requirements and is fit for its intended use.
- In the pharmaceutical manufacturing environment, this means the activities conducted to assure that the pharmaceutical product's identity,strength, purity, potency, and other quality attributes conform

# 2 Quality Systems Approach

- A management commitment to quality that is communicated throughout the organization
- Identifying quality requirements using risk management and other methods as appropriate
- Developing a quality policy, plan, objectives
- Establishing an organizational structure with identified responsibilities and authorities that allows quality objectives to be met
- Providing the resources needed to meet quality objectives
- Developing the required systems and processes
- Establishing methods for the ongoing objective evaluation of the performance of systems and processes including quality auditing
- Initiating corrective and preventive actions as needed to assure that quality objectives are consistently and reliably met

# 2 Quality Systems Approach

- The use of risk management techniques in identifying product requirements, establishing processes and process control and monitoring methods, evaluating quality data, identifying appropriate corrective and preventive actions to address quality problems, and for other quality-related activities can increase the overall efficiency and effectiveness of the quality system

# 2 Quality Systems Approach

- In a modern quality system, the organizational unit responsible for quality related activities within the organization generally has a central role in the development and management of the overall quality system.
- These activities can include quality control, quality assurance, quality planning, and quality improvement.
- The cGMP regulations do not define or employ these terms, But the activities the regulations assign to the quality control unit

# 2 Quality Systems Approach

- Current quality system models involve quality-related activities and terms that are not included in the cGMP regulations.
- important for organizations adopting a quality systems approach to unambiguously define the terms and quality concepts they will be using
- include these definitions as appropriate in training all staff in the organization who will be involved in quality-related activities.
- This will help assure effective communication throughout the organization and with vendors and others

# 2 Quality Systems Approach

FDA guidance on the quality systems approach the following definitions:

- Quality Assurance (QA) Proactive and retrospective activities that provide confidence that requirements are fulfilled.
- Quality Control (QC) The steps taken during the generation of a product or service to ensure that it meets requirements and that the product or service is reproducible.
- Quality Management (QM) Accountability for the successful implementation of the quality system.
- Quality System (QS) Formalized business practices that define management responsibilities for organizational structure, processes, procedures, and resources needed to fulfill product/service requirements, customer satisfaction, and continual improvement.
- Quality Unit (QU) A group organized within an organization to promote quality in general practice.

# 2 Quality Systems Approach

Other cGMP-assigned responsibilities of the QU that are consistent with modern quality system approaches include the following:

- Ensuring that controls are implemented and completed satisfactorily during manufacturing operations
- Ensuring that developed procedures and specifications are appropriate and followed, including those used by a firm under contract to the manufacturer
- Approving or rejecting incoming materials, in-process materials, and drug products
- Reviewing production records and investigating any unexplained discrepancies

# FDA has designed and implemented quality system can do the following

- Reduce the number of (or prevent) recalls, returned or salvaged products, and defective products entering the marketplace
- Harmonize the cGMP regulations to the extent possible with other widely used quality management systems, which is desirable because of the globalization of pharmaceutical manufacturing,
- When the use of effective risk management practices, handle many types of changes to facilities, equipment, and processes without the need for prior approval regulatory submissions
- Potentially result in shorter and fewer FDA inspections by lowering the risk of manufacturing problems
- Provide the necessary framework for implementing quality by design , continual improvement, and risk management in the drug manufacturing process

# 2 Quality Systems Approach

- The major elements of the quality system model described in the FDA's pharmaceutical QS guidance document,These elements are as follows:
- Management responsibilities
- Resources
- Manufacturing operations
- Evaluation activities

# Management responsibilities

Current quality system models assign management a major role in operation of a successful quality system

- Provide leadership ,communicated throughout the organization
- Create an organizational structure with clearly defined responsibilities and authorities to perform quality functions associated with achieving quality objectives
- Building and documenting a quality system to meet specified quality and regulatory requirements and achieve quality objectives
- Establishing a quality policy and objectives, and quality plans and communicate this throughout the organization
- Assure that appropriate corrective and preventive actions are taken in response to quality problems using effective change control procedures and documented

# Management responsibilities

- Under a comprehensive quality system the QU can expect an expanded and more visible role within the organization with greater accountability to and interaction with upper management.
- the QU should be structured to reflect management's strong commitment to quality and to facilitate achieving quality objectives.
- The structure (e.g., organizational relationship to other organizational units, reporting relationships) should provide clear lines of responsibility and authority that support the production, quality, and management activities necessary to achieve quality objectives.

# Management responsibilities

- The cGMP regulations require quality-related activities to be conducted during all phases of manufacturing from the acceptance of raw materials through batch release, packaging, and labeling.
- the role of quality personnel can be significantly expanded to include internal quality auditing, expanded review and analysis of quality data, investigation of nonconformance, root cause analysis, risk analysis, and other quality-related activities.
- Quality staff should have sufficient scientific and technical knowledge and training (e.g., statistical methods, risk analysis)

# Resources

- Inadequate staffing, training, manufacturing equipment and facilities, environmental controls, analytical equipment, and other resources can be sources of variability leading to the production of product that does not meet specified requirements
- Modern quality system standards specifically address the issue of resources by requiring the organization to determine and provide the human, infrastructure, and work environment resources necessary for the quality system.

# Resources

- The cGMP regulations address the resource issue in the adequacy of personnel (including consultants), manufacturing facilities including contract facilities, equipment, and laboratory facilities. The QU has significant responsibility in this regard.
- The FDA, in its pharmaceutical QS guidance document, discusses the need for adequate resources in developing, implementing, and managing a quality system that complies with the cGMP regulations.

# Resources

- Management is responsible for identifying resource requirements and providing resources accordingly, including providing training that is appropriate to the assigned activities
- Personnel should understand the impact of their activities on their assigned duties and be familiar with cGMP requirements and the organization's quality system.
- Management should establish a working environment that encourages problem solving and communication in identifying and acting upon quality-related issues.

- the QU and other organizational units should be involved in the identification of the resources required to achieve quality objectives, including regulatory compliance, evaluating the effect of personnel, facility, product, process, regulatory
- The FDA notes that the cGMP regulations place as much emphasis on processing equipment as testing equipment and contain specific requirements for the qualification, calibration, cleaning, and maintenance of production equipments

- the specification of facility and equipment requirements may be performed by technical experts (e.g., engineers)
- The cGMP regulations require the QU to be responsible for reviewing and approving all initial design criteria and procedures pertaining to facilities and equipment and any subsequent changes
- A requirement of both the cGMP and current quality system models is that such review and approval be conducted by persons who are qualified by education, training and experience to do so.

- the control of outsourced operations, the cGMP regulations require that the QU approve or reject products or services provided under a contract.
- Under current quality system models, the organization must follow a formal vendor qualification process to qualify outsource providers and verify through inspection or other To comply with the regulation, these operations should be conducted by the QU

# MANUFACTURING OPERATIONS :

- This requirements contained in current quality system models such as ISO 9001-2000 and the GMP regulation requirements for manufacturing.
- The FDA has identified four major elements of QS approach to manufacturing operations.

# CFR cGMP REGULATIONS RELATED TO MANUFATURING OPERATIONS

| Quality system elements | Regulatory citation |
|---|---|
| Design and develop product and process | Production :§211.100(a) |
| Examine inputs | Material:§§210.3(b),211.80-211.94,2110110,211.111,211.113 |
| Perform and monitor operations | Production:§§211.100,211.103,211.110,211.111,211.113 |
| Address nonconformities | Discrepancy investigation:§§211.22(a),211.100,211.115,211.192, 211.198 recalls 21 CFRpart7 |

# Design, Develop and document product and process

- In a modern quality system manufacturing environment, the significant characteristics of the product being manufactured should be defined and verified as meeting requirements from design to delivery, and control should be exercised over all changes.
- This is consist of the cGMP regulations.
- That require quality and manufacturing process and procedures, and changes to them to be defined approved and controlled.

Document is required and can include the following :-

- Resource and facilities used
- Procedures to carry out the process
- Identifications of the process owner who will maintain and update the process as needed
- Identification and control of important variables

- Quality control measures, necessary data collection, monitoring, and appropriate controls for the product and process
- Any validation activities, including operations ranges and acceptance criteria
- Effect on related process, functions, or personnel

- labling controls.
- So packaging and labelling requirements, process and controls should be included in a QS based approach to product and process design and development.
- The FDA acknowledges that the reluctance to pursue potentially innovative changes in pharmaceutical manufacturing can be undesirable from a public health perspective and has published a process analytical (PAT)guidance document.

- This guidance is intended to address this by promoting the use of analytical tools to gain process understanding and meet regulatory requirements for validating and controlling manufacturing process.
- The FDA has published the guidance document and other pertinent PAT information on its website at www.fda.gov. companies interested in PAT methods should contact the FDA.

- FDA internal implementation of PAT include the following:
- A PAT team approach of CMC review and cGMP inspections
- Joint training and certification of FDA PAT review, inspection, and compliance staff
- Scientific and technical support for the PAT review, inspection, and compliance staff

# EVALUATION ACTIVITIES :

- The evaluation component of a QMS is intended to provide objective information and data that allow the organization to assess the conformity of the product, evaluate the performance of its quality system, and maintain and improve its effectiveness.

# CFR cGMP REGULATIONS RELATED TO EVALUATION ACTIVITIES

| Quality system element | Regulatory citation |
|---|---|
| Analyse data for trends | Annual review:§211.180(e) |
| Conduct internal audits | |
| Risk assessment | |
| Corrective action | Discrepancy investigation:§§211.22(a),211.192 |
| Preventive action | |
| Promote, improvement | §211.110 |

# TREND ANALYSIS

- Trend analysis is one statistical tool specifically recommended by the FDA in its pharmaceutical QS guidance document.
- That can be very valuable monitoring process and quality system performance to identify emerging problems and to assess the effectiveness of improvement efforts.
- Traditional statistical process control and other methods also provide valuable support in the objective and ongoing analysis of quality data and can be helpful in implementing real-time quality assurance practices as recommended by the FDA.

# CONDUCT INTERNAL AUDITS

- Internal audit is not specifically required by the cGMP regulations, but manufacturers have traditionally used internal audits as a self-assessment tool and to prepare for FDA inspections.
- International standards provide guidance on auditing.
- Audits procedures should be developed and documented to ensure that the planned audit scheduled takes into account the relative risks of the quality system activities.

Factors that can incorporated into a risk-based approach to planning audit frequency and scope include the following :

- Exiting legal requirements (e.g., cGMPs)
- Overall compliance status and history of the company or facility
- Robustness of a company’s quality risk management activities
- Complexity of the site
- Complexity of the manufacturing process

- Complexity of the product and its therapeutic significance
- Number and significations of quality defects (e.g., recall)
- Result of previous audits/inspections that can include prior internal audit results as well as regulatory (e.g., state, federal, or other regulatory agencies) and third-party audits.
- Major changes of building, equipment, process and key personnel
- Experience with manufacturing of a product (e.g., frequency, volume, number of batches )
- Test results of official control laboratories

- Different audit approaches may be applied depending on the intended purpose and scope of the audit.
- A top-down approaches first evaluates the overall structure of the quality system and its subsystem.
- Subsystem may be chosen for review.
- Systems identified and developed by the FDA in a SIX-SYSTEM inspection model for the inspection of drug manufacturers.

- Overall quality system
- Facilities and equipment
- Materials system
- Production system
- Packaging system
- Laboratory controls

| [COMPANY NAME ] QUALITY SYSTEM AUDIT CHECKLIST | | | |
|---|---|---|---|
| FROM: | REV: | DATE: | APPROVED : |
| AUDIT DATES (S): | Refs: | | |
| Auditor: | | TITLE | SIGNATURE : |
| REQUIREMENT | cGMP SECTION CROSS REFERENCE | CONFORMS (Y/N/NA) | OBJECTIVE EVIDENCE AND COMMENTS |
| SUBSYSTEM 1 | | | |
| REQUIREMENTS 1.1 | | | |
| REQUIREMENTS 1.2 | | | |
| SUBSYSTEM 2 | | | |
| REQUREMENTS 2.1 | | | |
| REQUIREMENTS 2.2 | | | |
| SUBSYSTEM 3 | | | |
| REQUIREMENTS 3.1 | | | |
| REQUIREMENTS 3.2 | | | |
| SUBSYSTEM N | | | |

# CORRECTIVE AND PREVENTIVE ACTION

- A corrective and preventive action may be initiated based on reviewed and analysis of quality data from a verity of sources including adverse experiences, product complaints, quality audits, FDA inspection, third-party inspections, nonconforming materials reports, process control information, trend analyses, and other sources.

- A firm's CAPA system and process should be designed to analyse and respond to quality issues in a systematic way that is commensurate with the risk.
- The system should provide for the verification or validation of corrective and preventive actions to assure their effectiveness and to assure that actions do not adversely affect the finished product.
- The system should also assure that pertinent CAPA information is appropriately disseminated throughout the organization as necessary to assure the effective operation of the quality system and for management review.

# TRANSITIONIG TO QUALITY SYSTEM APROCH

- The GMP regulations assign significant responsibilities to the organizational unit responsible for quality-related activities.
- Organizations implementing a quality system model will be responsible for additional quality-related activities including but not necessarily limited to, conducting quality audits, analysis of quality data, risk assessment, and preventive actions based on review and analysis of quality data to prevent the occurrence of product nonconformities.

# Some points to consider in planning the transition :-

- Create a transition team: A cross functional team should be developed involving key managers and staff from throughout the organization to plan and execute the transition.
- The transition team should have a clear understanding of its mission and the organizational objectives associated with the transition.

- Train the transition team: management should assure that all individuals on the transition team receive proper training on quality systems requirements, risk management, and FDA ‘s recommended approach to quality system.
- Develop a transition plan: a transition plan, based on clearly defined objectives, should be developed by the transition team.
- Identify staffing requirements: The transition will likely affect individual job descriptions and create additional duties that will have to be addressed through the reassignment of staff, and providing necessary training to all affected staff.
- Define roles and responsibilities: The plan should clearly define the roles and responsibilities of those responsible for development and execution of the plan for quality system implementation as well as staff roles and responsibilities under the quality system.

- consider organizational structure requirements: In order to function properly, person responsible for quality-related activities must have the responsibilities and associate authority defined and appropriately communicated within the organization.
- Consider benchmarking: If possible, arrange with other organizations that have successfully made the transition to meet with them, review their system , and discuss transition issues and how they were solved.
- Communicate regularly: clear and ongoing communication within the transition team and with management is essential to effectively coordinate plan activities, report progress, resolve issues, and identify evolving resource needs
- validate the system
- Maintain regulatory compliance.

# REFERENCE :-


- Active Pharmaceutical Ingredients Committee (APIC). Auditing guide; 2016. Available from: http://apic.cefic.org/pub/Auditing/APIC_CEFIC_AuditingGuideAugust2016.pdf. [Last accessed 19 Mar 2018] Place Unknown: Word Press; 2008. Available from: https://drpotdar.wordpress.com/2008/04/30/audit/.
- BSI standards publication: European committee for standardization. Guidelines for auditing management systems; 2011. Available from: http://qic-eg.com/wp-content/uploads/2015/08/BS-EN-ISO-19011-2011.pdf.
- Roger CPA Review Blog. The 10 steps in planning an audit; 2009. Available from: https://www.rogercpareview.com/ blog/10-steps-planning-audit.

# UNIT-3
# AUDITING OF VENDORS AND PRODUCTION DEPARTMENT

# BULK PHARMACEUTICAL VENDOR AUDIT :

INTRODUCTION :

- Manufacture of medicinal products and the active pharmaceutical ingredients {APIs} , bulk pharmaceutical ingredients {BPIs } used as starting materials in the production of these products is subject to strict good manufacturing practice regulations that are dissigened ensure their quality , safety, and efficacy .
- This ensures that patients worldwide and at any time can have confidence in the quality ,safety ,and efficacy of medicines .

# WHY VENDOR AUDIT :

- The quality system requirements to idenity , select , approve and quality vendors of all materials used in the manufacture of BPIs and medicinal products are clearly defined in the GMP guidelines .

✓ Non critical raw materials

✓ Critical raw materials

✓ Registered intermediates

✓ APIs

# CONTINEUED ……

In addition to GMP regulatory the excipient vendor qualification is particulary important .

✓To provide adequate assurance of drug product performance .

✓To aviod the potential risks mentioned below.

- Presence of extraneous matter e.g., metal , paper , particles
- Cross contamination with other chemicals [ either excipients or APIs or breakdown products ]

# CONTINEUED…..

- Contamination with melamine risk materials which is not permitted by legislation .
- Inconsistent manufacture such that the quality of final products cannot be assured .
- Mislabeling of containers leading to product mix –up

✓Concept of quality by design {QbD} involves understanding of product variability in which contribution of excipient also needs special consideration

# AS PER GMP THE GUIDELINES FOLLOWED FOR AUDITS .

- Registered intermidiates usually involve custom synthesis or process development by the supplier .
- The quality system requirements to identify , select , approve and qualify suppliers of all materials used in the materials used in the manufactutr of APIs and medicinal products are clearly defined in the GMP guidelines .

# TERMS WHICH FOLLOWED ….

- We are also referring to existing APIC quidance documents whenever applicable to futher clarify expectations and provide consistency to the processes .
- E.g :
- Quality agreements
- Auditing guide ,
- APIC audit programme

# DIMENSIONS ….

- Following different dimensions could be assessed :

- ❑ Assurance of suppy
- ❑ Quality and regulatory compliance
- ❑ Cost / procurement aspects
- ❑ Technical /innovation
- ❑ Communication capabilities and responsiveness

# AUDITING PACKAGING MATERIAL VENDORS :

- Goals :

➢ Perform a packaging component supplier audit .

➢ Understand which worldwide requirements apply to packaging component suppliers .

➢ Use a range of information tools , including the contents of this module , in support of a packaging component supplier audit .

# DEFINITIONS :

1. GANG – PRINTED LABELLING :

- Labeling derived from a sheet of material on which more than one item of labeling is printed .{ see example below } . Gang printing is considered to be an un acceptable practice for some industry since it increases the potential for label mix –up .

# 2 .PACKAGING MATERIALS :

- Any material employed in the packaging of a medicinal product , excluding any other packaging used for transportation or shipment.

3.PACKAGING COMPONENT –CRITICAL {PCNC}:

- Is any printed packaging component ,primary {product contact } component or device , futhermore any secondary packaging component critical to the microbiological intergrity ,stability and /or administration of the product { e.g alumninium pillow packs around semi permeables }

4. PACKAGING COMPONENT –NON CRITCAL {PCNC} :

Is any non–printed or secondary {non contact }packaging component or device that does not fall with in the defintion of a pcc .

5. PRINTED PACKAGING COMPONENT :

Packaging materials that are printed and /or otherwise decorated . Examples would include cartons ,lables ,leaflets .

# AUDITING PACKAGING MATERIAL VENDOR :

a. LINE CLEARANCE : Line clearance is an essential in product mixup prevention and needs to focus on :

i. Input materials on the line from the previous batch

ii. Samples and waste from the previous batch

iii. Documents on the line from the previous batch

iv. Verification that any electroinc data is wiped from consoles etc.

- CONTAMINATION CONTROL :
- The facilities should be designed and laid out to appropriately reduce the risks of contamination from the environment and permit effective cleaning .
- Personnel growning and hygiene practies are part of contamination control efforts that may be applicable .

- The supplier should define the appropriate environmental conditions for handling and storage of the component (s) being manufactured . Guidance for minimum conditions can be found in PS 9000 pharmaceutical packaging materials , as well as programs such as ISO 9001 : 2000 and ISO 9004: 2000 for pharmaceutical packaging materials .

- VALIDATION AND QUALIFICTION :
- Ensure the process are adequately validated ,qualified and /or demonstrated according to the quality critical parameters of the component being manufactured .this may be demonstrated in the form of capability studies.

- SAMPLING :
- There should be an SOP that definies package components sampled be representive of the batch and sampling should be conducted to prevent contamination from the sampling mathod .
- Any packaging materials that meet appropriate written specifictions should be formally approved and released for use . Any components fail to meet such specifications must be rejected to prevent distribution .

- DOCUMENTATION :
- The appropriate SOPs and batch records must be followed when documenting any information or data associated with a component manufacture . Other pertinent types of documentation include :
- Records of how and who set up a particular machine .

# AUDITING WAREHOUSE AND DISTRIBUTION SYSTEM :

- GOALS :
- Perform an audit of warehouse and distribution .
- Assess and understand warehousing and distribution requirements , including licensing requirements .
- Use a range of tools and information , including the contents of this module and the internet , in support of auditing warehousing and distribution

# DEFINITIONS :

- FEFO : an inventoory management system where the products expired first are the ones sold first known by the abbreviation “FEFO , first expire ; first out .
- FIFO : an inventory management system where the products received first are the ones sold first or the oldest inventory is the first to be distributed . Known by the abbreviation “FIFO , first in ; first out .

FINISHED PRODUCT :

- A product which is packaged and labeled for supply to a wholesaler . hospital pharmacy , docter or patient .
- The use of this definition in the document includes medicinal products /prescription drugs

- INVESTIGATIONAL MEDICINAL PRODUCT :
- A pharmaceutical from of an active substance or placebo being tested or used as a reference in a clinical trial , including already with a marketing authorization but use or assembled [formulated or packaged] in a way different from the authorized form or when used for an unauthorized indication or when used to gain futher information about the authorized form.

# TABLETING

## General:

- Whether the unit has provide effective air extraction systems with discharge points to avoid contamination of other.
- products and process. Filters to be installed to retain dust.
- Whether the unit has taken precaution to avoid contamination of fiber shedding materials like wood.
- The unit is monitoring environmental conditions of pressure differential between rooms.

- The unit is monitoring environmental conditions of pressure differential between rooms.

- Temperature and humidity is controlled while processing of aspirin , ferrous  sulphate  ,tablets etc.

- Whether metal detector provided.

# Sifting, Mixing and Granulation

- Whether mixing , sifting and blending equipment are fitted with dust extractors unless operated as a closed system.
- Whether filter bags fitter to fluid bed drier are used for different products without being washed in between used.
- Whether air entering in to the drier is filtered.

# Compression (tablets)

- The tablet compressing machine are provided with effective dust control facilities and installed in separate cubicles.

- Whether tablets are being de-dusted and monitored for the presents of foreign materials and collected in clean labeled containers.

- Whether tablets are being inspected and checked for suitable Pharmacopeia  parameters like appearance weight variation , disintegration , hardness , friability and thickness and record maintained.

- The compressed tablets are stored properly.

# Equipment and area in the tablet section

1. Mass Mixer
2. Drum Mixer
3. Rotary tablet machine
4. Hot air oven
5. Multi mill
6. Coating pan
7. Sifter
8. Polishing

# AUDIT CHECKLIST

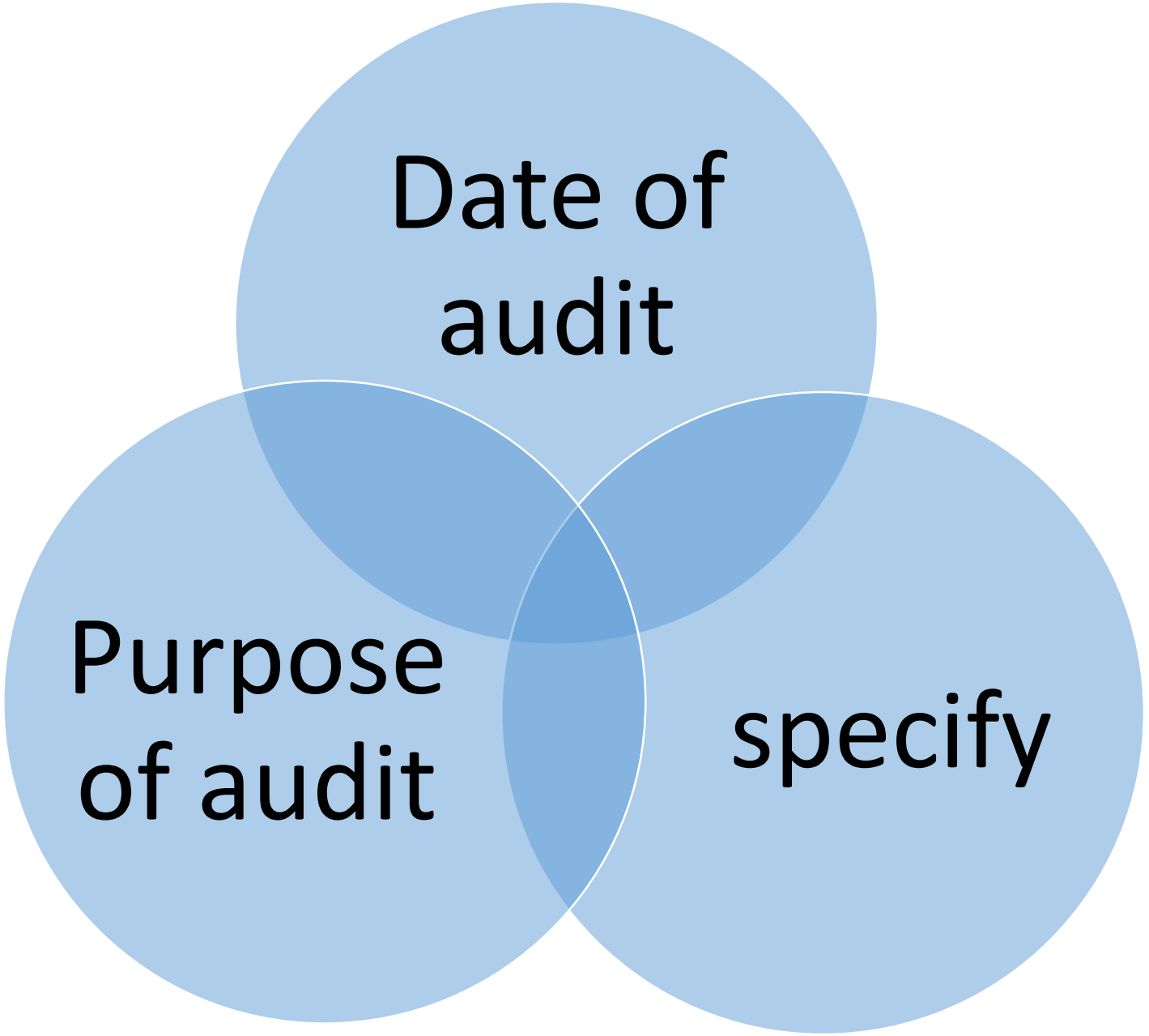
Edition no

Approved

Effective Date

Department

Dry Production : Tableting


Date of audit
Purpose of audit
specify

A . Documents Reviewed:

1. SOP
2. Personnel

B . Data Reviewed:

1.Facilities
2.prevention of cross –contamination
3.Equipment and facility cleaning
4.In-process control

# SOP

- Is a complete index and a complete set of application sop available in the department.
- Are the index and the SOP current.
- Is the set of SOP correctly organized according to the index.

# Personnel

- Select three employees working in the department. Are their training records up-to-date.

- Have the employees undergone training in the following area during the last year.

    1. GMP
    2. SOP

# Facilities

- Is the department maintained in a good state of repair.
- Is the department neat and orderly with sufficient space for equipment and operation.
- Are all work areas clearly labeled with the name and the batch number of the product being processed.

# Prevention of cross-contamination

- The doors closed at all time.
- Is personnel clothing clean , unstained and dust free including shoes.
- Is there a shoe-cleaning device in the department.
- Is there a record of the pressure.

# Equipment and facility cleaning

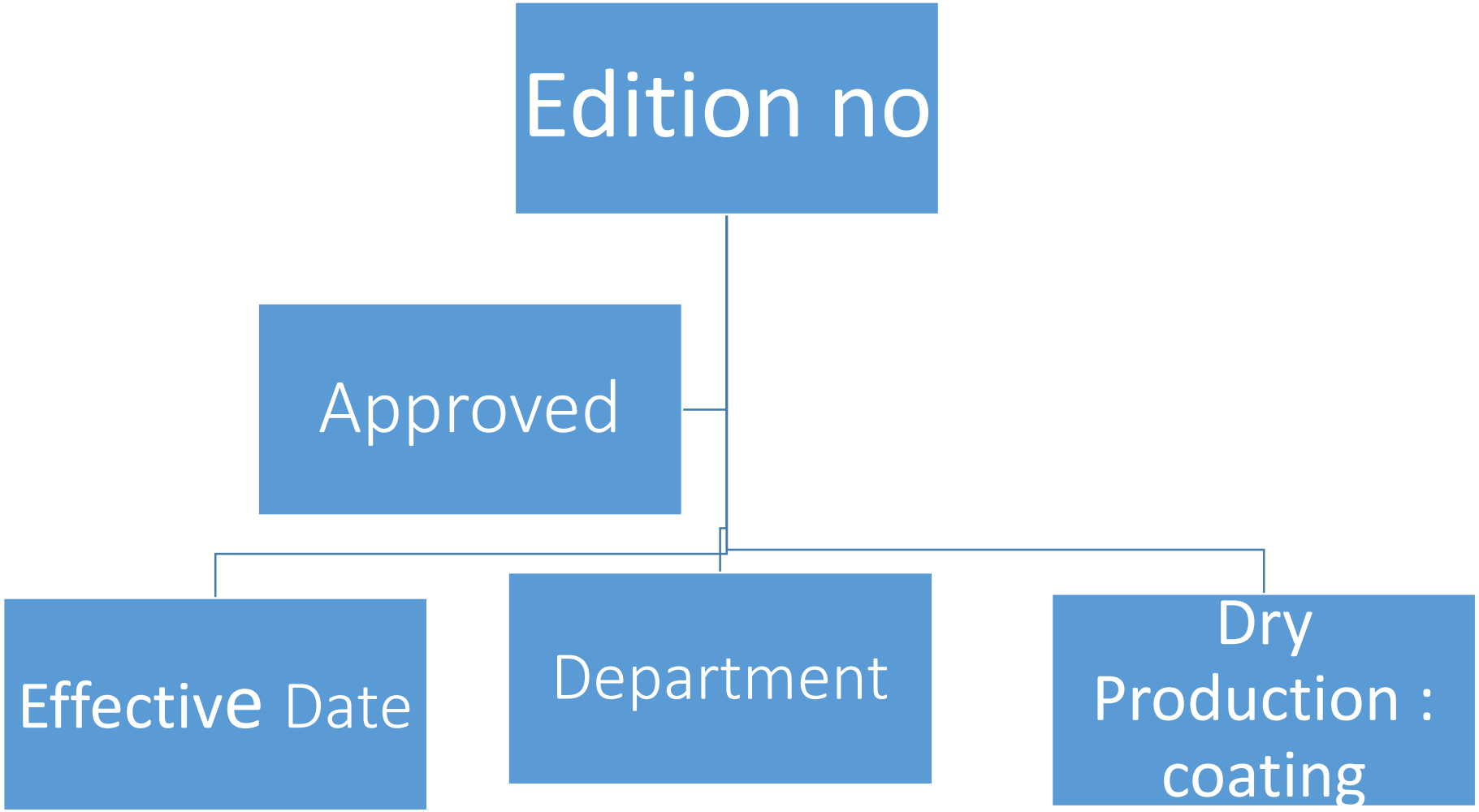
- The pallets and drums brought into the area clean and free from powder or dust.
- Is the equipment neat clean and rust free.
- Are there specific procedures for the cleaning of tableting machines.

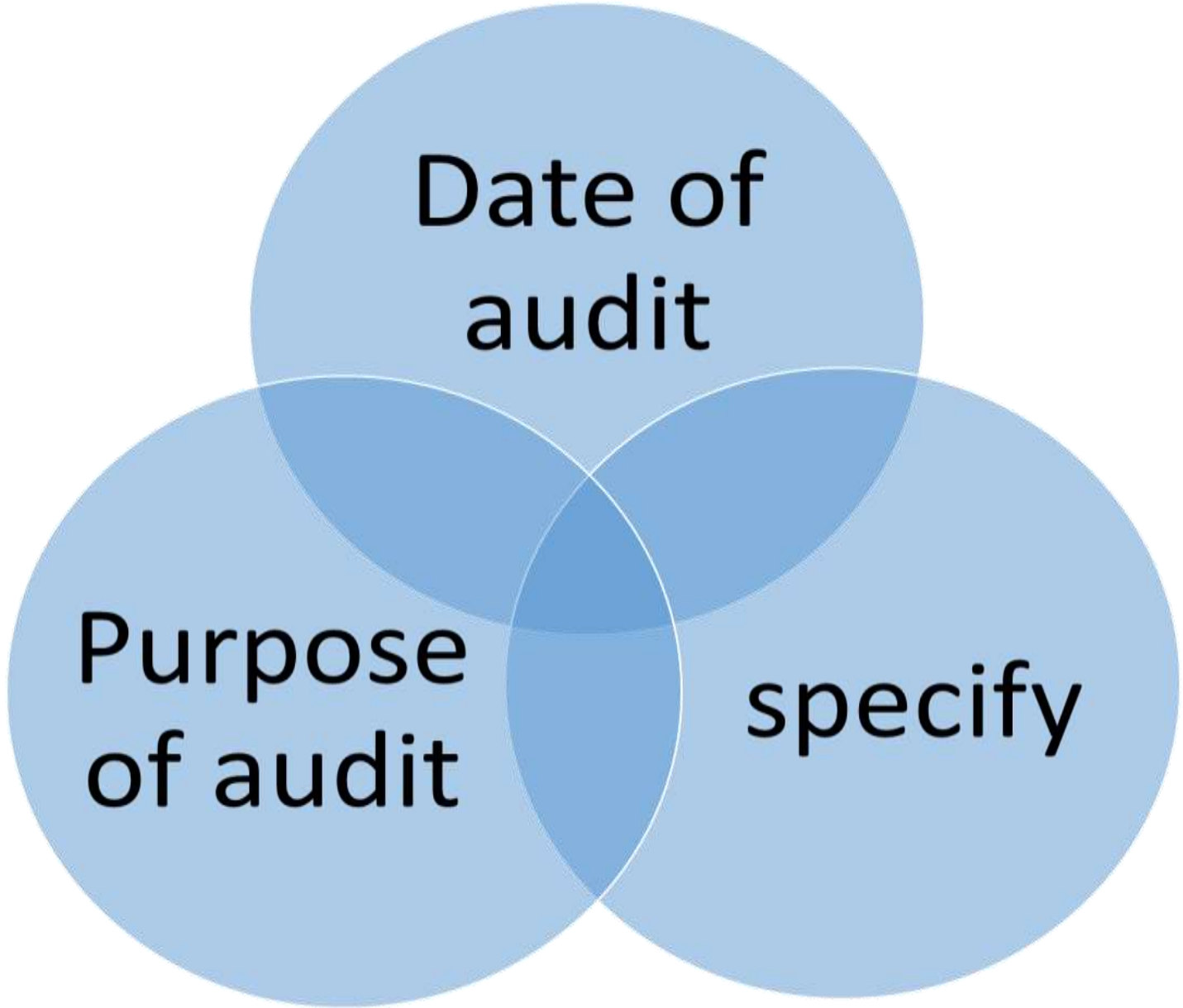
# In-process control

- Is there an approved SOP for in-process control.
- Do all test result conform to specification.
- Are there printouts available for all in-process test result labeled .

    1. Product name
    2. batch number
    3. Date and time of testing
    4. Signature of the tester

# Coating


Edition no
Approved
Effective Date
Department
Dry Production : coating


Date of audit
Purpose of audit
specify

A . Documents Reviewed:

1. SOP
2. Personnel

B . Data Reviewed:

1.Facilities
2.prevention of cross –contamination
3.Equipment and facility cleaning
4.In-process control

# SOP

- Is a complete index and a complete set of application sop available in the department.
- Are the index and the SOP current.
- Is the set of SOP correctly organized according to the index

# Personnel

- Select three employees working in the department. Are their training records up-to-date.

- Have the employees undergone training in the following area during the last year.

1. GMP
2. SOP
3. Coating techniques

# Facilities

- Is the department maintained in a good state of repair.
- Is the department neat and orderly with sufficient space for equipment and operation.
- Are all work areas clearly labeled with the name and the batch number of the product being processed.

# Prevention of cross-contamination

- The doors closed at all time.
- Is personnel clothing clean , unstained and dust free including shoes.
- Is there a shoe-cleaning device in the department.
- Is there a record of the pressure.

# Equipment and facility cleaning

- The pallets and drums brought into the area clean and free from powder or dust.
- Is the equipment neat clean and rust free.
- Are there specific procedures for the cleaning of coating machines.

# In-process control

- Is there an approved SOP for in-process control.
- Do all test result conform to specification.
- Are there printouts available for all in-process test result labeled .
    1. Product name
    2. batch number
    3. Date and time of testing
    4. Signature of the tester

# Capsules

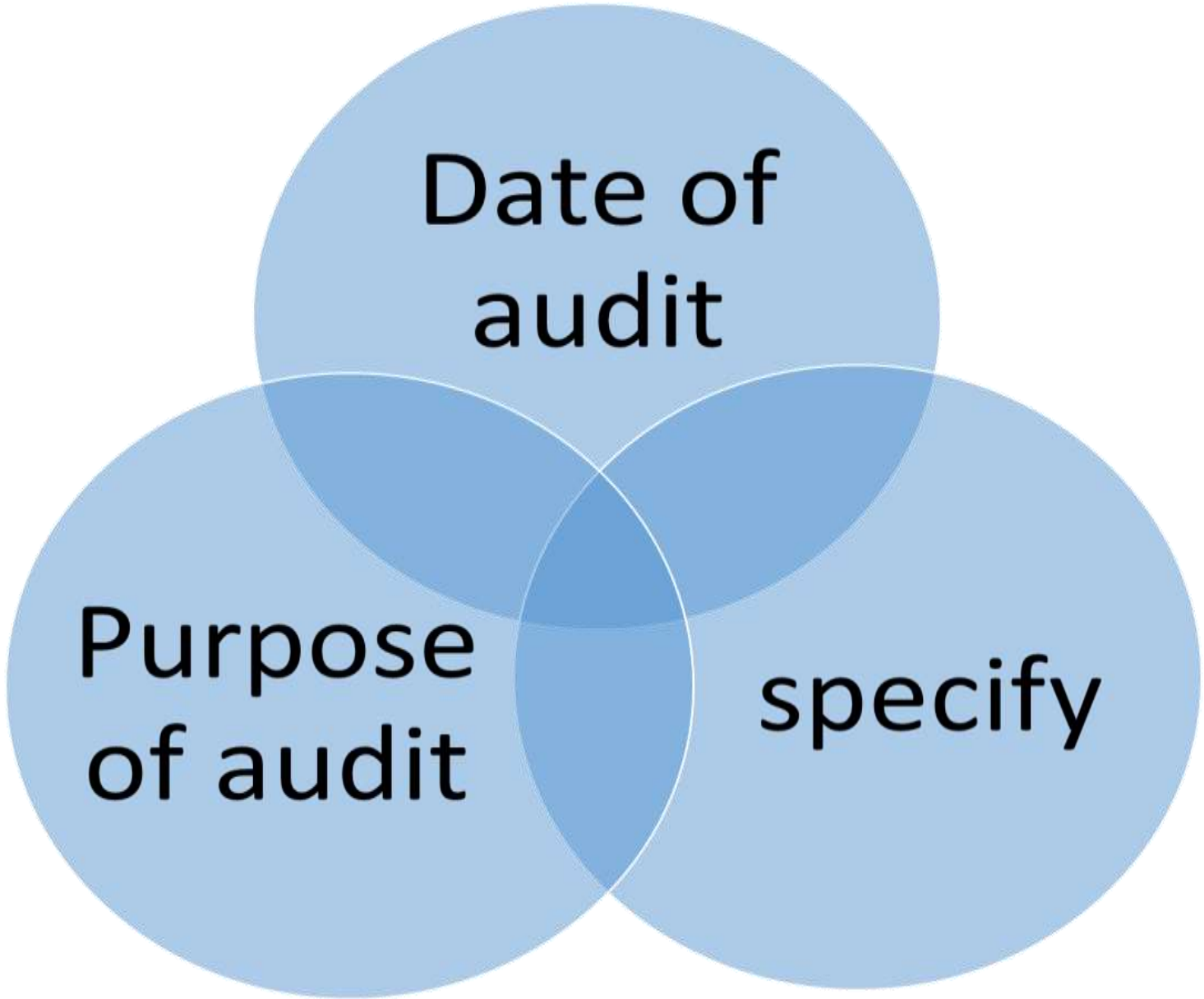
Edition no

Approved

Effective Date

Department

Dry production : capsules


Date of audit
Purpose of audit
specify

A . Documents Reviewed:

1. SOP
2. Personnel

B . Data Reviewed:

1.Facilities
2.prevention of cross –contamination
3.Equipment and facility cleaning
4.In-process control

# SOP

- Is a complete index and a complete set of application sop available in the department.
- Are the index and the SOP current.
- Is the set of SOP correctly organized according to the index.

# Personnel

- Select three employees working in the department. Are their training records up-to-date.

- Have the employees undergone training in the following area during the last year.

    1. GMP
    2. SOP

# Facilities

- Is the department maintained in a good state of repair.
- Is the department neat and orderly with sufficient space for equipment and operation.
- Are all work areas clearly labeled with the name and the batch number of the product being processed.

# Prevention cross-contamination

- The doors closed at all time.
- Is personnel clothing clean , unstained and dust free including shoes.
- Is there a shoe-cleaning device in the department.
- Is there a record of the pressure.

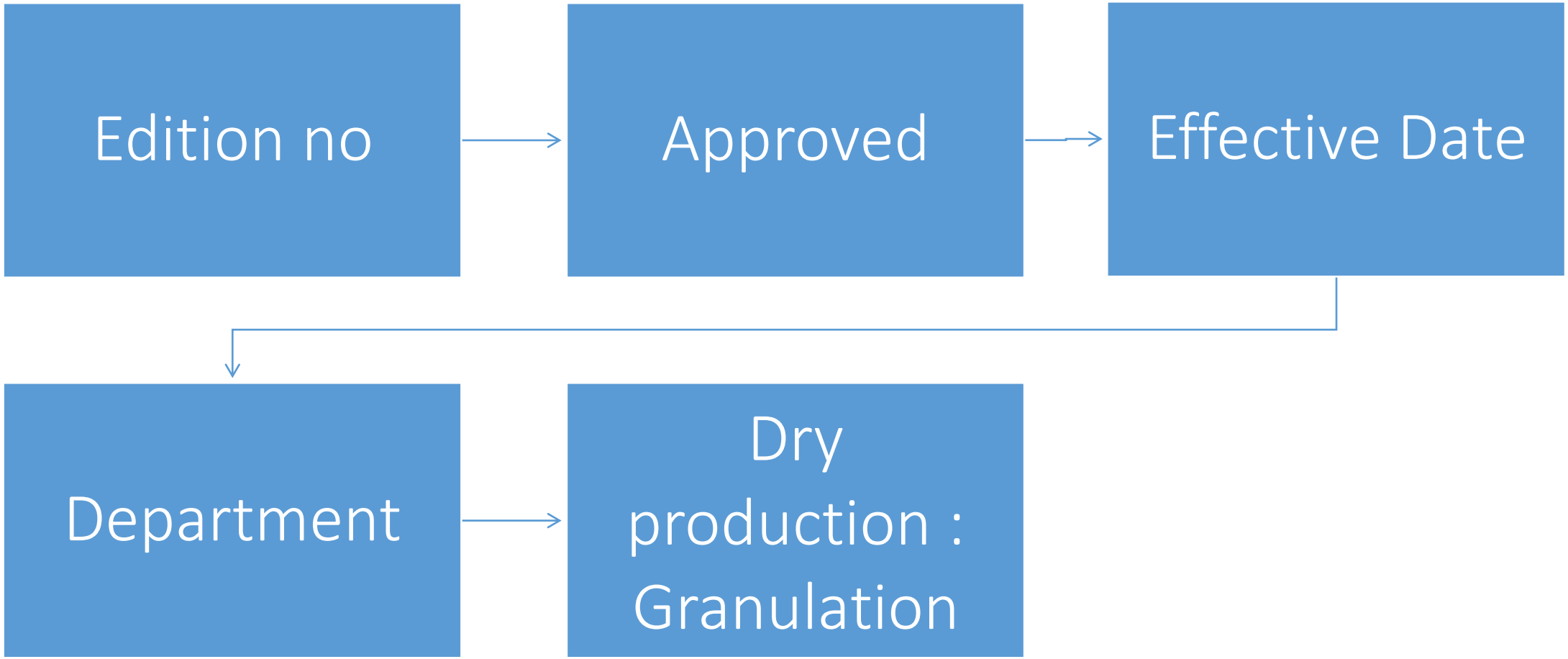
# Equipment and facility cleaning

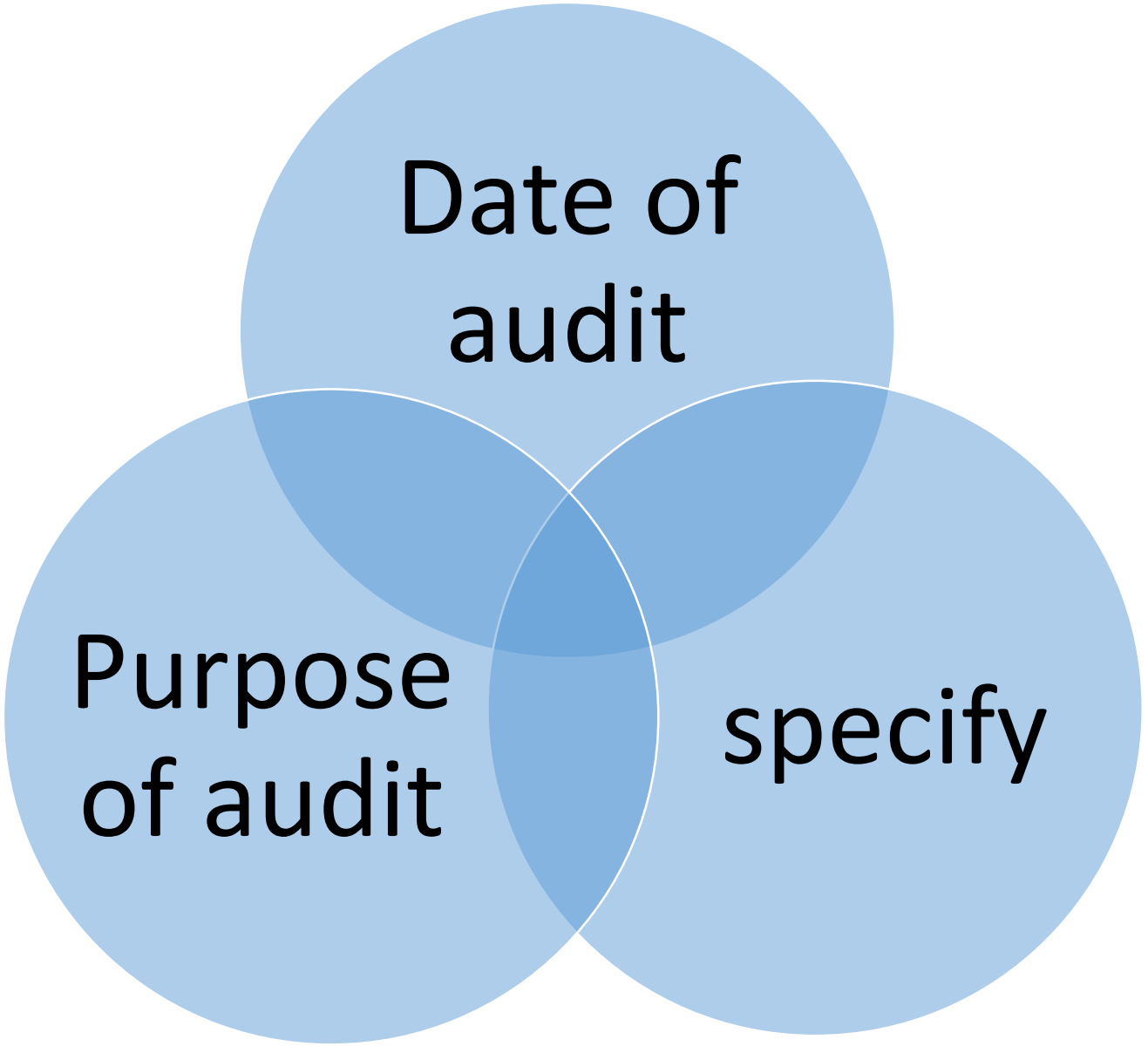
- The pallets and drums brought into the area clean and free from powder or dust.
- Is the equipment neat clean and rust free.
- Are there specific procedures for the cleaning of tableting machines.

# In-process control

- Is there an approved SOP for in-process control.
- Do all test result conform to specification.
- Are there printouts available for all in-process test result labeled .
    1. Product name
    2. batch number
    3. Date and time of testing
    4. Signature of the tester

# Granulation




Date of audit
Purpose of audit
specify

A . Documents Reviewed:

1. SOP
2. Personnel

B . Data Reviewed:

1.Facilities
2.prevention of cross –contamination
3.Equipment and facility cleaning
4.Lubricants

# SOP

- Is a complete index and a complete set of application sop available in the department.
- Are the index and the SOP current.
- Is the set of SOP correctly organized according to the index.

# Personnel

- Select three employees working in the department. Are their training records up-to-date.

- Have the employees undergone training in the following area during the last year.

    1. GMP
    2. SOP
    3. Granulation techniques

# Facilities

- Is the department maintained in a good state of repair.
- Is the department neat and orderly with sufficient space for equipment and operation.
- Are all work areas clearly labeled with the name and the batch number of the product being processed.

# Prevention of cross-contamination

- The doors closed at all time.
- Is personnel clothing clean , unstained and dust free including shoes.
- Is there a shoe-cleaning device in the department.
- Is there a record of the pressure.

# Equipment and facility cleaning

- The pallets and drums brought into the area clean and free from powder or dust.
- Is the equipment neat clean and rust free.
- Are there specific procedures for the cleaning of major equipment.

# Lubricants

- Is there a written procedure for the receipt and approval of such lubricants.
- Is a record made of the catalog number of the lubricant used when maintenance is performed.
- The lubricants available in the department. They clearly labeled and stored in a sanitary manner.

# Sterile Production

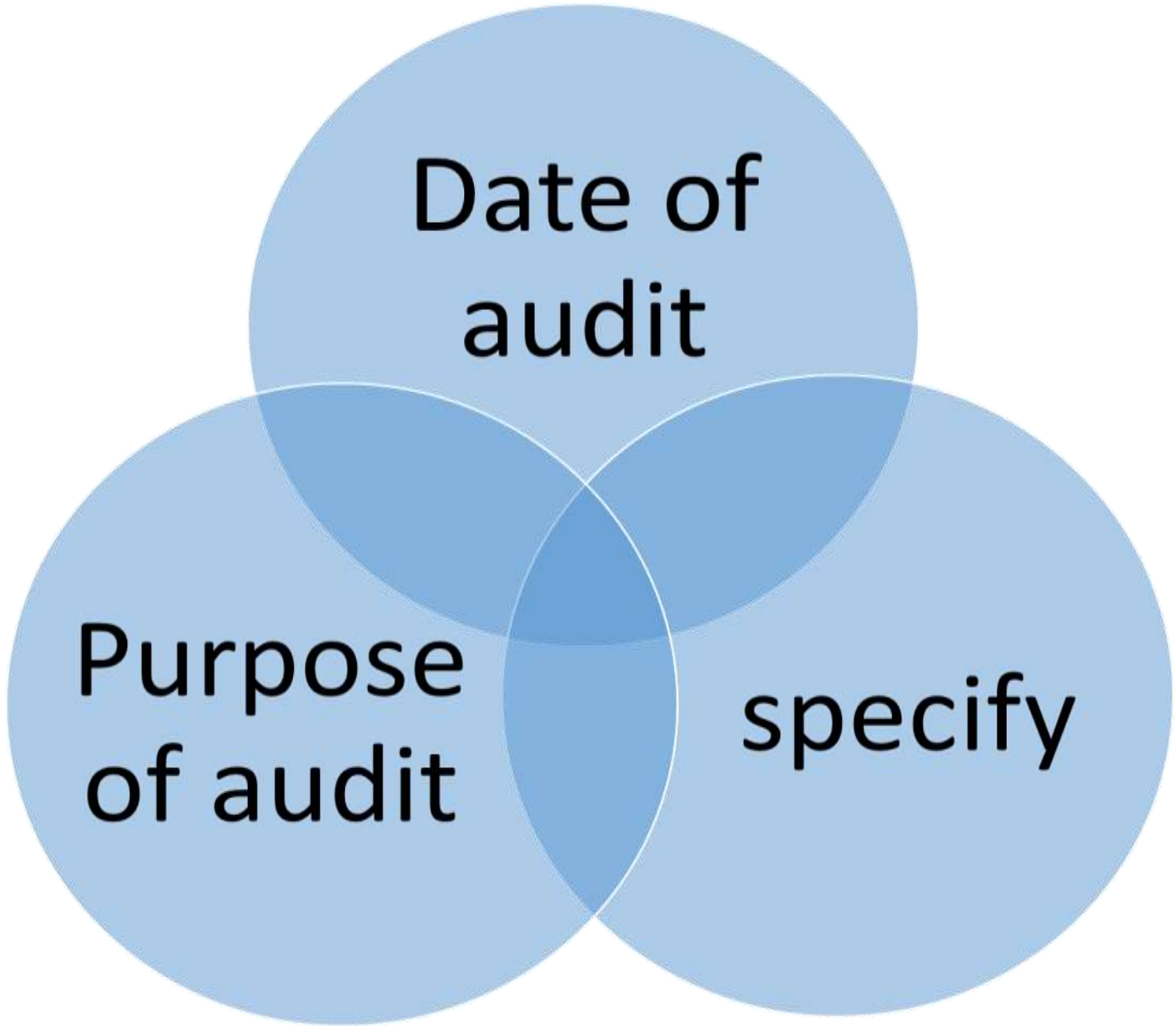
Edition no

Approved

Effective Date

Department

Dry production: sterile production


Date of audit
Purpose of audit
specify

A . Documents Reviewed:

1. SOP
2. Personnel

B . Data Reviewed:

1. Facilities
2. Batch records
3. Monitoring

# SOP

- Is a complete index and a complete set of application sop available in the department.
- Are the index and the SOP current.
- Is the set of SOP correctly organized according to the index.

# Personnel

- Select three employees working in the department. Are their training records up-to-date.

- Have the employees undergone training in the following area during the last year.

    1. GMP
    2. SOP
    3. sterile manufacturing techniques

# Facilities

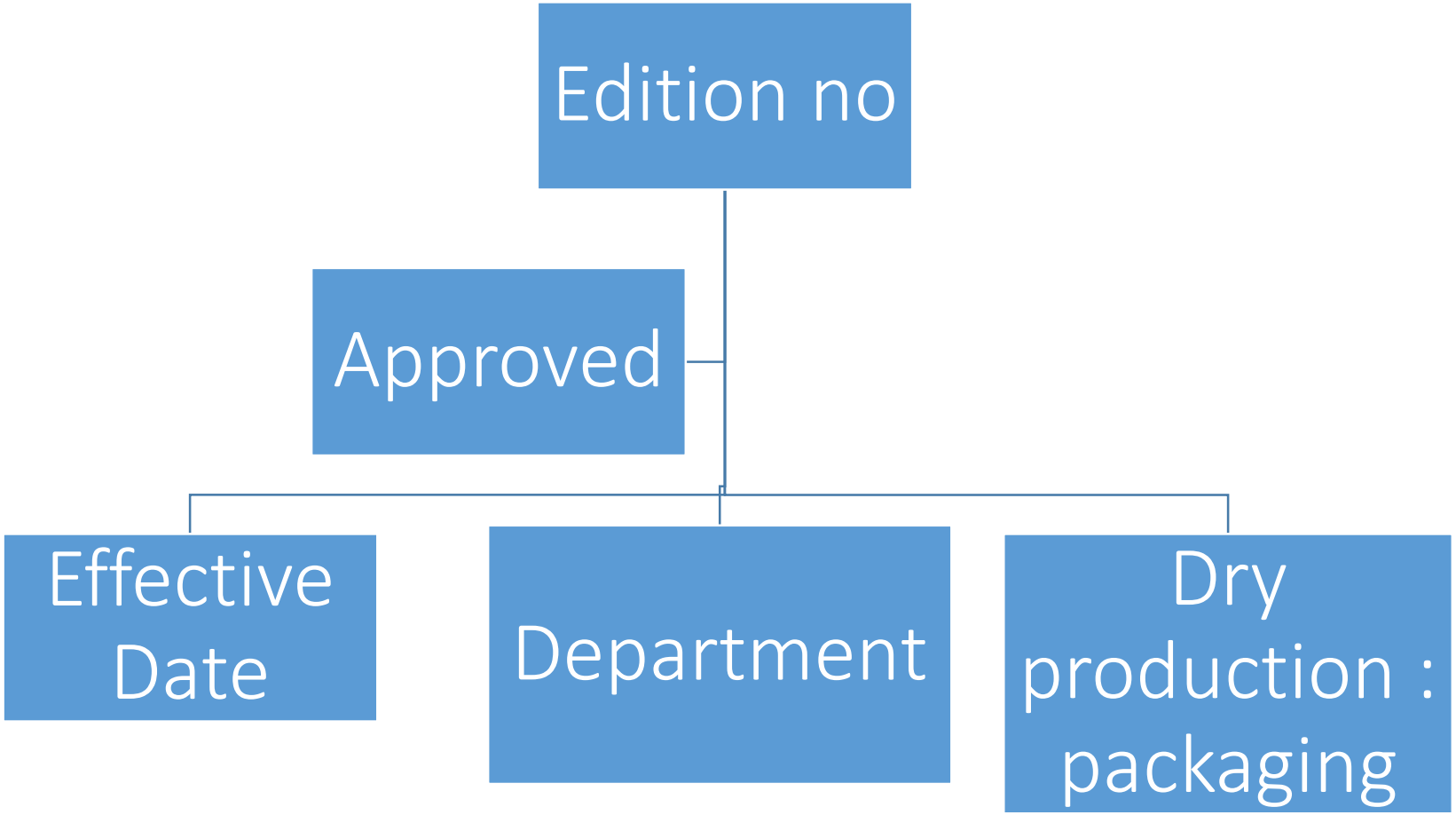
- Is the department maintained in a good state of repair.
- Is the department neat and orderly with sufficient space for equipment and operation.
- Are the cleaning and sanitizing solution labeled with an expiration date according to the relevant SOP.

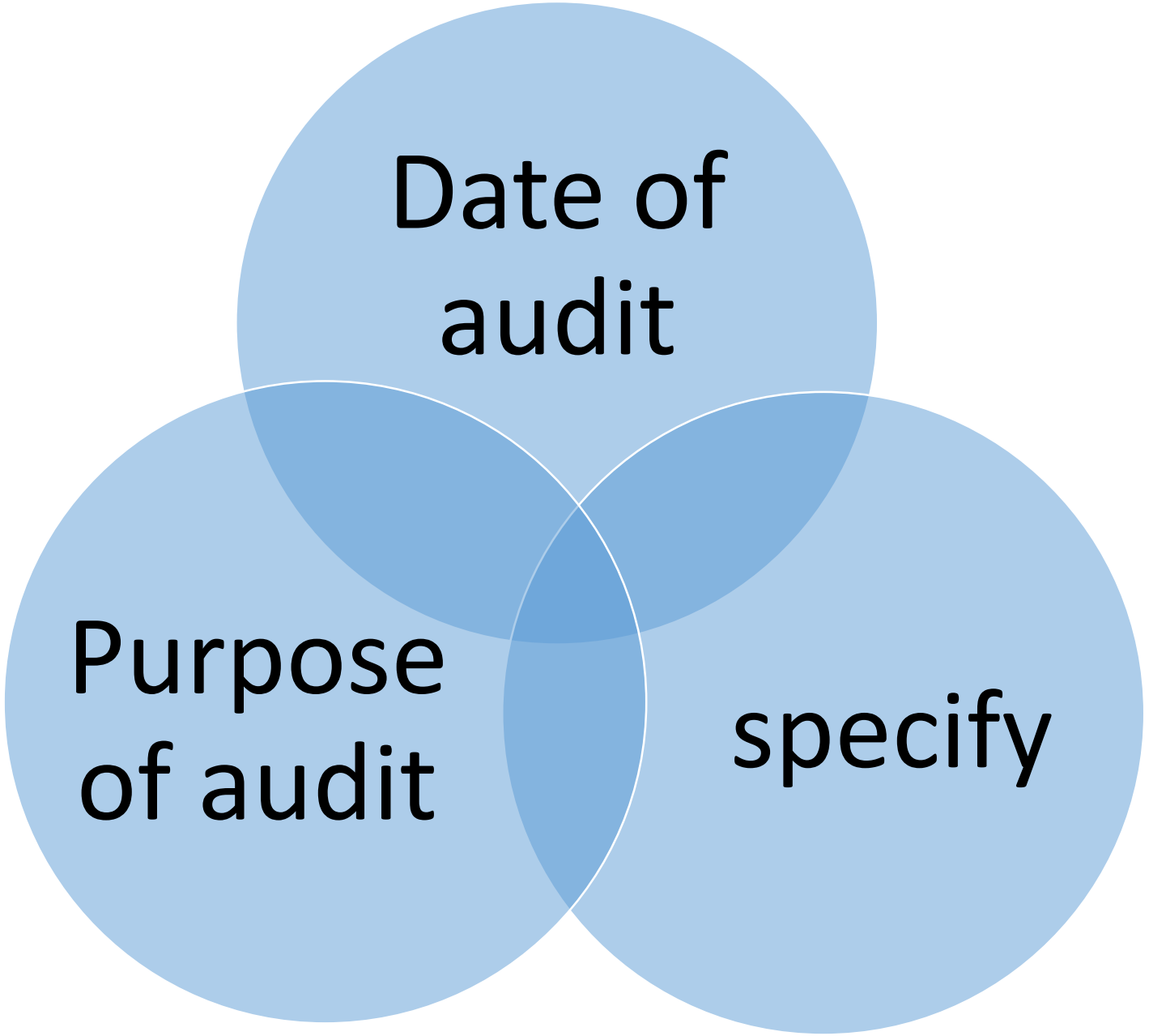
# Monitoring

- Is there a valid calibration label affixed to monitoring sensors for pressure , temperature , and relative humidity.

- Are records according to the relevant SOP.

# Packaging


Edition no
Approved
Effective Date
Department
Dry production : packaging


Date of audit
Purpose of audit
specify

A . Documents Reviewed:

1. SOP
2. Personnel

B . Data Reviewed:

1.Facilities

2.cleaning procedures

3.In-process control

# SOP

- Is a complete index and a complete set of application sop available in the department.
- Are the index and the SOP current.
- Is the set of SOP correctly organized according to the index.

# Personnel

- Select three employees working in the department. Are their training records up-to-date.

- Have the employees undergone training in the following area during the last year.

    1. GMP
    2. SOP
    3. Packaging techniques

# Facilities

- Is the department maintained in a good state of repair.
- Is the department neat and orderly with sufficient space for equipment and operation.
- Are all work areas clearly labeled with the name and the batch number of the product being processed.

# Cleaning procedures

- Is there a written procedure for the cleaning of the packaging facility.
- Is there  documented evidence that the cleaning procedure is being followed.
- The procedure specific to a particular machine.

# Reference


1.Kumar S, Tanwar D, Arora N. The role of regulatory GMP audit in pharmaceutical companies. Int J Res Dev Pharm Life Sci 2013;2:493-8.

2. Kaur J. Quality audit: Introduction, types and procedure [Internet]. Place Unknown: Pharma Pathway; 2017. from: http://pharmapathway.com/quality-audit-introduction-types-and-procedure/.

3. Biswas P. ISO 9001. Internal audit [Internet]. Place Unknown: Word Press; 2015. Available from: http://isoconsultantpune.com/iso-90012015-internal-audit-by-pretesh-biswas-apb-consultant/.

4. Bernacchi T. The pharmacy audit: what is it and are you prepared? J Managed Care Pharm 1999;5:94-8.

5.Vedanabhlata S, Gupta VN. A review on audits and compliance management. Asian J Pharm Clin Res 2013;6:43-5.

# UNIT-4
# AUDITING OF MICROBIOLOGICAL LABORATORY

# Definition:

- Quality audit is defined as a systematic and independent examination to determine whether activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable to achieve objectives.

# Scope and Objectives:

- To ensure quality of the Product
- To assess effectiveness of QA system
- It permits timely correction of problems
- It established high degree of confidence

❖Auditee :

An organization, facility or person being audit.

Auditee’s Responsibility

✓Inform relevant employees about the objectives and scope of the audit

✓Appoint responsible members of staff to meet with members of the audit team

✓Provide all resources needed for the audit team in order to ensure an effective and efficient audit process

✓Determine and initiate corrective actions based on the audit report

# What is the process for audit?

- A process audit is an examination of results to determine whether the activities, resources and behavior that cause them are being managed efficiently and effectively.
- A process audit is not simply following a trail through a department from input to output - this is a transaction audit.

# How to Audit a Manufacturing Process

- An audit of a manufacturing process is a comprehensive examination of the process to verify that it is performing as intended.
- Processes generate results, and process audits determine if the results are accurate and being generated by an effectively managed process...

- Manufacturing process audits should ensure that procedures are properly followed, problems are quickly corrected, there is consistency in the process, and there is continuous improvement and corrective action as needed.

# There are many reasons for conducting a manufacturing audit:

- ❖Assures procedures reflect actual practice (what we say is what we do);
- ❖Uncovers inaccuracies so they can be quickly corrected;
- ❖Reveals the consistency of a process (from person to person, or day to day);
- ❖Demonstrates a proactive approach to process improvement; and
- ❖Encourages ongoing corrective action

# A good manufacturing audit requires:

- Announcement in advance. Manufacturing audits are not meant to catch people doing something wrong. On the contrary, during an audit you hope to catch people doing things right.
- A rating scheme to classify problems discovered. A rating scheme allows you to rank problems in order to prioritize corrective actions.
- Trained auditors. Auditors should be familiar with both the area they are observing and with auditing techniques.
- Planning and clear procedures. A manufacturing audit is more than just walking into a work area and looking for trouble

# The steps listed below can help in planning and conducting an audit.

- **Select a process to be audited**. Prioritize the processes that can be audited in terms of importance and risk to the overall operation. Begin auditing the highest-risk areas first.

- **Select a team to conduct the audit**. The audit team should be familiar with the process being audited. They should also be familiar with audit techniques such as sampling and analyzing results. They must have the necessary expertise to identify problems and determine the corrective actions needed.

- **Decide how often the process should be observed** (the frequency of the audit). If there are significant problems or noncompliance, the process should be observed more often until the situation is under control.
- **Announce the audit in advance so there are no surprises**. The objective is to improve the process, which will require the cooperation of everyone involved

- **Set up an audit schedule for the entire shift and follow the established audit schedule**. The number of observations will be your sample of the work for that shift. The audit schedule should be determined in advance and should be as random as possible. Once established, the audit schedule should be followed to provide results based on a random sample.

- **Document any problems discovered and inform all those affected**. The idea is not to assign blame but to find a solution. The problems discovered become the basis for corrective actions and follow-up. Everyone affected by the problem should be informed so they are aware and can provide input to the resolution. Also, the process being audited will likely affect other processes in the over-all operation.

- **Determine and perform corrective actions**. Let employees make suggestions for corrective actions and select any that are appropriate, but management should make the final decision as to which corrective actions to implement.

- **Monitor corrective-action results**. Perform follow-up monitoring to determine if the corrective actions have actually eliminated the problem or if further action is required. Also verify that no new problems have developed or entered into the process.

# Product and Process Information

# Contents

- ❑Process audit
- ❑Product audit
- ❑Quality goals
- ❑Process audit vs Product Audit
- ❑Reference

# What is Process Audit

- A process audit is an examination of results to determine whether the activities, resources and behavior that cause them are being managed efficiently and effectively.

- A process audit is not simply following a trail through a department from input to output - this is a transaction audit.

- In contrast with rear-facing product inspections, process audits focus on how your team prepares, produces, packages and distributes those products.
- This approach provides a more comprehensive view of the value stream than product audits, which only sample the finished output.

Process audits look at details of manufacturing process such as:

- ❑Fabrication steps
- ❑Safety measures
- ❑Temperature settings
- ❑Pressure readings
- ❑Calibration of gauges

# What is Product Audit

- The product audit is the assessment of the final product/service and its qualification for use evaluated versus the intent of the purpose of the product/service.
- It ensures a thorough inspection of a final product before delivery to a supplier or a customer.

# PRODUCT AUDIT…

- Product audits take place after manufacturing is complete, but before the product reaches the customer.
- If a product doesn’t meet standard requirements or specifications, the auditor documents the findings and logs a non-conformance.

While each company will have its own procedures for addressing non-conformances, the process typically includes:

- ❑ Identifying the problem
- ❑ Containing the non-conformance
- ❑ Reworking or repairing the products, if possible
- ❑ Disposing of nonconforming products if you can’t rework or repair them
- ❑ Determining the necessary countermeasures for preventing recurrence

# PRODUCT AUDIT…

- Product audits can help a manufacturer improve quality, profits, customer satisfaction, and loyalty.

# Product and Process Audits Go Hand-in-Hand

- An effective manufacturing process audit program that ensures the highest level of quality requires both product and process audits. Though nearly all manufacturers conduct product audits, fewer of them have defined process audit procedures in place

# Process audits are critical to quality goals that include:

- **Standardizing processes** to ensure compliance with specific requirements such as time, components, accuracy or temperature

- **Continuously reducing risk** through systematic identification and correction of process errors

- **Monitoring key metrics** for evaluating overall process performance
- **Assessing effectiveness of process controls** such as procedures, instructions and specifications
- **Reviewing production resources**, work standards and the manufacturing environment itself

# What is the difference between Process audit & Product audit

## Process Audit

- Auditor will concentrate on process at each stage & its relevant parameters process parameters like temperature, pressure, speed etc

## Product Audit

- Auditor will concentrate only on output of the process & its relevant parameters.

CONTENT

1.General areas interest in the building:

i. Walls and celling's

ii. Floors and drains

iii. Doors ,windows and fittings

iv. equipment

v. pipelines

2.RAW MATERIALS

3.WATER

i. Microbiological results

ii. Essential document

iii. PQ is divided into 3 phases

iv. Microbiological procedure reviewed

4.PACKAGING MATERIALS

5.EFFECTIVE VENTILATION

# GENERAL AREAS OF INTREST IN THE BUILDING RAW MATERIALS

## GENERAL AREAS INTREST IN THE BUILDING

## 1.WALLS AND CELLINGS:

- moulds are most commonly encountered microbes on walls celling's , particularly when poor ventilation, temperature, and relative humidity control lead to high level of moisture.
- contamination may be excessive where damaged surfaces expose the underlying plaster.
- surfaces should be smooth ,impervious and cleanable; damaged surfaces should be repaired promptly.

# 2.FLOORS AND DRAINS:

- Flours should be impervious to water, cleanable and resilient to day to day wear and tear.
- flours should be laid flat to minimize the risk of excessive surface water(e.g. washing bays) or ,ideally should slope towards drain.
- The auditor should pay particular attention to joints, seals and floor to wall coving to ensure that surfaces should be repaired promptly.
  Where floor drainage channels are needed , they should be open shallow easy to clean drain effectively.
- The auditor must be aware that any ‘static’ water can act as reservoirs for gram negative organisms , particularly pseudomonas species.

# 3.DOORS ,WINDOWS AND FITTINGS

- These should be flush-fitting whenever possible. Wood readily absorbs moisture and can generate high number of moulds; where present, it should be sealed with a high –glass paint and any surface damage repaired immediately.

# 4.EQUIPMENT

- The ability of bacteria to attach to surfaces such as stainless steel and plastic and survive should not be under estimate.
- Every piece of equipment has its own particular nooks and crannies where microbiological contamination can reside; internal threads and dead legs cause particular problem.

# 5.CLEANING OF EQUIPMENT

- Cleaned equipment can be readily recontaminated before use .
- The auditor should review :the quality water used in final rinsing stage
- and how equipment is dried and stored to minimize the risk of contamination by pseudomonas and other gram –negative bacteria .

# 6.PIPELINES

- Pipeline must be completely drainable to ensure that trapped fluid does not provide a hospitable environment for growth of bacteria.
- Internal surfaces should be smooth and polished to min imize pits where microbes may lodge.
- Joints and welds should be kept a minimum, since they may provide a protective haven for a microorganism. Its sealed with lagging material.
- If the protective outer seal is damaged and may provide a rich source of mould contamination.

# RAW MATERIALS

- Raw materials pose a major contamination threat to the product and the production environment, and warrant special attention from auditor.
- Untreated raw material of natural origin contain an extensive and varied microbial population ,including potentially pathogenic organisms, such as E.coli and salmonella species .
- In case of excessively high bioburden , pre-treatment may be needed to reduce the bioburden to an acceptable level , using process such as heat filtration, irradiation ,recrystallization from a biocidal solvent or ,where compatible ,ethylene oxide gas.
- Irrespective of the type raw material used, the auditor should confirm that the material is provided by an ‘approved ‘supplier…

- Confidence in the supplier ‘s manufacturing process and their quality system, which have been challenged through audit. likewise the sampling programme used should be satisfactory ,based upon the nature of the raw material(natural /synthetic),the history and performance of the supplier ,and end use of raw material.
- Sampling procedure should be reviewed.
- Reduce the risk of contamination both sample and bulk.
- Sampling equipment should be dedicated and clean. Samples should be properly trained in aseptic techniques.
- Warehouse storage condition should also be reviewed: temperature control should be satisfactory ;pest control should be effective; and containers should be positioned so that they do not come into contact with damp ,cold surfaces such as walls and floors.

# Water

- Water is principle of raw material used in pharmaceutical industry. When reviewing water systems usually as part of a ‘product based audit', the auditor must establish quickly an understanding of the system and how it performs.
- Key facts to know include whether water is used directly manufacture ,and what's grades of water used .
- Management and operational issues include who owns the system, its complexity(one or multiple plants).
- A schematic of the system should be provided.

# MICROBIOLOGICAL RESULTS

- In establishing whether an adequate system of control operates ,data from samples taken from user points over the past 6 to 12 months should be reviewed noting user points sampled , the range of results and underlying trend ,whether action and alert limits are visible and appropriate, and whether trend analysis has been applied to improve interpretation and reporting of results .
- The time of monitoring should also be noted with reference to when the system was sanitized.
- Even in the event of zero counts, the microbiological sampling practices and test procedures should be challenged .

# ESSENTIAL DOCUMENTS

- Validation documents relating to design qualification ,installation qualification ,operational qualification and performance qualification (DQ,IQ,OQ AND PQ) should be complete , available and current fir the water system concerned.
- Only  when this has been thoroughly reviewed and approved may any microbiological considerations be addressed.
- protocol should be prepared and approved.
- final reports should have been completed, reviewed and approved highlighting areas of non compliance together with justifications and recommendations for corrective action.

performance qualification should have been spread over an extended period divided into three phases.

Phase 1 ; all parameters should have been reviewed and approved at all sample and user points during every day of a 20 to 30 day period .

Phase 2 ; all user points and worst case locations should have been examined using a reduced sampling scheme over a 2 to 3 month period …..

Phase3:The final phase should have investigated similar sample points on a rotational basis for a period of 6-12 months.

microbiological procedure to be reviewed include following:

1.media preparation and fertility testing

2.methods used

- filtration ,plate counted,etc..

3.incubation conditions (temperature/time)

# PACKAGING MATERIALS

- Cardboard ,paperboard and pulpboard, unless sealed or treated , can provide a rich source of contamination, particularly moulds and gram positive bacteria , often as resistant spores .
- Materials become moist through poor storage ,levels of microbiological contamination can increase significantly .
- Material such as glass, synthetic rubbers, plastics and laminates have minimal surface microbial counts.
- However ,if stored with limited protection in dusty or damp conditions and packed for transportation in cardboard boxes ,often on damp ,dirty wooden pallets, they may contain moulds and bacterial spores...

# EFFECTIVE VENTILATION

- The aerial route of contamination is common and can be significantly reduced by an effective heating ventilation and air conditioning system.
- Humidity and Temperature control is important , since this not only provides a pleasant working environment ,but also reduces the risk of mould contamination.

## CLEANING AND DISINFECTION

- Although routine sanitization of surfaces is key to controlling environmental contamination ,its importance is often over looked . The sanitization programme and procedure should be reviewed to confirm the frequency and precise method of cleaning and their scientific basis ….

- The cleaning records should confirm procedural compliance (when , where , and by whom).
- The activity of any disinfectant used should be appropriate for the wide range of environmental contaminants likely to be present .
- The manufacturers instructions should be followed and fresh disinfectant solutions should be made up before use.
- Mops, sponges and cloths can provide an ideal environment for rapid and extensive growth of water –bone organisms such as pseudomonas species.
- Inadequately stored and maintained cleaning equipment can be highly efficient vehicles for spreading micro-organisms throughout the environment.

# Reference


- Quality assurance of pharmaceuticals, volume -2; second updated edition, world health organization, chapter:17, page no.:54.
- QA Manual,D.H.Shah; chapter:12, page no.:184-190
- Ruud Lighting, Inc , 2003; wisqa.org
- www.elsar.com accessed on Nov.2011
- Guidelines for quality and/or environmental management system auditing, 1st Edition, 2002
- www.cityu.edu.hk, Internal Quality Audit Scheme.
- Handbook of microbiological quality control, edited by Rosamand M.Barid Norman A .Hodges and Stephen P.Denyer.

# UNIT-5
# QUALITY ASSURANCE MAINTENANCE, CRITICAL SYSTEMS

# Critical systems

1. overview qualification
2. HVAC Qualification
3. Water System qualification

# General principles and Practices

- Guidance to industry issued by the **FDA** in January 24 ,2011 .
- Inline with the principles advanced in **ICH Q8 , ICH Q9 , ICH Q10** and in **ASTM E2500** .

**FDA Guidance :**

General principles and practices

- Replaces the guidance issued in 1987
- Quality of the product cannot be assured by simply inspecting or testing in process and finished products . It must be built into the product –process a-prior
- Focusing exclusively on the qualification effort without understanding the process and ensuring the process is maintained in a state of quality.


# FDA Guidance To Industry January 2011

Three stages of process validation

- Process design stage ( process is defined based on development and scale up)
- Process qualification stage ( design is confirmed as being capable of reproducible production)
- Continued verification and improvement (continuously gaining assurance the process remains in a state of control )

# The Design Stage

- Understanding the science
- Understanding the risk
- Building quality into the process
- Establishing control strategy
- Proper design of the facility and utility serving the process

# Implementation and process qualification

- Qualification of utilities and equipment

("....design of the facility and qualification of the equipment and the utilities)

- performance qualification and PQ protocol

(..PQ combines the actual facility , utilities , equipment , and the trained personnel with the commercial manufacturing process , control procedures , and components to produce commercial batches .)

Protocol execution and report

# Continued process verification

- Monitoring appropriate parameters to ensure process in a state of control , including the performance of the utilities (e.g Environmental monitoring for HAVC and water system verification )
- Use CAPA , PAT and change control as well as data collected in monitoring to continually improve the process .
- Proper maintenance of the facility , utilities , and process equipment

# Science and Risk Based compliance : An Overview

# Risk to What ?

- In GMP Compliance
  - -Risk to product quality
  - -Risk to the patients well being
- In Manufacturing
  - - Risk to personnel
  - -Risk to the environment
- In Business
  - -Financial  risk to the company

# Focus for this workshop

- Risk is always present
- You need to know what it is and how it manifests itself a priori
- We will focus on risk to product quality during manufacturing and the patients wellbeing
- Thus we will focus on GMP issues

# FDA Initiative August 2002

Pharmaceutical CGMP for the 21st century : A Risk –based approach

A science and risk –based approach to product quality regulation incorporating an integrated quality system approach

# FDA Guidance August 2002

- Early adoption of new technology .
- Adoption of modern quality management techniques and implementation of the quality system approach .
- Focus on understanding the science & technology associated with what you are making .
- Priority to mitigating the highest risk elements of the manufacturing operation.

# FDA Guidance August 2002

- Take home :

- You must understand what you are doing .

-You must focus on critical areas (highest risk to product ) of your operation

- You should utilize automation and data collection to reduce risk associated with the operation and allow for continuous improvement .

-You must build the quality into your operation.

# ICH Q8 –Pharmaceutical Development

- Deals with product development and its manufacturing process .
- Defines the need for good Design Of Experiments(DOE).
- Use data from product development studies to manage the risk associated with the product (Quality cannot be tested in the product but rather built into it ).
- Managing quality through out the product life cycle from initial development through discontinuation .
- Defines continuous process verification as an alternative to process validation .
- Defines the knowledge space , the design space and the normal or control space.

# ICH Q8 –Pharmaceutical Development

- Benefits :

  -Manufacturing knowledge

  -Manufacturing improvement within DS are not changes

  - Operational robustness

  - Reduce Post –approval submissions

  -Real time release and reduced product testing

  -Continuous process / product improvement

# ICH Q8 (R1)-Pharmaceutical Devoplopment

- Introduces the concept of quality by design (QbD)
- Emphasize use of design of experiments and prior knowledge to define the design space.
- Identifies critical quality attributes (CQA) of the product and critical processing parameters (CPP) That would affect it .
- Defining a control strategy based on

  CQA =(CPP)

# ICH Q8 (R1)

Quality by Design (QbD):

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control , based on sound science and quality risk management .

# ICH Q8 (R1)

Critical quality Attribute (CQA):

It is a physical , chemical , biological or microbiological property or characteristic that should be within appropriate limit, range , or distribution to ensure the desired product quality . CQAs are generally associated with the drug substance , excipient , intermediates , and drug products .

# ICH Q8 (R1)

Critical Processing parameter (CPP):

A process parameter whose variability has an impact on a critical quality attribute (CQA) and there fore should be monitored , “alarmed “ , and controlled to ensure the process produces the desired quality.

# ICH Q9

- Outlines quality risk management principles for product lifecycle .
- Phases of QRM include risk assessment , risk control , and risk review .
- Defines risk and how to measure it.
- Outlines the principle of focusing on the critical aspects of the drug manufacturing based on the level of risk .
- Use of change management to reduce risk.

# What is Risk ?

The combination of the probability of occurrence of harm and the severity of that harm *.

## Risk is always present :

- Risk to the patient / public (Drug side Effects , Adulterated Drugs)
- Risk to the product (Contamination )
- Risk to the personnel
- Risk to the neighbors and environment
- Risk to the company (regulatory recalls )

# Defining Level of Risk

Function of :

-severity

-Frequency

-Detectability

- These three factors determine the numerical Risk Priority Number (RPN)
- Qualitative risk (low , medium ,high

**ASTM E-2500 Consensus Standard**

published in august 2007

What is it ?

-A consensus standard developed with input from industry and FDA

-it is called “standard Guide for Specification , Design , and verification of pharmaceutical and biopharmaceutical manufacturing systems and Equipment ”

-Applies to elements of manufacturing systems of biopharmaceutical products including facility equipment , utilites , control , etc .

# ASTM standard E2500

Objective

- Insure that manufacturing systems are fit for the intended use and while reducing work duplication and cost of the required validation .
- Accomplish through building quality into the design , specification and construction of such systems .
- Verify and certify suitability.

# ASTM Standard E2500

Tools :

- Use of User Requirements Specification (URS).
- Use of Good Engineering Practice (GEP).
- Use Scientific and Technical Knowledge and enlist Subject Matter Experts (SME).
- Relating Critical Quality Attributes (CQA) to Critical Processing parameters (CPP).

# Overall Approach to Verify Manufacturing Systems

- Define user requirements
- Conduct risk –and science –based analysis to define critical aspects of the operation
- Ensure that quality was designed into the operation a priori
- Ensure that quality was designed into the operation a priori
- Ensure that Good Engineering Practices were used in the design , specification and construction of the operation .
- Utilize subject matter experts (SME) to plan and define verification strategy.
- SME to execute the tests and review the results.

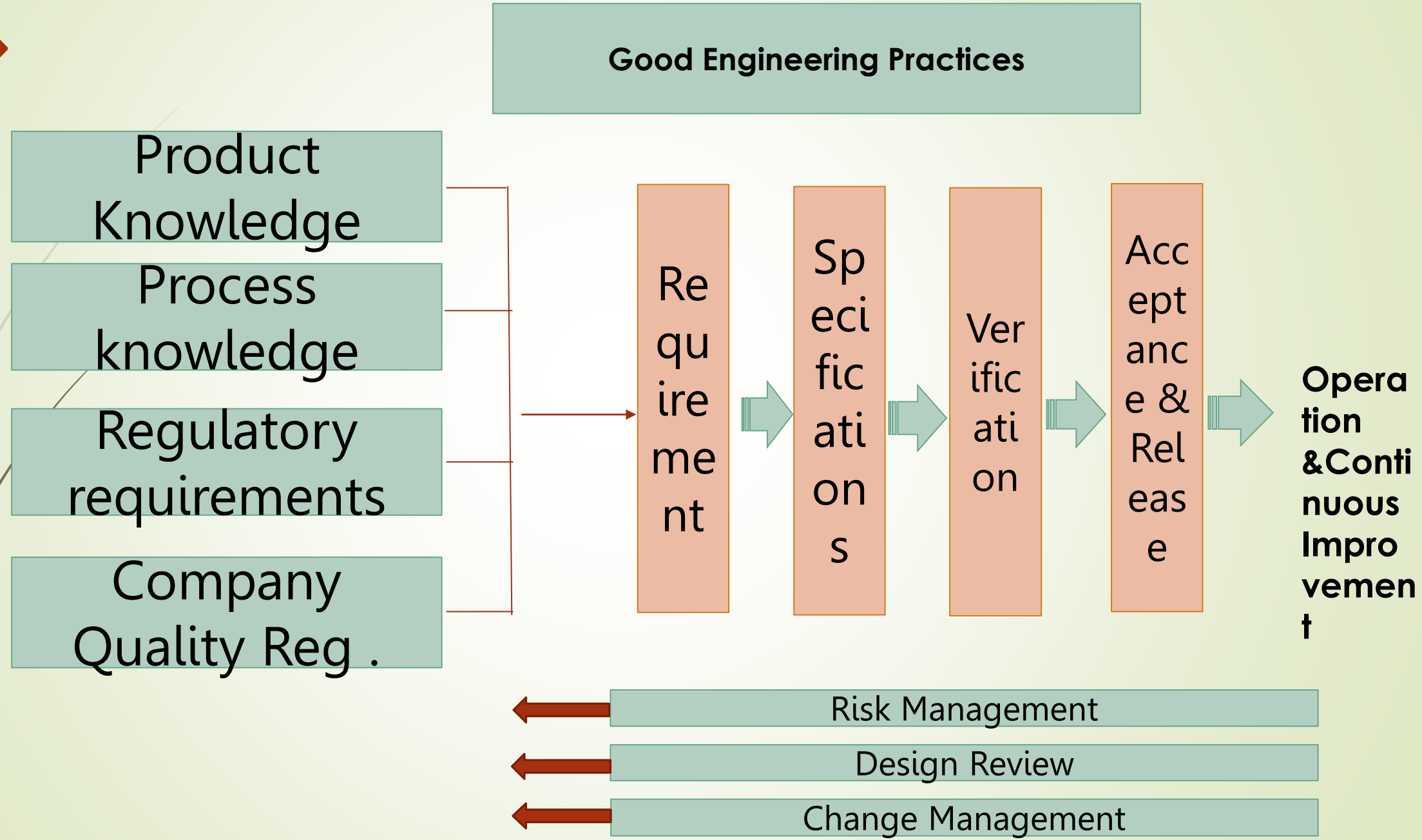
## **Overall Approach to Verify Manufacturing Systems (**cont.)

- SME to define acceptance criteria and selection of appropriate test methods .
- SME to review and accept the verification testing and certify the systems is “Fit For Intended Use”
- Utilize vendor documents and testing information to support the verification effort .

  - confirm acceptable vendor quality system and technical

    capability
- Avoid duplication of effort / testing by using GEP commissioning data to support the verification .

# The Process


Good Engineering Practices
Product Knowledge
Process knowledge
Regulatory requirements
Company Quality Reg .
Requirement
Specifications
Verification
Acceptance & Release
Operation &Continuous Improvement
Risk Management
Design Review
Change Management

# Qualify / Validate Verified System

- Provide documented evidence that the process will consistently produce product which meets predetermined characteristics and quality attributes . Ensure system remains in a validated state .

# Heating Ventilation Air Conditioning (HVAC) System

- HVAC or “aitch-vak” systems are mechanical arrangement that treat outside air to produced cleaned (from dust and microbes) and conditioned air (temp. & Humidity )for use in controlled and critical areas within the pharmaceutical manufacturing space .
- The systems normally consist of filtration , heating , cooling , dehumidification , and humidification steps .
- It is the technology of indoor environmental control and /or comfort.
- The most important utility in the manufacture of drug products .

# HVAC

- Controls the environmental conditions in the manufacturing space , which may affect product quality , safety , and Efficacy (temperature and Humidity).
- Control the cleanliness of the manufacturing space (room classification –particle number both viable and non viable ).
- Prevent cross contamination (relative pressurization between spaces).

# Regulatory Imperatives

- Control Temperature , Humidity , pressure , Dust (particulate ), and Microbial load (21 CFR 211.46)
- The need to filter the air coming into manufacturing space (21 CFR 211. 46)
- Protect product from extraneous contamination by microorganisms or their byproducts . Most intermediates and materials used in the industry are excellent promoters of microbial growth.
- The need to ensure that the product is not cross contaminated by other products being processed in adjacent space .

# Process Validation and HVAC Systems

An HVAC system can be viewed as a process using outside air as a raw material and producing conditioned air . The conditioned air comes into contact with the drug product and hence has a direct impact on the drug product.

Additionally , HVAC is a system that is a utility and part of the facility in which production occurs and as such must be qualified and maintained as part of stage 2 of the proposed FDA guidance on process validation.

## HVAC System consists of

1. **AIR Handling Unit (AHU)**

-Air filtration and conditioning .

-Pump and meter the air into the distribution system.

2. **Air Distribution System –Duct Work**

- Distribute the air to the various areas .

- Temperature , humidity and smoke detection controls

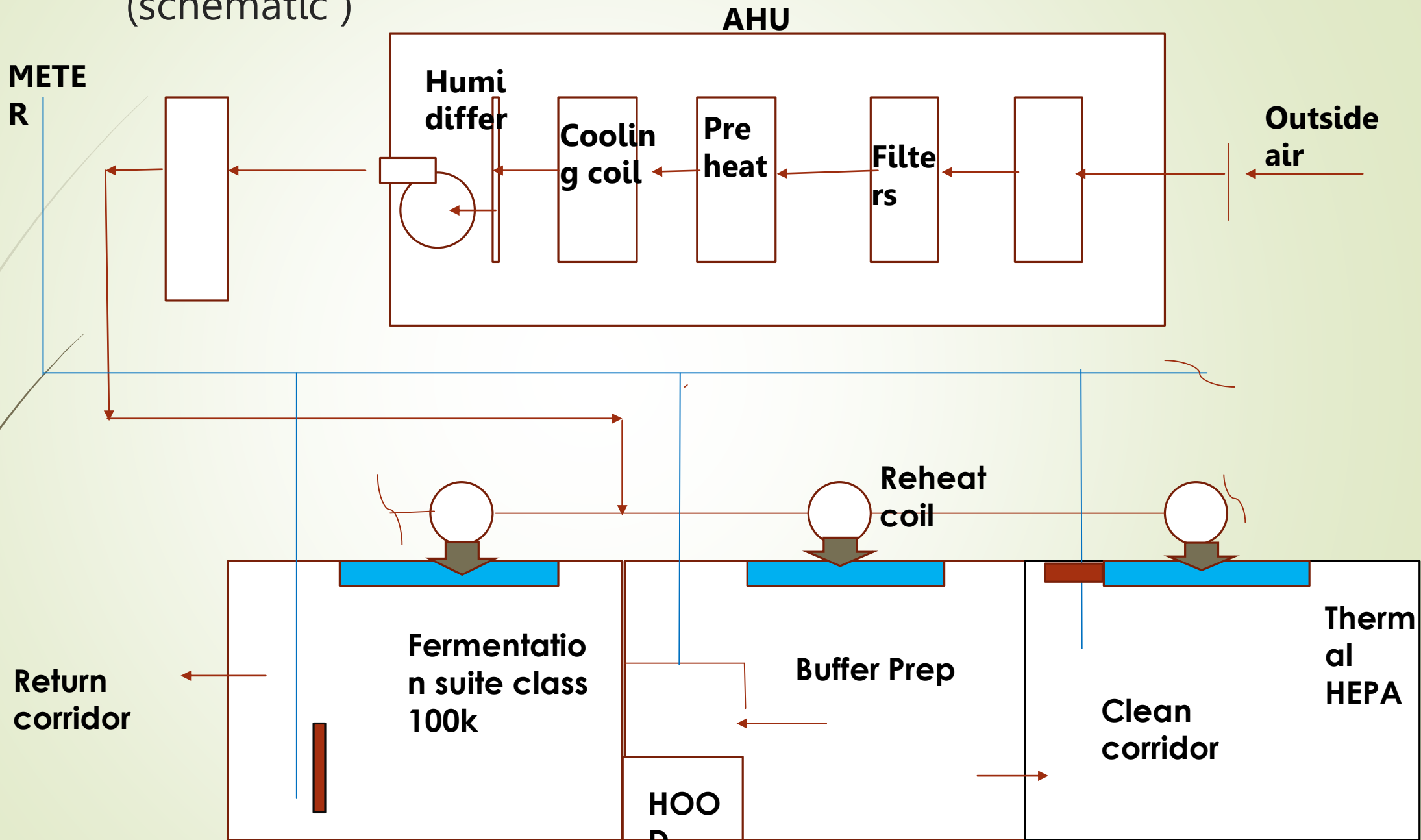
- Final filtration and heating if necessary

-Returning or exhausting the air .

3. **Use Areas**

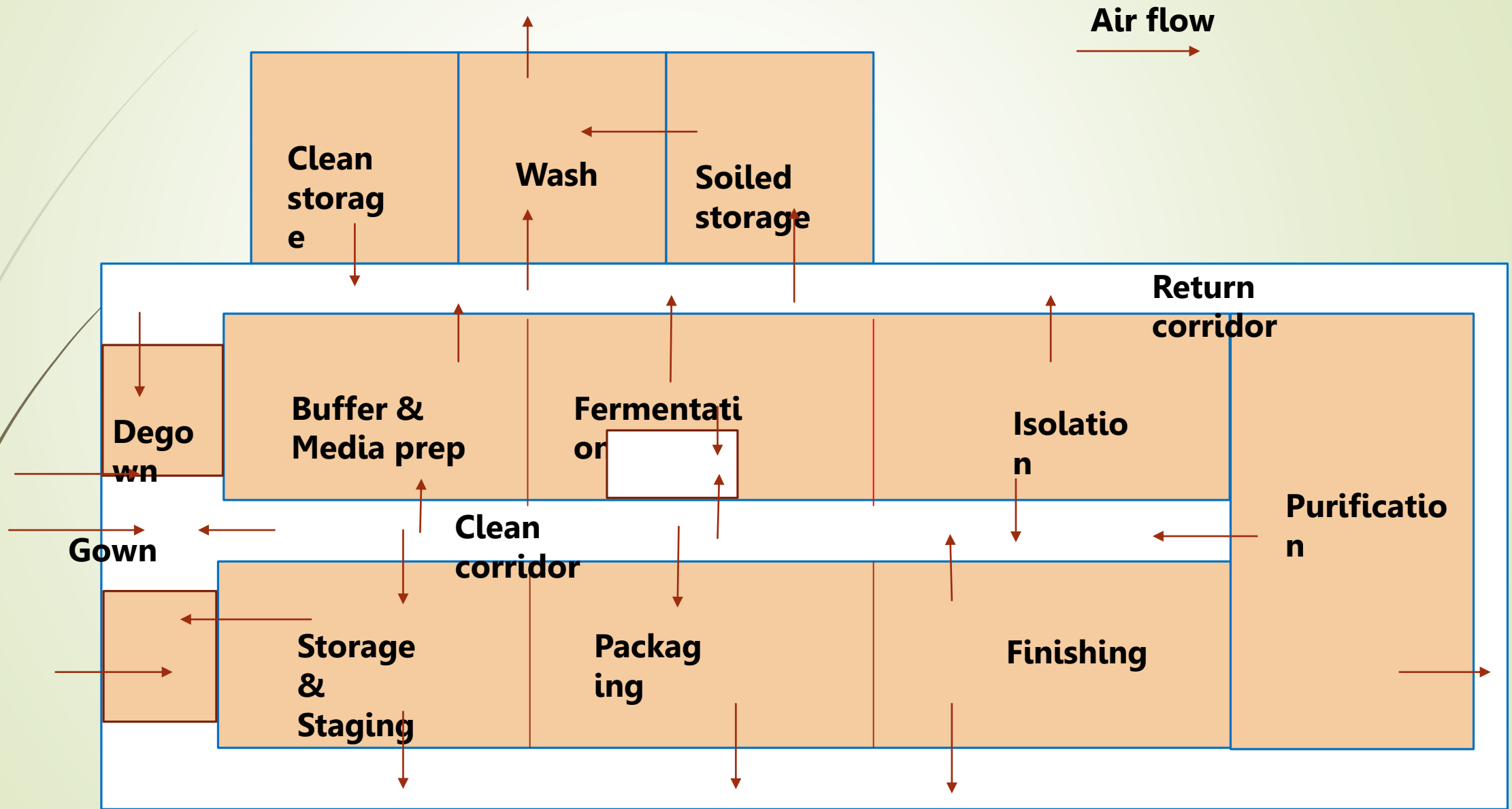
-Manufacturing spaces & support spaces

# Typical HVAC System for a Biotech Facility
(schematic )



# Schematic of Biotech Facility

(Air flow pattern for cleanliness and contamination control )



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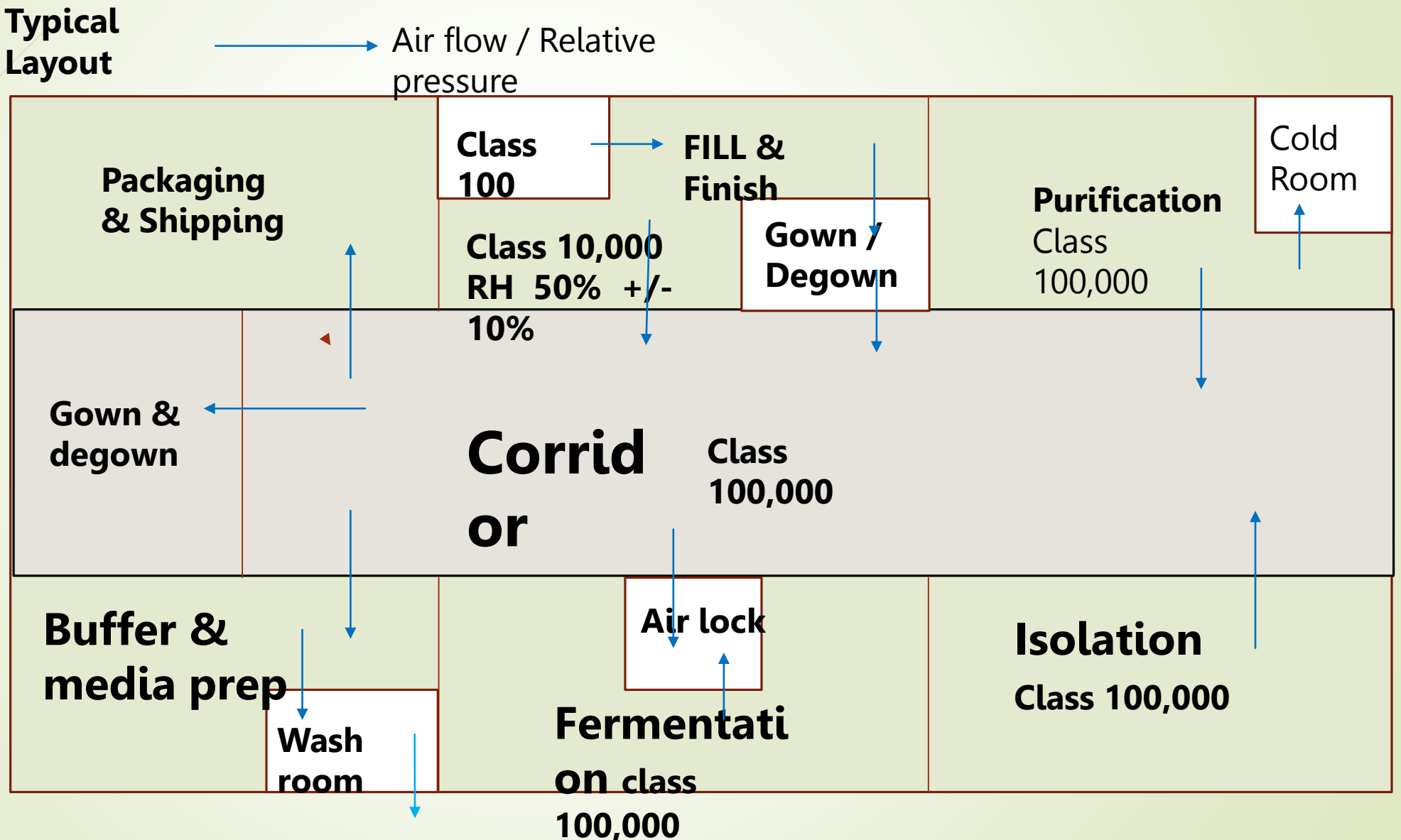


# Design stage

- User requirements :

  -Defines , temperature , humidify , cleanliness requirements for the product as

  defined by the design organization and others .

- Risk assessment :

  -Identifies issues associated with maintaining the user requirements such as

  required levels of cleanliness and air flow parameters .

- Functional specifications :

  -Identify how conditions can be reached using the appropriate technology and

  technical knowledge .

- Control strategy :

  -how will the conditions .

# What to Qualify ?

- The mechanical system
  - its installation and operation
  - The controls
- The air distribution system
  - Installation
  - Adequacy
  - safety issues
- The conditions prevailing in the
  - Temperature and humidify
  - Air changes

# Documents you need

- User requirements
- Engineering specifications
- Contractors submittals
- Engineering drawings
  - -Mechanical drawings
  - -Architectural layout dra
- Test and Balance Report

# Qualification of the HVAC system

- First step  is to confirm that the system has been installed per the design and is capable of operating within the required parameters .
- Second is to verify that the system is capable of providing the needed conditions within the space and maintain them.
- Finally a report summarizing the effort and reaching the condition that the system is acceptable for the intended use has to be developed.

# Performance Qualification

## Particulate count

USP 23 and FDA guidance on sterile Drug products , 2004

| Room classification | Particles /ft3* | cfu/ft3 |
|---|---|---|
| 100(M3.5; ISO 5) | 100 | <0.1 |
| 10,000(M5.5; ISO 7) | 10,000 | <0.5 |
| 100,000 (M6.5; ISO 8) | 100,000 | <2.5 |

*Less than the indicated number of particles of diameter < 0.5 micron/ft3

# Air changes

Based on : ISO Standard 14644 and IFEST-RP-CC012.1

| Room classification | Air changes per hour |
| --- | --- |
| - 100(M3.5) | -500-700 |
| - 10,000(M5.5) | - 60-90 |
| - 100,000(M6.5 ) | - 12-40 |

*Relative pressurization standard is 0.05 of water relative to adjacent les clean areas .

# Temperature

Based on USP ; 8th supplement , dated May 15 ,1998

| Room (condition )description | Temperature Range |
| --- | --- |
| Freezer | 25º C to - 10º C |
| Cold | 2º C to 8º C |
| Cool | 8 º C to 15º C |
| Controlled room temperature | 20º C to 25º C |
| Warm | 30º C to 40º C |
| Excessive Heat | over 40º C |

# Instruments use

- Data Loggers for temperature and humidity monitoring .
- Particle counters for particulate monitoring
- Smoke sticks or magnahelic gauges for airflow/ relative pressurization.
- Active microbial sampling techniques
- Possibly use data from BAS and its instruments .

# Why Monitor ?

- It is the law (21 CFR 211.42 -10 )
- Identify and correct potential environment control equipment problems
- Complete the validation effort by collecting DATA which takes into account the seasonal variations
- Validate cleaning of environment / manufacturing area
- Establish alert and action levels ( by establish baseline conditions and identifying hot spots )
- Insure that the manufacturing space is always in a validate state and GMP compliant

# Why Monitor ?

- Insure conditions within the manufacturing space remain within the appropriate ranges required by the product

  a. No biological contamination for sterile space

  b. No cross contaminating particles from other manufacturing operations or

  due to re-circulation of air .

  c. Appropriate temperature and humidify conditions .

- Use information collected from the monitoring program / system to control the operation of the HVAC system

# Where to Monitor ?

- All production areas ( including corridors and airlocks )
- Storage areas for product , intermediates , and raw materials

(especially if affected by environmental conditions ,

especially in critical areas near doors , ceilings , etc .)

- Clean rooms and laminar Flow Hoods
- Critical surfaces
- Environmental controlled rooms / chambers
- Freezers, Refrigerators , Incubators

# What you should Monitor ?

- Temperature
- Humidity
- Pressure
- Particulate
- Microbial / Biological Load

# How to Monitor ?

- Temperature probes , thermocouples , chart recorders
- Humidity probes , chart records
- Temperature and humidity mapping devices and data loggers
- Magnahelic gauges
- Building Automation systems (BAS) when several HVAC systems are used (T, RH , pressure deferential )
- Particle counters
- Active microbial air sampling
- Settling plates *

- use appropriate media for organisms to be detected ,

e.g .TSA for bacteria , SDA for mold and yeast

# Validation of Pharmaceutical Water Systems

# Pharmaceutical Water System

- Water in the pharmaceutical industry must be treated prior to use . Treating the water ensures that bit would have consistent quality and be free of contaminations that may negatively impact product quality , safety and / or efficacy.
- Water systems normally consist of filtration , deionization , microbial removal / reduction , conditioning of water , and distribution to use points .

# Water in the pharmaceutical industry

- One of the most important if not the most important utility in the manufacturing of the drug products .
- Water systems control the quality of the water , which may affect product quality , safety , and efficacy ( chemical content , solids , microbial content , etc ).

# Where is water used ?

- In manufacture .
- In formulation .
- In cleaning of equipment .
- In cleaning of the facility.

# Problems with untreated water

- Chemical content
- Dissolved Gases and odour
- Microbial and endotoxin content
- Inconsistent quality
- Seasonal variation

# Regulatory Imperatives

- The introduction of undesirable chemicals or other contaminants through the use of water in the manufacture of drugs would result in adulterated product .
- Water should be supplied in a fashion that would not contribute to contamination of drug (ICH Q7a)

# Regulatory Imperatives

- Potable water (this should apply to any water supply) shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product (21 CFR 211.48(a))
- Where water used in the process is treated by the manufacture to achieve a defined quality , the treatment process should be validated and monitored with appropriate action limits (ICH Q7 a)

# Water systems consist of

## 1 . Water Conditioning

- Water filtration and removal of inorganic .
- Microbial content

## 2 . Water Treatment

-Deionization

-Distillation

-Microbial  control .

## 3. Water distribution

- Storage of treated water
- Pump  and meter to use points
- Condition water at use point
- Microbial control
- Recycle the water

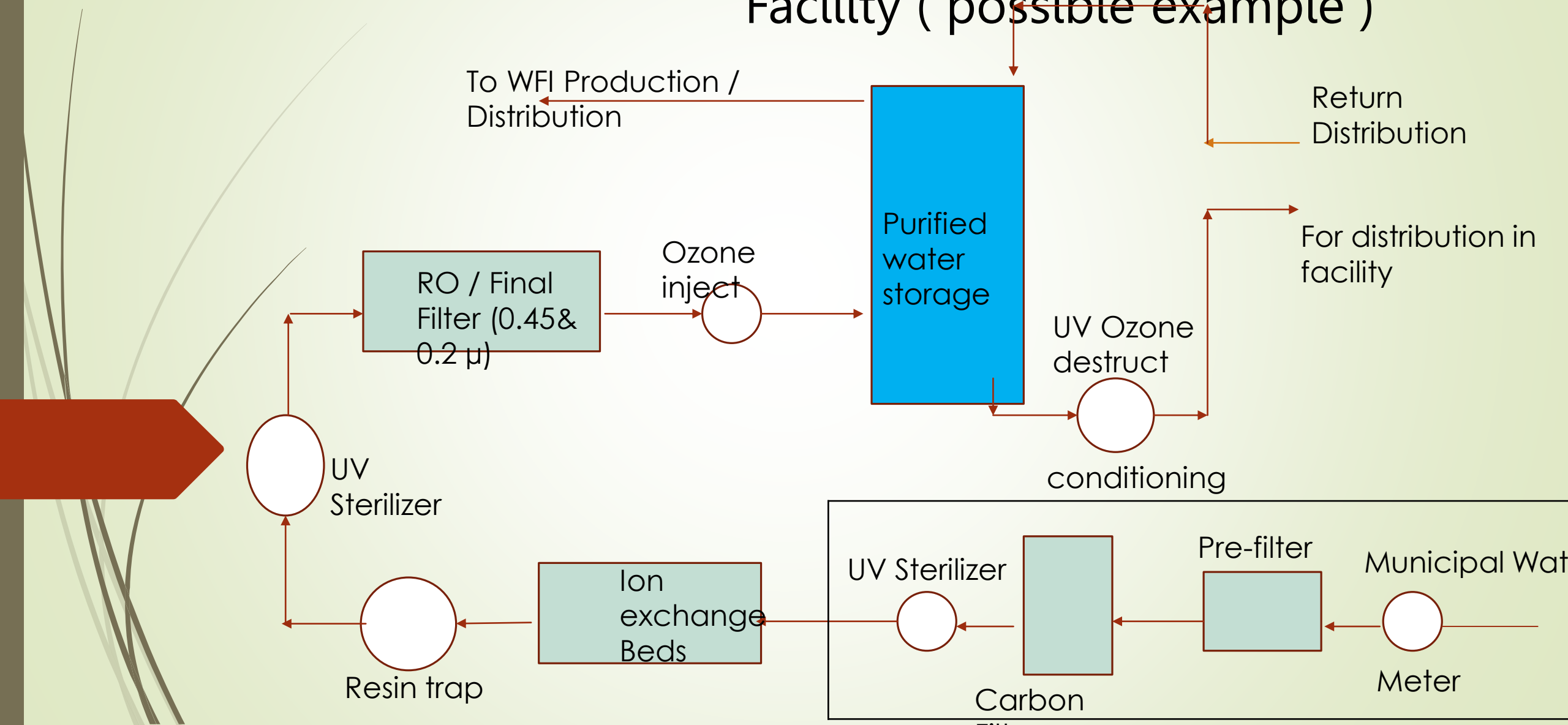
# Types of Water

- Potable Water
- Deionized Water
- USP  purified water ( DI – RO)
- Water for injection (WFI)

# Water Properties

- Water properties :
  - -Organic chemical content (TOC)
  - -Inorganic chemical content ( conductivity )
  - - Microbial and endotoxin content
  - - Dissolved gases
- Water system variables
  - -Flow rate
  - -Pressure

# Schematic diagram for purified water production in Biotech Facility ( possible example )



# Water system Design Issues

- Sanitary piping , valves and fittings requirements ( design)
- Materials of construction and passivation requirements ( design –ss vs PVDF , PVC )
- Dead legs and loop design consideration ( design)
- Regular cleaning and sanitization (Maintenance –design )
- Hot vs cold system (Energy consideration , material of construction – design )
- Purification methods to be used ( design ; DI-RO ,DI only ,etc )
- Control of microbes and endotoxin ( include and ozone generators , etc )
- Operating procedure of the system ( design and initial testing )

# What to Qualify ?

- The treatment system
  - -its installation and operation
  - -the controls
- The water distribution system
  - -Installation and operation of use points
  - -Adequacy
  - -cleaning and sanitization issues
- Water quality at the use points
  - -flow rate
  - -Ph
  - -chemical content
  - -Microbial and endotoxin content

# Documents you need

- User requirements
- Engineering specifications
- O&M  Manuals
- Engineering drawings and documentation

-System Description

-Mechanical drawings showing mechanical components (M series )

-plumping drawings showing sampling points (P series )

-Architectural layout drawings (A series )

# Sampling Requirements

- Sample daily after each step in the process
- Continue sampling for a minimum of 2 to 4 weeks
- Samples at use points should reflect how the use points will be used ( e.g . If hose to be used sample with hose in place )

# Instruments to use

- Mass  flow meters .
- Stop watches and graduated containers .
- Pressure meters .
- Temperature

# Example Data Sheet Attachment

Stage : 2  Measured conductively not to be greater than 2.1 µs/cm .

Use point Location :  Use point ID :

Time :  AM/PM

Date :

| Item | Result |
|---|---|
| Temperature of sample @25° C -/+ 1·C° ? | ❑YES<br>❑NO |
| Conductivity of sample | |
| Acceptance  Criteria Met | ❑YES<br>❑NO |

# Where to Monitor ?

- Incoming feed water
- Water quality at all use points .
- Critical processing parameters (CPP) within the system ( e.g. Temperature of the still , UV intensity , etc .).
- Storage tanks ( e.g . Temperature , Microbial content , etc .)
- Filter integrity .
- Water quality at critical processing / purification points within the systems .

# What you should Monitor ?

- Chemical content ( TOC , Ph , Conductivity , etc .)
- Microbial / biological load .
- Endotoxin content .
- Flow .
- Dissolved gases ( Chlorine –for RO protection ).
- Solids , colour , odour .
- CPP ( temp , pressure , Ozone concentration, etc .)
- Other ( e.g , failures , deviations , maintenance issues , OOS ,etc .)

# How to Monitor ?

- TOC analyzers ( on– line and in the laboratory )
- Conductivity meters ( Laboratory and on –line )
- PH Meters and mass flow meters
- Turbidity meters
- Temperature sensors and indicators
- In-line pressure and flow meters
- Sampling for microbial (plating ) and endotoxin (LAL)content

- WATER FOR INJECTION
- ❑ A clear and colourless liquid and odorless
- ❑ Water for injection is pyrogen free .it contain no added substance
- ❑ Water for injection is obtained from potable or purified water by distillation in
- an apparatus
- ❑ The distillate is collected and stored in conditions designed to prevent growth
- of microorganisms and to avoid any other contaminations

- MANUFACTURING OF WATER FOR INJECTION
- ❑ USP specified distillation and reverse and osmosis as methods to prepare
- water for injection
- ❑ Only these two methods is it possible to separate adequately various liquids ,
- gas and solid containing substances from water
- Preparation methods are very similar to a particular point however water for injection preparation process in pharmaceutical must include distillation or double pass reverse osmosis techniques

- FACTORS INFLUENCE PRODUCTION OF WFI
- The quality of feed of water for distillation will effect the quality of distillate
- The size of the eveporator
- The baffles (condensing surface ) determine the effectiveness of refluxing
- Volatile impurities
- Contamination of vapor and distillate from the metal part of the still can occur

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- Dechlorination
- This refers to the removal of chlorine from the water
- There are several ways to dechlorination
- This include injection of a reducing agent like sodium metabisulfite and exposure
- to a high dosage of UV rays can dechlorinate .
- However the most common one is filtration through activated carbon media

- Water for injection preparation process in pharmaceutical is dechlorinated by
- carbon .
- Carbon dechlorinates by chemically reacting with the free chlorine in water to form
- hydrochloric acid carbon monoxide or dioxide
- High doses of UV light rays are widely used in water purification system for both
- disinfection and TOC reduction
- Another use of UV is dechlorination though it is relatively new process

- Ion removal
- There are basically three types of ion reduction processes
- ❖ Membrane processes
- ❖ Ion exchange processes
- ❖ Distillation processes
- Membranes are used in water purification systems to remove ions ,
- particulate,organic compounds and living organisms
- Membranes are different from one another in terms of pore size , molecular
- weight and even on ion rejection .

- Ion removal membranes include membranes such as reverse osmosis
- membranes and nanofiltration membranes
- These are used in ion reduction processes
- The ion exchange system provide additional ion reduction processes making the
- water much lower in conductivity than required and it also provides a back up for
- membrane processes
- Distillation can also be used to remove ion however it is very expensive

- Bacteria control is usally applied during processing storage and even distribution
- UV  light is an exellent non chemical method of disinfecting water for injection
- Thermal sanitization involves the used since it is a very strong oxidizing agent it
- can there fore oxidize bacteria
- Chemical can also ne used to kill bacteria as a means of bacterial control

- Removal of specifc impurites
- There are various different sources of water for injection used during preparation
- process in pharmaceuticals
- Every source is different and therefore the possibilities of specific contaminant
- problem are possible
- These contaminants include iron , maganeese ,hydrogen , sulfide ,hardness ions ,
- particulate matter , and high conductivity
- Filtration can be used to remove any heavy loads .

# ETP

ETP (Effluent Treatment Plant) is a process design for the industrial waste water for its reuse or safe disposal to the environment

- Influent :Untreated industrial waste water
- Effluent :Treated industrial waste water
- Sludge :Solid part separated from waste water by ETP

# Need of etp

- To clean industry effluent and recycle it for further use
- To reduce the usage of fresh / potable water in industries
- To cut expenditure on water procurement
- To meet the standard for emission or discharge of environmental pollutants from various industries set by the government and avoid hefty penalties
- To safeguard environment against pollution and contribute in suitable development

# Design of etp

The design and size of the ETP depends upon :

- Quantity and quality of the industries discharge effluent
- Land availability
- Monetary consideration for construction , operation and maintenance

## Area dimension depends on:

- Quality of waste water to be treated
- Flow rate
- Type of biological treatment to be used

## In case of less available land

- CETP(Common Effluent Treatment Plant) is preferred over ETP

# TREATMENT LEVELS & MECHANISMS OF ETP

## Treatment levels

- Preliminary
- Primary
- Secondary
- Tertiary

## Treatment mechanisms

- Physical
- Chemical
- biological

# Mjor treatment units in etp

PRELIMINARY TREATMENT

- Screens
- Scrapers
- Grit chamber
- Skimming tanks
- Aeration

PRIMARY TREATMENT

- sedimentation
- Clarifloculator
- Equalization tank
- Neutralization tank

SECONDARY TREATMENT

- Activated sludge process
- Trickling filter
- Aerated lagoons
- Multiple evaporated

TERTIARY TREATMENT

- Sand/membrane filter
- Activated carbon filter
- Disinfection
- Ion exchange
- Nutrient removal

# Preliminary treatment level

- Physical separation of big sized impurities like cloth ,plastics ,wood logs ,papers and etc.....,
- Common physical  unit operations at preliminary level are
- Screening :a screen with openings of uniform size is used to remove large solids such a plastics ,cloth etc.
- Sedimentation : physical water treatment process using gravity to remove suspended solids from water
- Clarification  : used for separation of solids from solids

# PRIMARY TREATMENT LEVEL

- Removal of floating and materials such as suspended solids and organic matter
- Methods : both the physical and chemical methods are used in this treatment level
- Chemical unit processes
- Chemical unit processes are always used with physical operations and may also be used with biological treatment processes
- Chemical processes use the addition of chemicals to the waste water to bring about changes in its quality
- Example : PH control , coagulation , chemical precipitation and oxidation

# Secondary treatment

- Secondary treatment is a  biological treatment of effluent which is typically performed by indigenous, water borne ,micro organism managed habitat
- Secondary treatment removes dissolved  and suspended organic matter by consuming food and covert into new cell mass ,energy and co2
- The most common micro organisms are bacteria(areobic  , anaerobic) protozoa and rotifers ;common algae or fungi
- after secondary treatment almost 70-80%of BOD and 80-90% dissolved solid are removed from effluent.

# Tertiary treatment

- Tertiary treatment is the final treatment meant for polishing the effluent and removal of pollutant not removed in primary and secondary treatment.
- These pollutant may include soluble in organic compounds such as phosphorous or nitrogen which is support to algae growth in support receving waters.
- Also removes organic material contributing BOD ,COD color, taste, odour , bacteria ,viruses , colloidal solids with subsequent reuse of the water.
- prefered when treated water is ne to be reuse or discharge is into a highly sensitive or fragile ecosystem(low flow rivers ,coral reefs.ss

- Tertiary treatment additional cost to the treatment process but quality effluent which can be refuse further for commercial and industrial application.
- Treated water can be refuse for the irrigation of golf course green way or park, industrial process etc.
- if it is sufficiently clean it can also be used for ground water recharge .
- Treated water is sometimes disinfected chemically or physically depending upon the discharging location.

# Process description

- Sludge treatment : the under flow from clarifier and the secondary clarifier having the sludge consistency of around 1-1.5% is pumped into centrifuge for dewatering . the dewater sludge is disposed off suitably while the concentrate is taken back to the equalization tank.

# Process description

- BIOLOGICAL TREATMENT: the neutralized effluent will this the treated through the bio tower with aeration tank and clarifier the liquid over flow from the lamella clarifier is taken to the chlorination tank .the sludge underflow from the lamella clarifier is partially returned to the inlet of the aeration tank for maintaining the desired level .the excess sludge is treated through a basket type centrifuge
- FILTRATION: chlorinated water will be passed through a multigrade sand filter further reduction of suspended solids to less then 20ppm and then passed through a activated carbon filter for the polishing of BOD ,COD values.

# Process description

**Equalization** :the waste from main plant is first collected in the equalization tank through screening the equalization tank is designed for the hydraulic retention time is around 6 hours and with avoided air grids connected to a air blowers for maintaining the solid is suspension

**Effluent solid mixer flocculation tank& clarifier**: the equalized waste is then pumped of f into the flash mixer compartment of flash the flocculation compartment is aid the process of setting. The over flow of the flocculation compartment is taken into the clarifier for further treatment while the under flow is taken for sludge compartment.,

# REFERENCE:


- Professional Development Committee, the Institute of Cost Accountants of India. Exposure Draft: Guidance Note on Internal Audit of Pharmaceutical Industry; 2013. Available from: http://icmai.in/upload/Institute/Comments_Invited/ED-IA-Pharma.pdf.
- Vedanabhlata S, Gupta VN. A review on audits and compliance management. Asian J Pharm Clin Res 2013;6:43-5.
- Sharma S, Kohli S, Potdar M. Current good manufacturing practices: Audit.
- Active Pharmaceutical Ingredients Committee (APIC). Auditing guide; 2016. Available from: http://apic.cefic.org/pub/Auditing/APIC_CEFIC_AuditingGuideAugust2016.pdf. [Last accessed 19 Mar 2018] Place Unknown: Word Press; 2008. Available : https://drpotdar.wordpress.com/2008/04/30/audit/.
- BSI standards publication: European committee for standardization. Guidelines for auditing management systems; 2011. Available from: http://qic-eg.com/wp-content/uploads/2015/08/BS-EN-ISO-19011-2011.pdf.