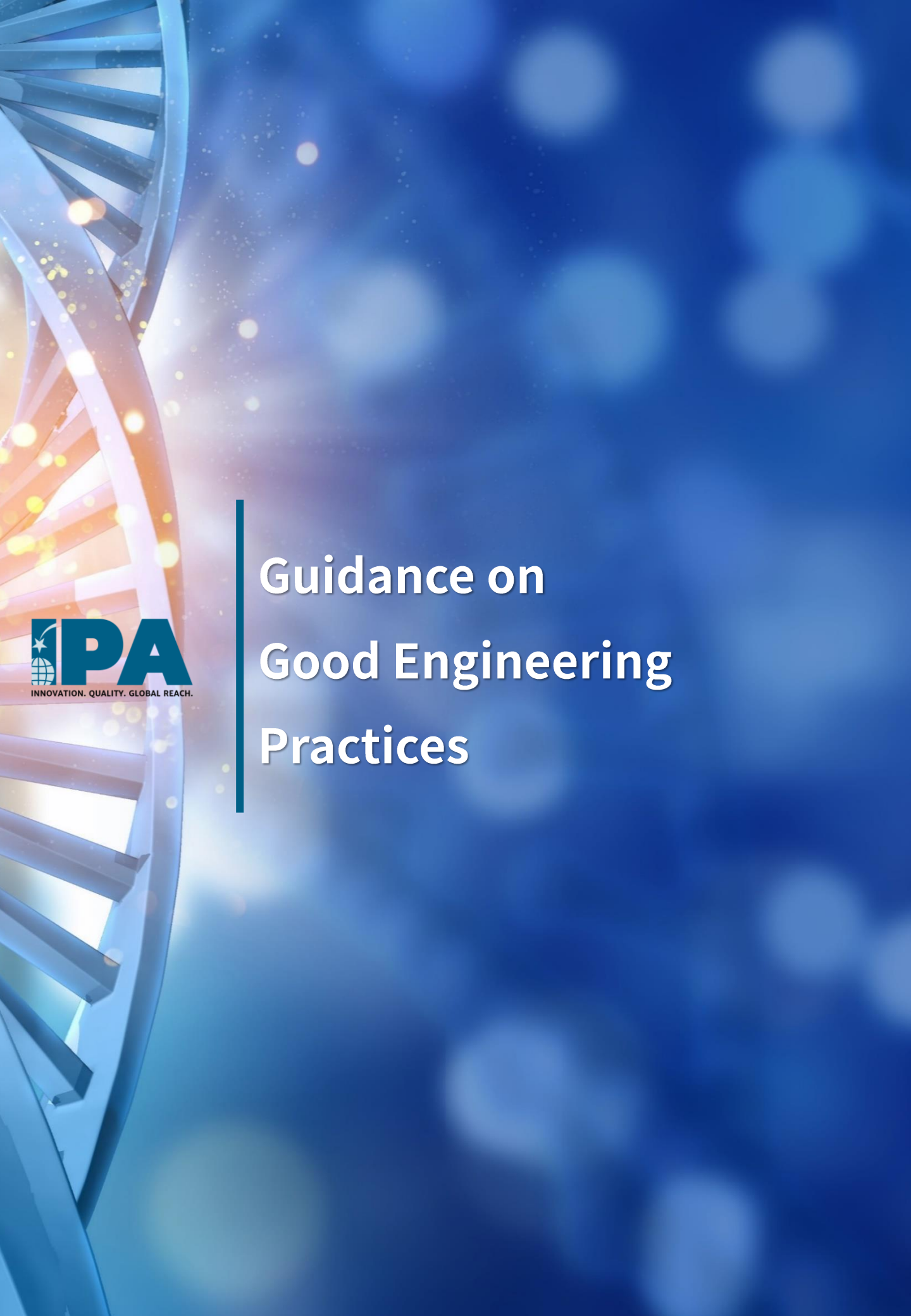
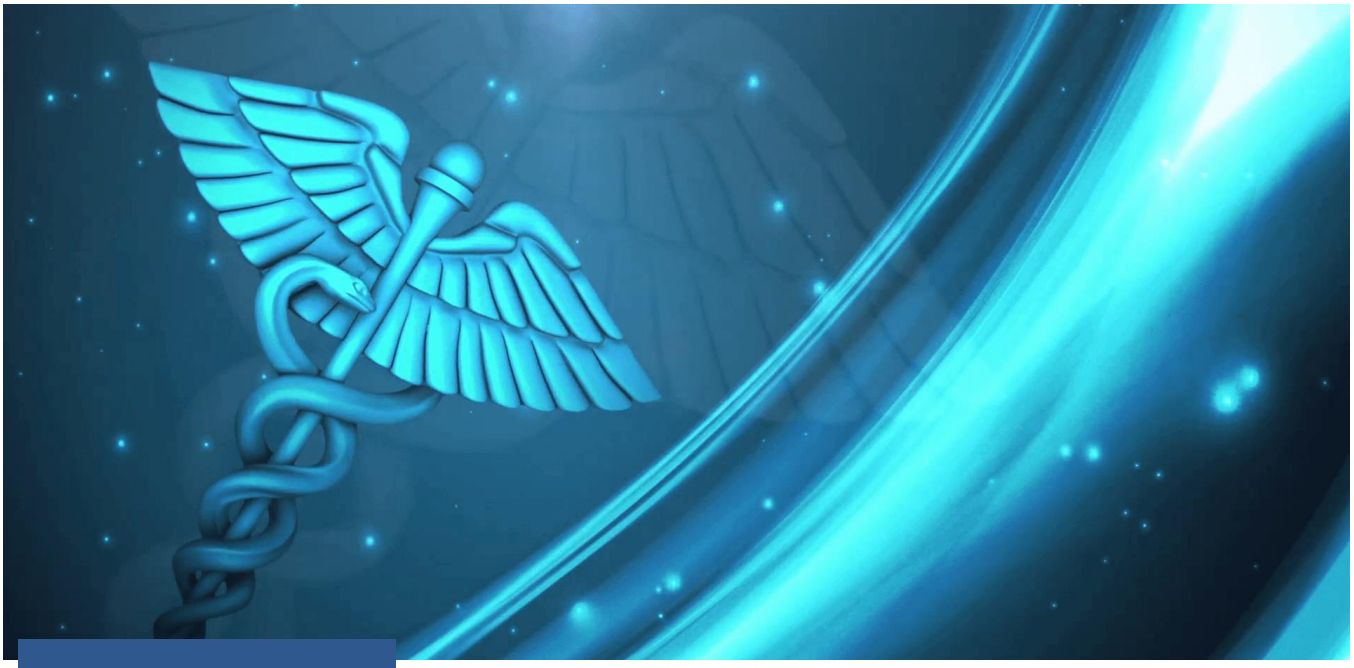


Guidance on Good Engineering Practices



PREFACE

In April 2015, The IPA launched its Quality Forum (QF) to help Indian pharmaceutical manufacturers to achieve parity with global benchmarks in quality. The QF made a commitment to a multi-year journey to address key issues facing the industry and develop best practices.

The QF focused on several priority areas in the last four years, namely, Data Reliability, Best Practices & Metrics, Culture & Capability, Investigations, etc. It took upon itself the challenge of developing a comprehensive set of Best Practices Documents for several of these topics. In this document, we focus on best practices for Good Engineering Practices – Maintenance of facilities and Equipments.

The six participating companies in the QF nominated senior managers to study the best practices and frame the guidelines. They are: Gurudatta Bhat (Lupin); Rajendra Das (Sun Pharma); K Madhusudhan Reddy (Dr Reddy's Laboratories); Nirav Trivedi (Torrent); Mangesh Kulkarni (Cipla); Ajay Joshi (Zydus). The IPA wishes to acknowledge their concerted effort over the last 12 months. They shared current practices, benchmarked these with the existing regulatory guidance from the USFDA and other regulatory bodies such as UK MHRA, WHO, etc., developed a robust draft document and got it vetted by a leading subject matter expert and regulatory agencies. The IPA acknowledges their hard work and commitment to quality.

The IPA also wishes to acknowledge the CEOs of six member-companies who have committed their personal time, human resources and provided funding for this initiative.

CONTENTS

4.1.1.3 Operations shall be performed within specifically defined areas of adequate size to prevent contamination or mix-ups during the following procedures:

4.1.1.3.1 Receipt, identification and storage of components, drug product containers, closures, and labeling, for sampling, testing or examination by the quality control unit before release for manufacturing or packaging.

4.1.1.3.2 Holding rejected components, drug product containers, closures, and labeling, before disposition.

4.1.1.3.3 Storage of released components, drug product containers, closures, and labeling.

4.1.1.3.4 Storage of in-process materials.

4.1.1.3.5 Manufacturing and processing operations.

4.1.1.3.6 Packaging and labeling operations.

4.1.1.3.7 Quarantine storage before release of drug products.

4.1.1.3.8 Storage of drug products after release.

4.1.1.3.9 Control and laboratory operations.

4.1.1.3.10 The manufacturing areas shall be clearly separated into support areas (e.g., washing and component preparation areas, storage areas, etc.), preparation areas (e.g., bulk manufacturing area, non-aseptic blending areas, etc.) change areas, and aseptic areas.

4.1.1.3.11 Operations like removal of outer cardboard wrappings of primary packaging materials shall be done in the de-cartoning areas which are segregated from the washing areas. Wooden pallets, fiberboard drugs, cardboard, and other particle shedding materials shall not be taken inside the preparation areas.

4.1.1.3.12 Operations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used to handle other drug products for human use.

4.1.1.3.13 Aseptic processing, which includes as appropriate

4.1.1.3.13.1 Floors, walls, and ceilings should be smooth, impervious, non-shedding, non-flaking, and non-cracking hard surfaces that can be cleaned easily.

4.1.1.3.13.2 Flooring should be provided with a cove at the junction between the wall and floor, wall and ceiling, as well as wall and wall.

4.1.1.3.13.3 Walls shall be flat, and ledges and recesses shall be avoided. Wherever other surfaces join the wall/ceiling (e.g., sterilizers, UDAF's, freeze driers, electric sockets, gas points, etc.), shall flush and coving should be provided Ceiling shall be solid and joints shall be sealed.

4.1.1.3.13.4 Light-fittings and air-grills shall be flushed with the walls, and not hanging from the ceiling, in order to prevent contamination.

4.1.1.3.13.5 There shall be no sinks and drains in Grade A and Grade B areas.

4.1.1.3.13.6 Doors shall be made of non-shedding material, preferably of aluminum or steel material. Wooden doors shall not be used. Doors shall open towards the higher-pressure area so that they close automatically due to air pressure.

4.1.1.3.13.7 Windows shall be made of similar material as the doors, preferably with double panel, and shall be flushed with the walls. If fire escapes are to be provided, these shall be suitably fastened to the walls without any gaps;

4.1.1.3.13.8 The furniture used shall be smooth, washable, and made of stainless steel or any other appropriate material, but not of wood.

4.1.1.3.13.9 A system for cleaning and disinfecting the room and equipment shall be provided so as to produce aseptic conditions.

4.1.1.3.14 The manufacturing and support areas shall have the same quality of civil structure described above for aseptic areas, except the environmental standards which may vary in the critical areas.

4.1.1.3.15 Change rooms with entrance in the form of air-locks shall be provided before entry into the sterile product manufacturing areas, and then on to the aseptic area.

4.1.1.3.16 Solid sealed cross over bench is recommended for installation in all change rooms instead of bottom cleared cross over bench.

4.1.1.3.17 Separate exit room from the aseptic areas is advisable.

4.1.1.3.18 Two or more change room doors shall not be opened simultaneously. An appropriate inter-locking system and a visual and/or audible warning system shall be installed to prevent the opening of more than one door at a time.

4.1.1.3.19 Change rooms to the aseptic areas shall be clearly demarcated into black, gray, and white rooms with different levels of activity and air cleanliness. The black change room shall be provided with a sink for washing hands . The sink and its drain in the un-classified (first) change rooms shall be kept clean all the time. The specially designed drain shall be periodically monitored to prevent presence of pathogenic microorganisms.

4.1.1.3.20 Based on bio-burden control through dress code, change rooms shall be classified into grade & grade air classification. Qualification of the airlock shall be done with higher grade limits at rest condition while in operation; limits shall be different for floor and air. For lower grade side, quality of air (NVPC Limits) would be as per higher grade, while for floor (viable plate monitoring) shall be of lower grade. Airlock labelling shall be done as per the respective higher-grade nomenclature. The final airlock should be of same classification as per the final operation area classification.

4.1.1.3.21 For communication between aseptic areas and non-aseptic areas, intercom telephones or speaker phones shall be used. These shall be minimum in number.

4.1.1.3.22 Material transfer between aseptic areas and outside shall be through suitable airlocks or pass-boxes. Doors of such airlocks and pass-boxes shall have suitable interlocking arrangements. Materials movement from a lower grade to a higher grade will be made through a dynamic pass box, or, if required, VHP pass boxes should be considered.

4.1.1.3.23 Personal welfare areas like rest rooms, tea room, canteen, and toilets shall be outside and separated from the sterile product manufacturing area.

4.1.1.3.24 Automatic sensor tap shall be provided for hand wash and soap dispensing.

4.1.1.3.25 Automatic system for hand disinfectant dispensing shall be provided in all change rooms

4.1.1.3.26 Foot wiping towels with bucket shall be available in external change rooms

4.1.1.3.27 Animal houses shall be away from the sterile product manufacturing area and shall not share a common entrance or air handling system with the manufacturing area.

4.1.2 FACILITY DESIGN APPROACHES

4.1.2.1 Three basic facility types that show design approach implementation concepts as related to open sterile product manufacturing facilities are considered:

4.1.2.1 Open processing aseptic production in the absence of barrier technology (traditional method, requiring many procedural methods for product protection).

4.1.2.2 Open processing aseptic production utilizing barrier technology.

4.1.2.3 Open processing non-aseptic production for terminally sterilized products.

4.1.2.2 TRADITIONAL OPEN SYSTEM ASEPTIC PROCESSING: The design of the environment surrounding open processing should incorporate measures, such as those listed below, that prevent or mitigate the environment from contaminating the product :

4.1.2.2.1 The room air classification, zoning, and monitoring are requirements to protect the product, and performance of the HVAC system is critical in this regard.

4.1.2.2.2 Personnel gowning areas and material airlock areas provide a step-up transition to the cleaner room classifications. The cleaner the room HVAC classification, the more numerous the transitions between air classes.

4.1.2.2.3 A sufficient level of room cleaning should be established to remove potential residual chemical or bio contamination from the previous open process.

4.1.2.2.4 The room architectural finish and detailing requirements can be a factor in product protection. Coved corners at the floor, wall, and ceiling intersections can facilitate room cleaning, thereby helping to protect the product from residual chemical or bio-contamination.

4.1.2.2.5 "Flush" detailing is a term used for minimizing horizontal surfaces and difficult to clean areas in a room to facilitate room cleaning.

4.1.2.2.6 Material, process, personnel, waste, and equipment paths of travel are called "flows." The design of an open process facility should ensure that these "flows" do not facilitate the transportation of residual contaminates that could contaminate the product.

4.1.2.2.7 Examples of traditional open system aseptic processing include:

4.1.2.2.7.1 Open aseptic vial filling exposed to the room environment, but under a UAF hood with traditional limited barriers.

4.1.2.2.7.2 Open dispensing exposed to the room environment for formulation that is not filtered with traditional limited barriers.

4.1.2.3 Open system aseptic processing using isolator technology: When compared to traditional open processing, the room and facility requirements may be reduced when using uncompromised barrier technology. Key items include:

4.1.2.3.1 The room air classification, zoning, and monitoring requirements are reduced to the extent that the HVAC system may no longer be regarded as critical.

4.1.2.3.2 The gowning level requirements are reduced as a result of the closed process and the room classification reduction.

4.1.2.3.3 Personnel gowning areas and material airlock areas are reduced in number.

4.1.2.3.4 The level or extent of room cleaning is reduced. Sanitized walls are not included in the product protection equation for isolator systems.

4.1.2.3.5 The room finish and detailing requirements are reduced. Coved corners at the floor, wall, and ceiling intersection may not be required. Coved corners facilitate room cleaning and may be a factor in product protection in "open" processes, but not in isolator protected open processes. (They may, however, be "discretionary upgrades," along with other features critical to open processing).

4.1.2.3.6 Flush detailing may not be required.

4.1.2.3.7 Material, process, personnel, waste, and equipment paths of travel, and the segregation of these paths from each other, do not apply to truly closed systems. A closed system product vessel and a closed system waste container can be adjacent to each other. The contents of a closed system are not contaminated by adjacent closed systems. The exterior of each vessel should be cleaned to prevent the transport of residual contamination. The segregation of their paths of travel and storage may not be required.

4.1.2.3.8 It has become a convention to classify isolators as OPEN or CLOSED. This leads to some confusion when related to their use in open aseptic processing. Simply put, an open isolator is one which incorporates some form of opening, e.g., to allow the exit of filled units (mouse-holes). Such exit holes are designed to prevent any possibility of air from the surrounding environment entering the pressurized isolator environment. A closed isolator does not possess any form of openings which interface with the surrounding environment.

4.1.2.4 OPEN SYSTEM ASEPTIC PROCESSING USING RESTRICTED ACCESS BARRIER SYSTEMS (RABS):

4.1.2.4.1 The use of RABS offers considerable benefits over traditional open aseptic processing. However, while the aseptic critical zone is separated from the surrounding environment via the use of barrier walls and Grade A air overspill, if the majority of intrusions being undertaken using glove ports, occasional enclosure door openings may be required. If occasional door opening is required, the fabric and integrity of the surrounding area, including requirements for personnel gowning and procedures, are, as a result, identical to traditional open operations. Notwithstanding these requirements, the protection of the critical zone from the surrounding environment as afforded by RABS makes them a suitable choice for new and renovated facilities when isolator technology is inappropriate.

4.1.2.5 OPEN SYSTEM NON-ASEPTIC PROCESSING (FOR TERMINAL STERILIZATION):

The product does not rely on aseptic processing, so the environment is a lesser part of the product protection equation, but the process is protected by UAF hood and open to the room environment. The local environment should not add particulates or bio-burden to the product which the terminal sterilization process cannot remove.

4.1.2.5.1 Open system non-aseptic processing examples include open non-aseptic vial filling primary containers and stoppers prepared for non-aseptic filling.

4.1.2.6 CLOSED PROCESSING

4.1.2.6.1 This is a process condition when the product, materials, critical components, or container/closure surfaces are contained and separated from the immediate process environment within closed/sealed process equipment.

4.1.2.6.2 Examples of closed processes include:

4.1.2.6.1 Closed sterile vessel in transit through a work area.

4.1.2.6.2 API recrystallization vessel.

4.1.2.6.3 Closed sterilized pipework transporting product or materials.

4.1.2.6.4 Transporting and storage of sealed and capped vial or closed ampoule.

4.1.2.6.3 When closed processing is employed, there is no special control required for the immediate processing environment, provided that the integrity of the system is assured through equipment design and operation, and that there is appropriate monitoring to provide evidence that integrity is being maintained.

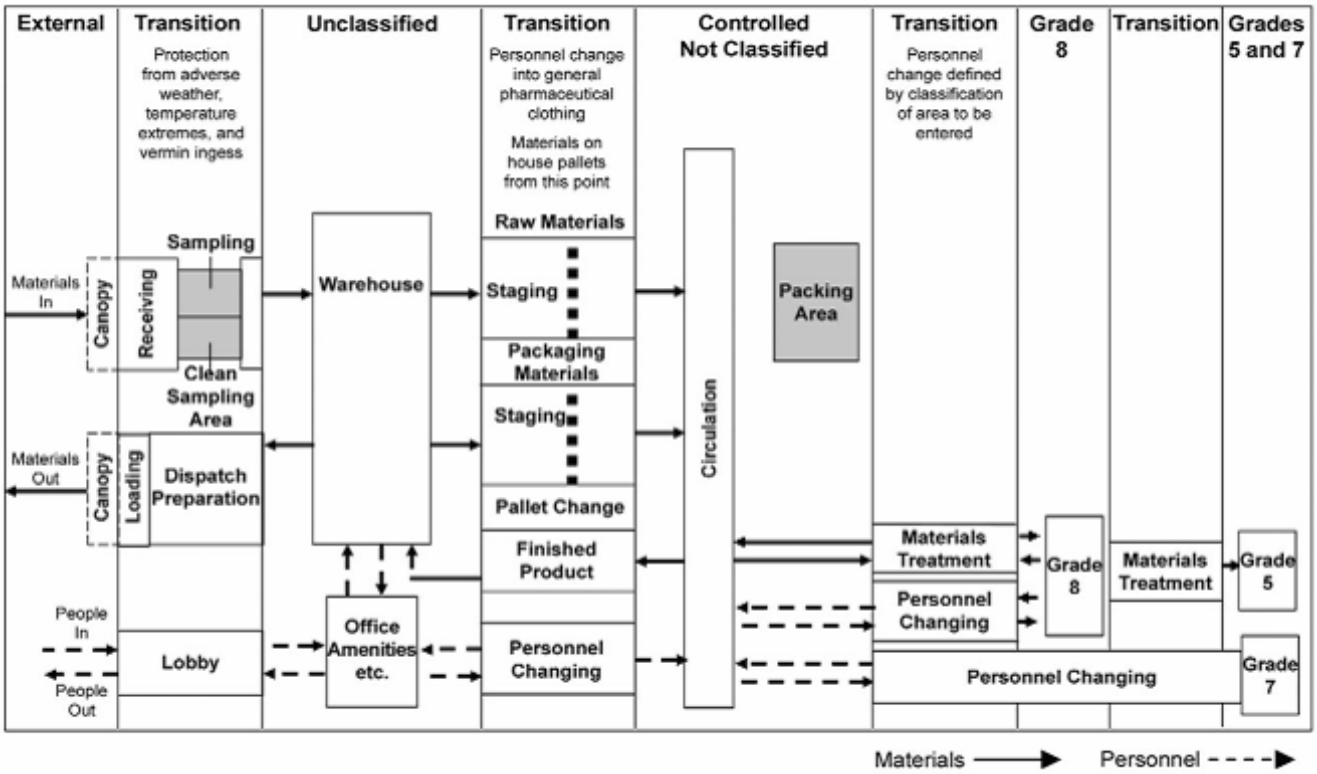


Figure 1

Flow Diagram of Personnel and Materials

Aseptic Processing

4.1.3 AREA CLASSIFICATION FOR TYPICAL PROCESS STAGES

Table 1 : Steps in Baseline Airborne Environmental Classification for Different Processes (Note: all air classifications refer to the “in operation” condition).

Steps in Baseline	Aseptically Processed Products		Terminally Sterilized Products	
	Background Environment	Product/Container /Closure Exposure	Background Environment	Product/Container /Closure Exposure
Raw Material Dispensing	“Grade C”	Local Protection	“Grade C”	“Grade C”
Compounding and (Sterile) Filtration Feed	“Grade C”	“Grade B”	“Grade C”	“Grade C”
(Sterile) Filtration	“Grade B”	“Grade A”	“Grade C”	“Grade A, B, or C”
Initial Prep/Washing Components	“Controlled not Classified with local monitoring”			
Final Rinse of Components	“Grade C”	“Grade C”	“Controlled Not Classified with local monitoring”	“Grade C”
Sterilization/Depyrogenation of Components – Loading	“Grade C”	“Grade C”	“Controlled Not Classified with local monitoring”	“Grade C”
Sterilization/Depyrogenation of Components – Unloading	“Grade B”	“Grade A” (or wrapped/sealed)	“Grade C”	NA
Aseptic Compounding and Formulation of Sterile Materials	“Grade B”	“Grade A”	NA	NA
Filling and Stoppering (for Open Aseptic Processing)	“Grade B”	“Grade A”	“Grade C”	NA
Filling and Stoppering (for Closed Aseptic Processing)	“Grade C”	“Grade A”	NA	NA
Lyophilization – Operation	-	Closed System	NA	NA
Transfer into and out of Lyophilizes (for Open Aseptic Processing)	“Grade B”	“Grade A”	NA	NA
Transfer into and out of Lyophilizers (for Closed Aseptic Processing)	“Grade C”	“Grade A”	NA	NA
Capping and Crimping (of Product Containers)	“Controlled Not Classified with local monitoring”	Local Protection	“Controlled Not Classified”	Local Protection
Terminal Sterilization	NA	NA	“Controlled Not Classified”	NA
Inspection	“Controlled Not Classified”	NA	“Controlled Not Classified”	NA
Labeling and Packing	“Controlled Not Classified”	NA	“Controlled Not Classified”	NA

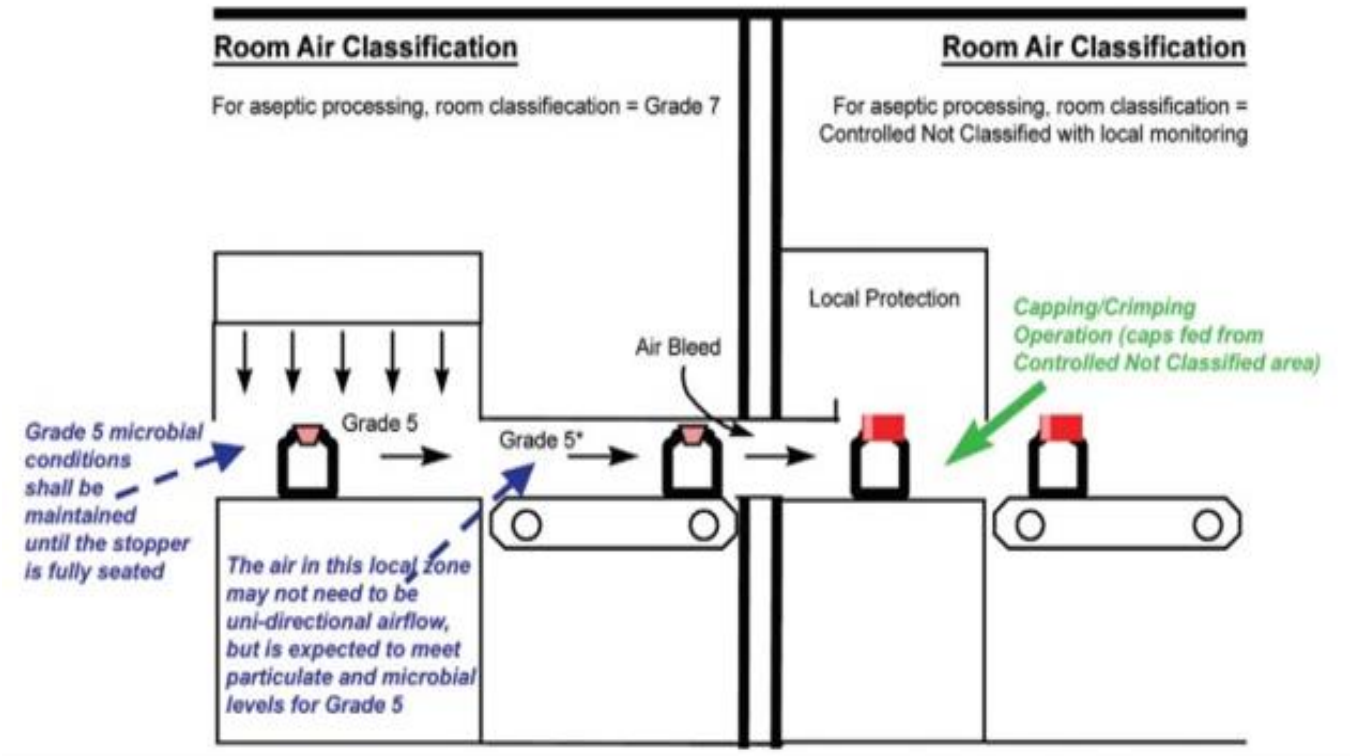


Figure 2
Baseline Environmental Requirements for Capping/Crimping Operations for Aseptically Processed Products

4.1.4 DESIGN CONSIDERATION FOR ARCHITECTURAL/FINISHERS MATERIAL IN DIFFERENT GRADES OF AREA

4.1.4.1 FLOORS

4.1.4.1.1 CNC: CONTROLLED NOT CLASSIFIED

- Standard construction practice is generally appropriate.
- Typical materials include sealed concrete or coatings with a high level of wear resistance, and to prevent dust generation.

4.1.4.1.2 GRADE D

- Standard construction practice is generally appropriate.
- Typical materials include sealed concrete, epoxy coatings, vinyl composition tile, welded seam vinyl, and terrazzo.
- Surfaces should be easily cleanable.

4.1.4.1.3 GRADE C

- Surfaces should be smooth and cleanable.
- Typical materials include sealed concrete, epoxy coatings, vinyl composition tile, welded seam vinyl, chemically resistant coatings, and terrazzo.
- Capped floor drains.

4.1.4.1.4 GRADE B & GRADE A

- Should not have joints or seams where microbial growth may occur.
- Should provide a solid, non-porous, clean, and sanitizable surface.
- Typical materials include terrazzo, welded seam vinyl and epoxy floor systems.
- Coved wall bases integral with the floor system.
- Floor drains and sinks are not permitted.

4.1.4.2 INTERIOR WALLS

4.1.4.2.1 CNC: CONTROLLED NOT CLASSIFIED

- Not required to separate operations, if installed typical materials include wire mesh, gypsum board, and concrete block.
- Note that as a method of separating stored materials, devices such as stanchions, chains, and moveable partitions are acceptable if proper production materials identification procedures are in place.

4.1.4.2.2 GRADE D

- Standard construction practice is generally appropriate.
- Typical materials include concrete block, gypsum board, metal panels, and glazed tile. Surfaces should be finished with a material appropriate to the necessary durability and cleanability requirements.

4.1.4.2.3 GRADE C

- Wall construction should provide a solid, non-porous surface.
- Typical substrate materials include concrete block, gypsum board and metal panels.
- Surfaces should be finished with a material appropriate to the necessary durability and cleanability requirements.

4.1.4.2.3 GRADE B & GRADE A

- Operationally classified cleanrooms require crevice free, smooth, non-porous, robust wall construction, and must not have joints or seams where microbial growth may occur.
- Aseptic processing areas are subject to rigorous cleaning and bio-decontamination regimes.
- Surfaces must be resistant to corrosion and degradation from the agents used.
- Typical materials include gypsum board finished with paints of chemically resistant coatings, welded seam vinyl or sprayed on wall finishes, and panel systems with metal or vinyl surface finishes.
- Curved/rounded corners are used to enhance cleanability.

4.1.4.3 CEILINGS

4.1.4.3.1 CNC: CONTROLLED NOT CLASSIFIED

- Ceilings are generally not required in these areas if material or product is not exposed (e.g., generally in a warehousing environment).
- A lay-in type ceiling is recommended for personnel areas where room pressure is low.

4.1.4.3.2 GRADE D

- Ceilings are generally required in these areas.
- Typical material includes suspended grid systems (Mylar encapsulated panels, fiber glass, reinforced panels, metal, or other cleanable, non-porous surface).

4.1.4.3.3 GRADE C

- Should provide required level of protection from contaminants from non-environmentally controlled areas, i.e., above the ceiling space.
- Typical materials include sealed (i.e., caulked in place) suspended grid systems (Mylar encapsulated panels, fiberglass reinforced panels, metal, or other cleanable, non-porous surface), sealed/painted gypsum board, and metal panels clipped in place to hold room pressure.
- Surfaces should be non-porous and easily cleanable.

4.1.4.3.4 GRADE B & GRADE A

- Should not have joints or seams where microbial growth may occur.
- Typical materials include gypsum board, finished with paints or chemical resistant coatings, welded seam vinyl or sprayed on wall finishes, panel systems with metal or vinyl surface finishes.
- Should provide a smooth, solid, cleanable, sanitizable, non-porous surface.
- Fixtures (lights, diffusers) should be flush mounted or not have any horizontal surfaces exposed below the ceiling; maintenance access from outside the room should be considered.
- Where possible, sprinkler heads should be recessed and, where feasible, capped to promote cleanliness, but not caulked.
- Grade A aseptic processing cleanrooms usually require Unidirectional Airflow (UAF). In order to achieve this, the ceiling is formed of a grid holding a horizontal array of HEPA filters. Air passes through the filters at a defined velocity to ensure the required uniform UAF is achieved.

4.1.4.4 JUNCTION DETAILS: (FLOOR/WALL, WALL/WALL AND WALL/CEILING)

4.1.4.4.1 CNC: CONTROLLED NOT CLASSIFIED

- Standard construction details are generally appropriate.

4.1.4.4.2 GRADE D

- Coved or splayed integral floor bases are not required; baseboards are suggested to protect wall bases, particularly when materials such as sealed gypsum board are used.
- Rounded wall/wall and wall/ceiling details are not required

4.1.4.4.3 GRADE C

- Coved or splayed integral floor bases are not required, but are commonly used to enhance cleaning ease and to protect wall bases, particularly when materials such as gypsum board is used.
- Rounded wall/wall and wall ceiling details are not required, but are commonly used to enhance cleaning ease.

4.1.4.4.4 GRADE B & GRADE A

- Caulked coved and splayed integral floor bases should be provided.
- In addition, wall/wall and wall/ceiling covings should be provided.

4.1.4.5 DOORS AND WINDOWS

4.1.4.5.1 CNC: CONTROLLED NOT CLASSIFIED

- Should meet general building code requirements.

4.1.4.5.2 GRADE D

- Should meet general building code requirements.

4.1.4.5.3 GRADE C

- Typical materials include metal with a painted finish, fiberglass reinforced panels in high wash-down or corrosive areas.
- Vision panels may be glass (regular or reinforced), Plexiglas, Lexan, or equivalent materials.
- Horizontal surfaces should be accessible for easy cleaning.
- Flush glazing is not required, but should be considered to enhance cleanability.
- Meet building codes.
- Drop sills on doors not needed if HVAC can accommodate leakage.

4.1.4.5.4 GRADE B & GRADE A

- Should meet building codes.
- Typical materials include metal, vinyl, PVC, or similar finish.
- Vision panels may be glass (regular or reinforced), Plexiglas, Lexan, or equivalent material.
- All surfaces should be designed and constructed to be accessible for cleaning.
- Stainless steel may be used for construction of the door, hardware, and kick/mop plates, but this is not mandatory.

4.1.4.6 DOOR HARDWARE

4.1.4.6.1 CNC: CONTROLLED NOT CLASSIFIED

- General purpose hardware, as required to comply with building and related codes.
- Suitability for industrial use is recommended.

4.1.4.6.2 GRADE D

- General purpose hardware, as required to comply with building and related codes.
- Suitability for industrial use is recommended.

4.1.4.6.3 GRADE C

- Designed to promote and provide access for cleaning.
- Typically, plated metals or stainless steel.

4.1.4.6.4 GRADE B & GRADE A

- Recessed and concealed, where possible, accessible for cleaning.
- Typically, plated metals or stainless steel.

4.1.4.7 LIGHTING FIXTURES

4.1.4.7.1 CNC: CONTROLLED NOT CLASSIFIED

- Industrial fixtures can be mounted suspended from the structure.

4.1.4.7.2 GRADE D

- Fixtures can be flush mounted or surface mounted tight to the ceiling to avoid any horizontal surfaces below the ceiling.

4.1.4.7.3 GRADE C

- Fixtures can be flush mounted or surface mounted tight to the ceiling to avoid any horizontal surfaces below the ceiling.

4.1.4.7.4 GRADE B & GRADE A

- Fixtures must be sealed to prevent contamination, and in Grade A areas, positioned to avoid disturbance of the Unidirectional Airflow (UAF).
- Consideration should be given to providing maintenance access from outside the area.

4.1.4.8 FIRE PROTECTION SPRINKLERS (WHERE REQUIRED BY CODES OR INSURERS)

4.1.4.8.1 CNC: CONTROLLED NOT CLASSIFIED

- Sprinkler systems can be conventional wet or dry systems, with exposed range pipes and sprinkler heads.

4.1.4.8.2 GRADE D

- Sprinkler systems can be conventional wet or dry systems, with concealed range pipes and conventional sprinkler heads passing through the ceiling.

4.1.4.8.3 GRADE C

- Sprinkler systems can be conventional wet or dry systems, with concealed range pipes and conventional sprinkler heads passing through the ceiling.
- Where there is a concern about ceiling, so called recessed or flush-heads should be considered.
- It is essential to avoid caulking or fixing the flush-head cap in any way.

4.1.4.8.4 GRADE B & GRADE A

- Sprinkler systems can be conventional wet or dry systems.
- In order to facilitate cleaning and bio-decontamination, so-called recessed or flush-heads should be considered.
- In Grade A areas, specialized sprinkler heads that do not disrupt unidirectional airflow should be used.

4.1.4.9 PENETRATIONS (THROUGH WALLS, FLOORS AND CEILINGS, INTO THE ROOM SPACE)

4.1.4.9.1 CNC: CONTROLLED NOT CLASSIFIED

- Sealing is generally not required, except as necessary for fire resistance and thermal requirements.

4.1.4.9.2 GRADE D

- Should be sealed with caulk to prevent contamination between areas, with escutcheon plates suggested.

4.1.4.9.3 GRADE C

- Should be sealed with caulk (silicone caulk generally acceptable) to prevent contamination between areas, with escutcheon plates recommended.
- If a fire-resistant sealant is required, it should be installed with silicone (or similar) caulking installed over its surface, or covered by an escutcheon plate if the fire-resistant material does not provide a smooth finish.

4.1.4.9.4 GRADE B & GRADE A

- Penetrations should be sealed.
- Silicone caulking is generally acceptable.
- If a fire-resistant sealant is required, it should be installed with silicone (or similar) caulking installed over its surface, or covered by an escutcheon plate if the fire-resistant material does not provide a smooth finish.

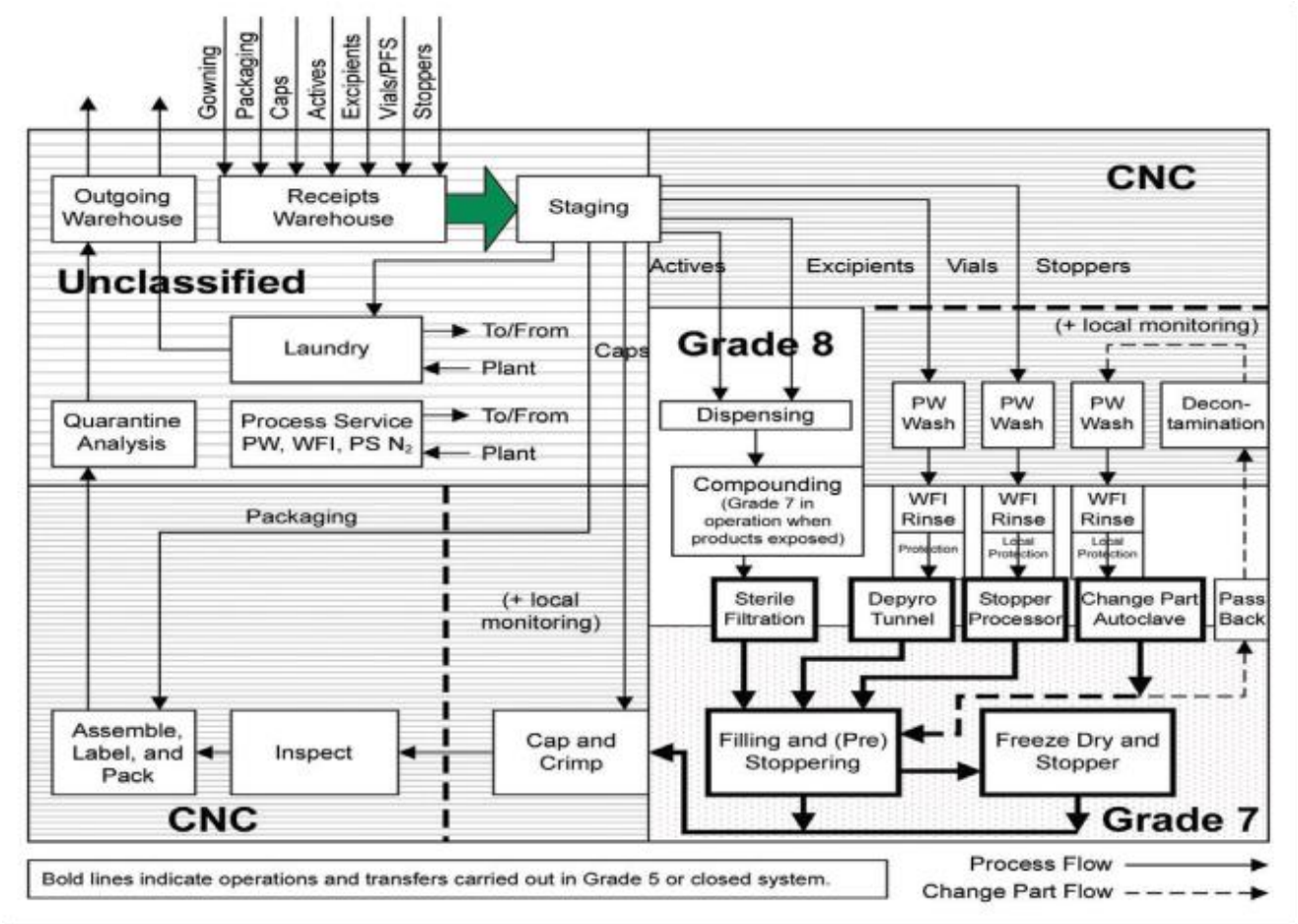


Figure 3

Baseline Environmental Requirements for Capping/Crimping Operations for Aseptically Processed Products

4.2 Oral Solid Dosage Forms Facility Design – Architectural

4.2.1 Introduction

This chapter provides a guide for requirements to be considered for OSD facility design and construction regarding building programs, building layouts, space definition, details, and finish materials. These aspects of the facility are developed in the context of GMP, risk, and process requirements in order to establish baseline guidance and parameters.

4.2.2 High Level Considerations

The architectural design of an OSD facility, both in layout and detail, is influenced by key product and process fundamentals. These fundamental requirements have an overriding impact on the design and should be understood and addressed in a facility and unit operation context when developing the design. The high-level considerations include :

- CGMP risk.
- Product and process characteristics.
- Material.
- Personnel and waste flows.
- Environmental health and safety aspects of the process and product.

4.2.3 CGMP Risk

The degree of CGMP risk is related to the :

- Level of material and product exposure.
- Potential for cross-contamination.
- Material and product hazard characteristics.
- Number of products.
- Level of production activity.

Risk should be minimized architecturally by providing appropriate space, designing for logical material and personnel flows, and designing for appropriate segregation within the building layout, as well as providing appropriate materials of construction and finishes. Appropriate space should accommodate manufacturing unit operations, manufacturing support functions, staging, and storage requirements. These functions are potentially more specialized and discrete as the level of risk increases. The facility design should provide for cleaning and maintenance operations. As risk increases, the cleaning routine and maintenance concerns may have a more significant impact on the design. The flow of all materials, including waste, parts, equipment information, and personnel through the building, should be of a logical and efficient design, promoting product control and necessary segregation, as well as operational efficiencies. Segregation and control requirements may rise as the level of CGMP risk increases.

The facility layout should accommodate suitable locker, gowning, corridor, doorways, and air lock arrangements (if required), providing controlled access and necessary segregation between CGMP areas and non-CGMP areas, and also between CGMP areas of dissimilar risk. The appropriate room materials and details should be developed to promote the established segregation, containment, and cleaning requirements. As the level or risk increases, the segregation, containment, and clean ability of materials may become more critical as determined by the level of risk.

4.2.4 Material Flow

Material flow is considered a critical element in the development of the layout of an OSD facility. The facility should enable the material flow process. The types of material transfer technologies employed, the frequency of transfer, and the quantities of materials transferred are important parameters that affect layout detail. Material transfer technologies include gravity transfer, pneumatic/vacuum transfer, and bin/container transfer. Facilities are normally driven by the primary method of material flow, but may incorporate other transfer options within the overall design.

Specific attributes of facilities designed to a governing material transfer technology may be as follows :

- Gravity Transfer: facilities designed to accommodate gravity transfer are developed as vertical facility arrangements with high-bay or multi-floor designs and stacked process operations. The direct gravity flow of materials avoids material handling operations between process unit operations where they are not restrained by intermediate batch or staging requirements.
- Pneumatic/Vacuum Transfer: pneumatic/vacuum transfer of materials provides opportunity to limit material movement space requirements and reduce operator presence, transfer time, and works well within horizontal facility arrangements. The process concerns of cleaning and material segregation are often limiting factors in the use of these technologies.
- Bins/containers: where materials are transferred in containers, a key decision is to provide Intermediate Bulk Containers (IBCs) in which the material can be subject to particular unit operations (e.g., bin blending), or provide transfer only containers such as drums. The container movement and manipulation, staging, storage, charging,

Discharging, blending, and cleaning requirements should be integrated into the overall facility design.

The method of material tracking should be incorporated into the facility design. The material within the bin/container and state of the bin/container may be tracked through paper-based procedures or electronically using bar code or tagging systems. The staging and docking space should be coordinated with the tracking system and the related protocols.

Key design criteria associated with the material flow and building arrangement include :

- Provision of logical, direct, and sequential flow, minimizing the potential for mix-up of materials and products.
- Provision of logical flow of dirty and clean equipment and components and avoid common staging areas.
- Minimization of movement distance.
- Provision of adequate protection against cross-contamination.
- Minimization of material handling steps.
- Provision of adequate staging and access.
- Provision of doorways, airlocks, and gowning points to support GMP controls and environmental conditions.
- Provision of adequate space to facilitate ergonomic material movement, e.g., lifting of bins, corridor, and door widths.

4.2.5 Product/Process Characteristics

Product/process characteristics with architectural impact include :

- Product hazard characteristic
- Explosivity
- Light/UV sensitivity
- Hygroscopicity
- Flowability
- Cleanability
- Chemical reactivity
- Product classification

Some of these characteristics may vary through the process steps and should be addressed at the appropriate unit operations. The requirements are inherent to the process and impact overall facility design and detail.

Product hazard characteristics affect layout by the requirement for specific features, identified in a risk assessment. Such features may include additional material and personnel air locks, gowning rooms, and spatial requirements for equipment and environmental sampling and testing.
Material explosivity affects layout by the potential requirement for facility blast resistant design and construction, the accommodation of explosion suppression equipment and containment systems. The specific requirements for each facility and system will be defined by code, guideline, and insurance regulation.

Light/UV sensitivity influences both natural lighting and building lighting systems and should be incorporated into the layout, lighting design, and detail aspects of the building. Hygroscopic sensitive materials have an effect on architectural detail and layout arrangement. This includes providing appropriate vapor barriers, as well as necessary airlocks to segregate low humidity areas from higher humidity areas.

Flowability is a process impact characteristic which affects transfer requirements. This may be critical in determining fundamental design criteria, such as horizontal versus vertical process flow/building arrangements, floor-to-floor height parameters, and mezzanines supporting a specific unit operation.

Cleanability may affect the architectural room design. All production rooms will be subject to a cleaning routine. The greater the exposure of materials to the room environment, the greater the risk of room contamination and the likelihood of a more demanding cleaning routine. Materials and details should be selected to support and withstand the prescribed cleaning materials and methods.

Chemical reactivity of production materials should be understood at the room level with the appropriate finish and substrate provided to resist degradation. Finishes that will require periodic repair and replacement should be avoided, and if such is selected, the effect on ongoing operations should be understood.

4.2.6 Health, Safety, and Environment

For an overview of HSE and controlled substance considerations, see Chapter 10 of this Guide.

Items to consider in HSE assessments include :

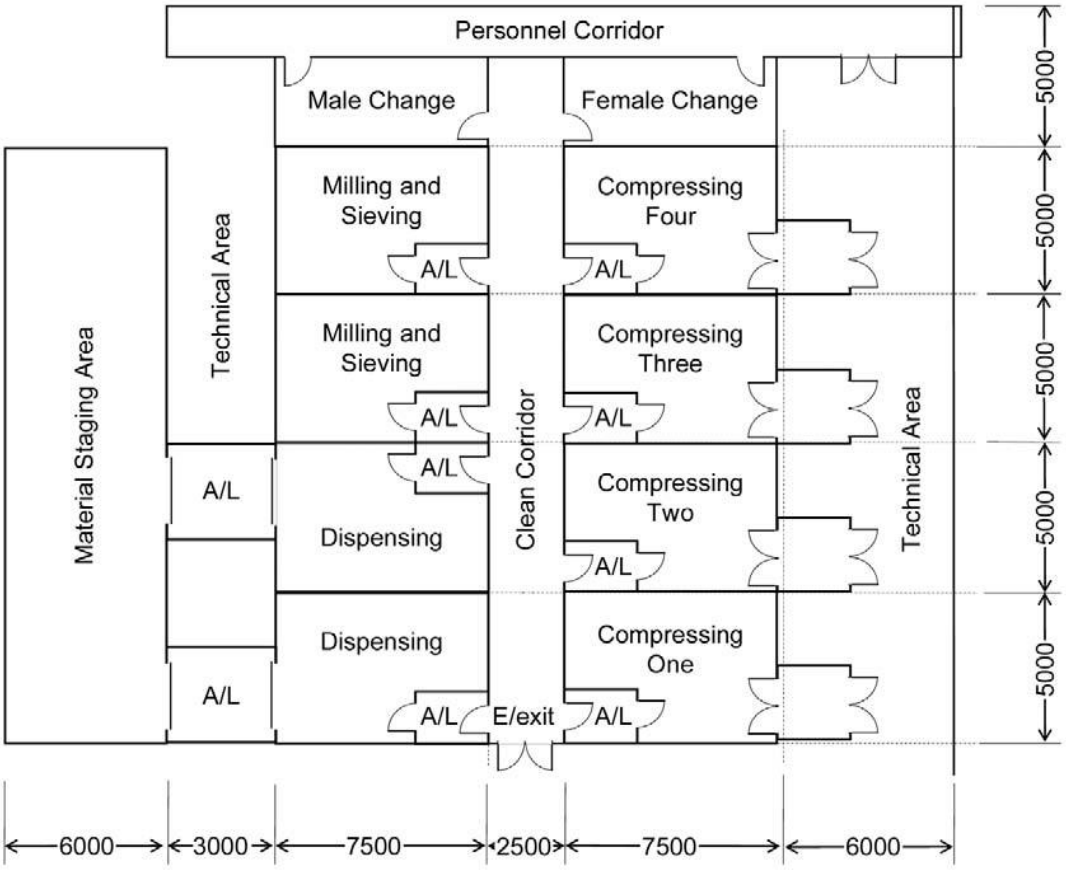
- Highly hazardous materials.
- Controlled substances.
- Hazardous operations.
- Environmental protection.

Each of these aspects should be understood and assessed and the facility designed appropriately. When designing for the processing of highly hazardous materials, a risk assessment should be performed to determine the containment and segregation requirements. Layout may need to allow for containment equipment, while considering safe and ergonomic operation, and the possible requirement for secondary protection measures.

Secondary protection measures could include :

- Specific segregation requirements (for materials, personnel, equipment, and waste).
- Additional air locks.
- Mist showers.
- Gowning rooms.

These measures should help to prevent migration of airborne or surface contamination from process areas into non-process areas. Requirements for support facilities, such as occupational health and PPE/RPE storage rooms, also may affect layout. In addition to CGMP requirements, controlled substances are classified and regulated by other regulatory agencies (e.g., the DEA in the USA). Security and control may involve space monitoring and surveillance, access restrictions, and specialized storage requirements. Process contact waste handling and exhaust systems may require specialized control and capture detailing. Hazardous operations may involve design considerations of individual pieces of equipment, a room, a portion of a building, or a complete building. Local and national codes should be consulted. Further details are required to address areas of hazard, including fire separation, spill control, firewater containment, and damage limiting construction. In addition to the design requirements and safeguards associated with applicable regulations and Fire and Building Codes, many insurance companies have additional requirements for maintaining facilities, and reducing the risk of business interruption. The appropriate insurance carrier should be consulted early during the design stage of the project to incorporate specific requirements.



Example of a Typical Conceptual Layout

4.3 HEATING VENTILATION AND AIR CONDITIONING (HVAC) SYSTEM DESIGN

4.3.1 Refer Chapter 2 of the Guidance document on HVAC design for more details.

4.4 UTILITY SYSTEMS

4.4.1 Utility systems used in sterile facility operations may be categorized as either Process Systems or Process Support Systems. This will provide the basis for determining the design, construction, commissioning, verification, and documentation requirements for the system.

4.4.2 PROCESS SYSTEMS

4.4.2.1 Process systems are systems that contact the product, contact materials that ultimately will become part of the product, control contamination of surfaces that contact the product, and/or could otherwise directly affect product quality as determined through a risk assessment process.

4.4.2.2 Process systems are considered to affect patient safety and product quality, and should be designed, constructed, commissioned, and verified to provide a service that meets a defined specification (considering product quality requirements), and prevent product contamination accordingly.

4.4.2.3 Selection of materials for fluid storage and distribution systems should take into account the nature of the fluid being conveyed. For non-corrosive liquids and gases, such as nitrogen, typical materials include copper, plastics, and stainless steel. The sterile product manufacturer should consider what type of cleaning and sterilant (if required) will be used. For example, if the nitrogen is a sterile feed to a vessel for blanketing, stainless steel would be used at least from the point of final filtration downstream to permit steam sterilization. If, however, the nitrogen manifold in the room merely requires a surface sanitization, chemical resistant plastics, which do not absorb, react, or add to the material being conveyed, could be acceptable.

4.4.2.4 Care should be taken to locate as much of the service components and piping outside the aseptic area as possible. Any surfaces inside the cleanroom will need to be sanitized or sterilized.

4.4.2.5 The engineer should consider the environmental conditions in which process systems can be located. For example, the design of a hydrophobic vent filter, e.g., housing, location etc., on a Water for Injection (WFI) storage tank should consider how the vessel's integrity is maintained or assured during filter maintenance.

4.4.2.6 For examples, purified water, WFI, and clean steam normally are categorized as process systems in that they are used in the manufacturing process itself. (See the ISPE Baseline® Guide for Water and Steam Systems and the ISPE Good Practice Guide for Commissioning and Qualification of Pharmaceutical Water and Steam Systems (Reference 12 and 14, Appendix 3)). Heating/cooling systems for a dehydrogenation tunnel, filling line, etc., would be categorized typically as process systems. (As the heat transfer medium, air does make contact with product contact components).

4.4.3 PROCESS SUPPORT SYSTEMS

4.4.3.1 Process support systems are systems that do not contact the product or materials that ultimately will become part of the product, are generally site or building systems that are not specifically tailored to sterile manufacturing operations, deal with an ancillary manufacturing process (e.g., waste disposal), and do not explicitly affect product quality as determined through a risk assessment process.

4.4.3.2 Process support systems generally do not affect patient safety and product quality, and should be designed and constructed in compliance with Good Engineering Practice and applicable codes and standards. Such systems typically are not located within a cleanroom, and, therefore, the materials of construction depend upon service requirements. If these services or their points of use have to be located in the aseptic area, the materials of construction should be:

4.4.3.2.1 Non-additive.

4.4.3.2.2 Non-reactive.

4.4.3.2.3 Non-absorptive.

4.4.3.2.4 Able to withstand repeated sanitation with harsh chemicals.

4.4.3.2.5 Care also should be taken to prevent accidental spills and possible contaminant release into the area (e.g., point-of use or vent filters for an instrument air supply line where instrument air may vent into a Grade A critical zone).

Table 2 : General Guidance on Typical System Classifications

System	Type: Process (P) or Process Support (PS)	GMP Important	Documentation/ Commissioning	Filter Requirements (Baseline)
Purified Water and WFI	P	Yes	Enhanced/Qualified	NA
Clean Steam	P	Yes	Enhanced/Qualified	NA
Nitrogen and Other Process Gases	P	Yes	Enhanced/Qualified	▪ Endpoint 0.2 µm ▪ Process Gases for sterility, 5 µm for ▪ Pre-filtration
Instrument Air	PS	No	▪ Good Engineering NA unless vented ▪ Practice (GEP)	▪ NA ▪ (unless vented to a Grade A zone)
Breathing Air	PS	No	GEP	NA
Heating/Cooling System for Process Equipment	P	Yes	Enhanced/Qualified	NA
Process Vacuum	P	Yes	Enhanced/Qualified	NA
Potable Water and Plumbing Drains	PS	No	GEP	NA
Mechanical Seal Fluids	Depends on use	Depends on use	GEP	NA
Chilled Water	PS	No	GEP	NA

4.4.4 MULTIPLE CATEGORIZATION

4.4.4.1 The design of systems that can be multi-categorized should be considered with regard to the cost/benefit derived from installing separate utility systems or distribution networks versus special treatment at points-of-use. Filters, with break tanks or non-return valves, are common applications. For example, a compressed air system may be used as both a process and a process support system. If there are many manufacturing uses, there may be economical justification for running separate compressed air systems throughout the facility. If there are only a few manufacturing uses, utilizing a process support system with point-of-use filters and stainless steel piping after the filter at the manufacturing use points may be the more economical design. Due consideration should be given to the upstream piping materials to ensure that the air quality is not compromised (e.g., use of low arsenic copper).

4.4.4.2 For example, if compressed air is used to operate a vial filler, and the pressure of the air dictates the line speed, independent of fill volume, then due consideration should be given to a substantive qualification regime, with high and low pressure alarms for the service.

4.4.4.3 These systems should be designed and constructed in compliance with Good Engineering Practice and applicable codes and standards.

4.4.5 SPECIFIC SERVICE CONSIDERATIONS

4.4.5.1 PURIFIED WATER AND WFI

4.4.5.1.1 Water used in the manufacture of sterile pharmaceutical parenteral products must meet USP Water for Injection (WFI) grade requirements or relevant pharmacopeial standard. Water used for cleaning product contact surfaces should be from a controlled source and meet WFI standards during the final rinse or rinses. Water used to clean non-product contact surfaces must not increase the background flora within the facility. Water used for initial rinsing, but not final rinsing, needs to comply with USP Purified Water requirements.

4.4.5.1.2 Additional water system information is contained in the ISPE Baseline® Guide for Water and Steam Systems, and the ISPE Good Practice Guide for Commissioning and Qualification of Pharmaceutical Water and Steam Systems (Reference 12 and 14, Appendix 3).

4.4.5.1.3 Refer “Guideline for the water system design and controls; Current version” for detailed water design concepts.

4.4.5.2 CLEAN STEAM

4.4.5.2.1 Clean steam must be free of boiler additives and have no impurities beyond that of the water used in production. The condensed steam must meet WFI specifications and clean steam must be made from a controlled source feed.

4.4.5.2.2 Design practices (such as sloping lines and minimizing steam traps) should eliminate potential microbial growth in condensate within the system. Process steam for sterilization should contain minimal superheat entering the autoclave.

4.4.5.2.3 Non-Condensable Gases (NCGs) should be controlled by preheat/pretreatment of feed-water or vented from the system, ideally at the steam generator. The values for NGCs, dryness fraction, and superheating of the steam supply should be periodically tested and controlled within specified limits where the steam is used for the direct sterilization of product contact equipment and components.

4.4.5.3 NITROGEN AND OTHER PROCESS GASES

4.4.5.3.1 If process gas is to be used in aseptic or sterile areas, it must be sterile-filtered at the point of use. The filter and downstream components will require sterilization or sanitization, as well as in situ integrity testing on a regular basis. If the service is not used in an aseptic process, but is a process support utility, standard materials of construction may be used. The following summarizes process gas system design considerations:

4.4.5.3.1.1 Process gas quality should meet product specification.

4.4.5.3.1.2 Materials of construction should be compatible with any external sanitizing agents or internal sterilants (steam), thus stainless steel is recommended in these areas; plastic, plastic lined steel, and copper may be suitable.

4.4.5.3.1.3 5 µm or better pre-filtration is recommended, although 0.2 µm filtration is required at point-of-use, if it is an aseptic or sterile application.

4.4.5.3.1.4 The gas distribution system design should include sampling points. Sterile-filtered points of use should also permit downstream aseptic sampling for physical and biological quality.

4.4.5.3.1.5 Backflow from other systems into process gas systems should be prevented.

4.4.5.3.1.6 Clear and visible labeling of process gas systems, to minimize risk of connecting to the wrong gas.

4.4.5.3.1.7 Terminal filters for compressed air and nitrogen system should have SS housing.

4.4.5.4 COMPRESSED AIR

4.4.5.4.1 PROCESS COMPRESSED AIR

4.4.5.4.1.1 Compressed air, such as used for blowing product or venting sterilizers, should be treated as a process gas.

4.4.5.4.2 INSTRUMENT AIR

4.4.5.4.2.1 Properly designed and maintained systems should not allow instrument air to come into contact with product; hence, these systems should be designed in accordance with good engineering practice. Care should be taken to vent instrument air away from Grade A areas, so as to preserve low particulate and microbial levels in the environment.

4.4.5.4.3 BREATHING AIR

4.4.5.4.3.1 Breathing air is a process support system, important for operator safety within a sterile manufacturing facility. The maximum allowable contaminant levels allowed by Occupational Safety and Health Administration (OSHA) and the Canadian Standards Association (CSA) are shown in Table no. 3. Other limits may also apply (such as dew point). Other countries may have their own standards. Point of use filtration may be required.

Table 3 : Breathing Air Contaminant Levels

Contaminant	OSHA	CSA
Carbon Monoxide ppm v/v	20	5
Carbon Dioxide ppm v/v	1000	500
Oil (condensed hydrocarbons)	5	1

4.4.5.5 HEATING AND COOLING SYSTEMS

4.4.5.5.1 Heating and cooling systems, including cooling and chilled water, glycol systems, and heat transfer fluid systems, do not contact the product, and, hence, should be designed in accordance with GEP. This assumes that equipment used for indirect heat transfer will not leak into the atmosphere or the product. Selection of the heat transfer medium should consider the potential risk of leakage. Provision should be made to monitor such system leakage through pressure testing and level monitoring.

4.4.5.5.2 The designer should consider that a heat transfer fluid that would leak from a tank jacket into a batch of formulated product would contaminate the batch, regardless of the properties of the fluid, so jacket integrity should be assured.

4.4.5.5.3 For temperature sensitive products, the temperature of the heat/cool medium may be a critical parameter if it is not possible to monitor the product temperature at the heat transfer surface.

4.4.5.6 STEAM AND HOT WATER SYSTEMS

4.4.5.6.1 Plant steam and hot water systems should not be used in applications where there is exposure to the product. These systems should be designed using GEP.

4.4.5.6.2 Care should be taken in the selection of boiler additives, especially when plant steam is used for HVAC humidification

4.4.5.6.3 The location of condensate and pressure controlling systems should be in plant areas, not within cleanrooms. It is not recommended to locate these types of devices above aseptic areas, in case of leakage.

4.4.5.7 PROCESS VACUUM SYSTEMS

4.4.5.7.1 If a single vacuum source is used for a mixture of process uses, the contamination risk increases. If vacuum or process exhaust systems are used within an aseptic area, steps must be taken to prevent pressure reversals or reverse flow (e.g., non-return valves or fail-safe vacuum pump/pressure arrangements), and to prevent material dropping from the system into the process. Sanitization or sterilization is recommended for points of use upstream (nearer to the process) of the local vacuum isolation valve. Appropriate steps should be designed to prevent possible cross contamination.

4.4.5.8 POTABLE WATER

4.4.5.8.1 Water used in various parts of the facility for amenities, and not to be used for process reasons, should be designed with GEP. Proper labeling and identification of these types of services is required. Potable water should not be used in the aseptic processing area.

4.4.5.9 MECHANICAL SEAL FLUIDS

4.4.5.9.1 If a pump is used for product transfer, the seal fluid should be of the same quality standards as the product. Typically, for aseptic facilities, sterile isopropyl alcohol, USP Purified, or WFI is used as a seal fluid. If the pump is not for product transfer, but for a process support service, then vendor recommended fluids should be considered. If there is any possibility that the seal fluid will contact the product, a pump with double mechanical seals, or equivalent, should be used.

4.5 ELECTRICAL SERVICES

4.5.1 GMP considerations when designing, selecting, and installing electrical equipment within aseptic processing areas are limited to ensuring that equipment is cleanable, ledge and crevice free, non-shedding, and sealed.

4.5.2 The selection and installation of all electrical equipment and wiring, as a minimum, should be in accordance with applicable local codes. All electrical components and materials should be compatible with the manufacturing process and operations.

Table 4 : Typical GMP Requirements for Electrical Systems

Electrical System	Room Classification		
	Pharmaceutical	Grade C Environments	Grade A and Grade B Environments
Power Distribution	None, outside area	None, outside area	None, outside area
Lighting	Cleanable, ideally non-shedding	Cleanable and sanitizable, minimum ledges, non-shedding, sealed, crevice free	Cleanable and sanitizable, minimum ledges, non-shedding, sealed, crevice free
Outlets and Miscellaneous Equipment	Cleanable, ideally non-shedding	Cleanable and sanitizable, minimum ledges, non-shedding, sealed, crevice free	Cleanable and sanitizable, minimum ledges, non-shedding, sealed, crevice free

4.5.3 Although the criteria for equipment appear to be identical from Grade A to Grade C environments, the degree of these aspects may differ (e.g., equipment in Grade A environments will require a higher standard). Recessed electrical devices will help achieve the standard required in each of these areas.

4.5.4 Sealed components are specified, not only to alleviate the risk of contamination, but also to cope with the different pressure regimes of adjacent rooms. In Grade A environments, the term "sealed" refers to being hermetically sealed, whereas in Grade C environments, the term "sealed" refers to a high degree of protection against the ingress of water and dust.

4.5.5 Electrical equipment within Grade A environments should be kept to an absolute minimum. Any services that can achieve their function by being placed in an adjacent room or area should be so located, e.g., a light switch for the room could be located outside the access door in the corridor.

4.5.6 Regarding the manufacturing process, electrical services may affect patient safety and product quality. Electrical services, therefore, should be designed in accordance with GEP.

4.5.7 POWER DISTRIBUTION

4.5.7.1 Both reliability and stability of the power supply are important.

4.5.7.2 The impact of surges, dips, or total power loss on the overall manufacturing process, HVAC/mechanical services, or individual equipment items, should be studied to determine risk and effects. Generally, the impact is economic (loss of production capacity). If these impacts are considerable, then a standby generator or uninterruptible power supply (UPS) should be considered.

4.5.7.3 For HVAC systems, momentary power losses may not be significant, if there are provisions for fan rotation to continue and room pressures are maintained within acceptance limits for short periods. The impact of any power loss potentially affecting the sterility of the product must be evaluated.

4.5.7.4 Power for monitoring of Differential Pressure (DP) will be a critical issue.

4.5.8 LIGHTING

4.5.8.1 There should be good uniform lighting levels in all manufacturing areas. Minimum levels in the personnel work areas should be no less than 500 lux one meter from the floor.

4.5.8.2 There should be good uniform lighting levels in technical service floor areas. Minimum levels in the personnel work areas should be not less than 300 lux.

4.5.8.3 Fixtures should be designed and selected to be cleanable, non-shedding, ledge free, or sealed, as appropriate for the different classifications of areas.

4.5.8.4 Lighting fixtures in manufacturing areas should be arranged to prevent accumulation of dust and be air tight and sealed to ensure that no foreign matter is released into the manufacturing environment.

4.5.8.5 Recess mounted, or teardrop fixtures may be appropriate in Grade A environments. The installation of surface mounted lighting in unidirectional Grade A airflow zones may interfere with airflow patterns and should be avoided.

4.5.8.6 Where the manufacturing process is open to the room, fixtures should be located so they are not directly above the work area.

4.5.8.7 Sealing properties of the fixtures should withstand water jet pressures in wash down areas.

4.5.8.8 Stainless steel or aluminum fixtures, because they are non-shedding and resistive to corrosive environments, may be considered appropriate. Materials should be compatible with room cleaning agents, which may be corrosive.

4.5.8.9 In Grade B environments, recess mounted fixtures are beneficial, because they can be i installed through the ceiling, with maintenance access provided from a walkable ceiling or floor (plant room) above.

4.5.8.10 Lamps or fixtures, maintained from within the room, may be changed on an annual basis to reduce the effects of unplanned disturbances to production due to occasional lamp failures. Redundant lighting units may also be considered.

4.5.8.11 If color rendition and intensity of lighting equipment used for inspection, or cleaning, etc., is considered critical, appropriate provisions should be made.

4.5.8.12 Emergency lighting should be provided in accordance with applicable local codes. Combining emergency fixtures with normal fixtures help to limit the amount of electrical equipment on ceilings or walls.

4.5.8.13 Since priority needs to be given to the HVAC systems (e.g., air supply diffusers) and services to process equipment, lighting fixtures cannot always be positioned to achieve ideal lighting distribution. Therefore, careful coordination of ceiling services should be considered at the design stage.

4.5.8.14 Design of lighting system depends upon following criteria :

- Light fixtures are decided as per the following mounting heights:
  - Up to 4.00 mtrs.: 45 W, LED lamp fittings
  - 4.00 mto 6.00 m.: 60 W, LED fittings
  - 6.00 m to 9.00 m.: 60 W, LED, mid bay fittings

- LUX levels: the following illumination levels (±10%) are suggested for the plant.
  - Clean room process area/packing area: 500 lux.
  - Airlock/change room/storage: 300 lux.

4.5.9 HAZARDOUS ENVIRONMENTS

4.5.9.1 The selection and installation of electrical equipment within hazardous environments (due to dust or solvent vapor) should comply with applicable local codes. Classification of an area to require explosion proof electrical equipment is likely to be very rare, because of the high air changes requirement and monitoring of the area.

4.5.9.2 Hazardous area classification is not a GMP issue, but the class of room may affect location of production equipment and it also may affect the selection of the electrical equipment. Some electrical equipment may suit a higher class of area in terms of cleanliness.

4.5.9.3 Electrical equipment within these areas should be kept to an absolute minimum. Any devices that can achieve their function while located in an adjacent room should be located externally and will not need to be classified.

4.5.9.4 Provisions should be made in these areas to dissipate possible static build-up on personnel, equipment, and materials. Conductive floors should be installed, if necessary.

4.5.9.5 Flame proof, double compression type, shall be provided for all flame proof equipment. The lugs provided shall be tinned copper crimping type.

4.5.10 WIRING

4.5.10.1 If possible, wiring and wiring accessories should be hidden within the building fabric to improve cleanliness, particularly in higher classification areas. Recessed boxes also would be appropriate in these instances. The number of penetrations through walls, ceilings, or floors for services to equipment should be minimized.

4.5.10.2 Where wiring is installed on the surface, installation should minimize the accumulation of foreign matter and allow easy and effective cleaning.

4.5.10.3 Enclosing wiring in conduit, or trunking, improves the level of cleanliness

4.5.10.4 Lengths of wiring to mobile equipment should be kept to a minimum and should be kept off the floor.

4.5.10.5 Sealing of conduits and trunking may be necessary to reduce the risk of contamination from outside and loss of air from pressurized rooms.

4.5.10.6 Where necessary, as part of the process operations, wiring and glands should withstand washing.

4.5.10.7 All lighting/power cables and wires shall be of XLPE insulated stranded copper conductor as per IS with appropriate color coding for phases, neutral and earth connections. Wherever concealed conduit is involved, the wires shall be of PVC insulated stranded copper conductor.

4.5.10.8 Lighting switches shall be concealed in walls/modular panels at a height of about 1.2m . above ground.

4.5.10.9 In case external earthing is additionally provided, same shall be carried out by using 1C x 2.5mm2 green PVC insulated, stranded copper conductor. All such earthing conductors shall be terminated at respective earthing terminals of LDBs/LSBs and PDB to plug points.

4.5.11 DOOR INTERLOCKS

4.5.11.1 Electrical interlocking of the doors of airlocks or changing rooms assists in maintaining pressure regimes and GMP practices. Alternatively, an audible local alarm could be installed to indicate if more than one airlock door is open at the same time. If interlocks are provided, over-ride features should be included in case of emergency.

4.5.11.2 Door interlock system should be installed across the plant in order to ensure that pressure difference between two areas is maintained within specified range. This will prevent cross contamination between cleaned and uncleaned area.

4.5.11.3 Proximity or "show hand'' sensor should be provided in respective areas which will facilitate opening and unlocking of the door.

4.5.11.4 Emergency button should be provided to override door interlocking.

4.5.11.5 Biometric readers should be provided in some areas to restrict movement to authorized personnel only.

4.5.12 OUTLETS AND MISCELLANEOUS EQUIPMENT

4.5.12.1 Electrical components should be designed and selected to be :

4.5.12.1.1 Cleanable.

4.5.12.1.2 Non-shedding.

4.5.12.1.3 Ledge and crevice-free or sealed.

4.5.12.1.4 Appropriate to the classification (HVAC Grade) of area.

4.5.12.2 Fittings in process areas should be arranged to prevent accumulation of dust, and be air tight and sealed, in order to ensure that no foreign matter is released into the manufacturing environment. Recess mounting of fittings in these areas provides distinct benefits.

4.5.12.3 Installation of aspirated fire detection, or systems able to detect fire within the HVAC extract systems for Grade A environments, may not require installing conventional fire/smoke detection equipment within the room. Flashing lights, in place of conventional sounders, also may be beneficial.

4.5.12.4 Sealing membranes on loudspeaker systems located within Grade A and Grade B environments should be considered. A membrane in the wall between two adjoining rooms may provide acceptable voice communication between those rooms.

4.5.12.4 Sealing membranes on loudspeaker systems located within Grade A and Grade B environments should be considered. A membrane in the wall between two adjoining rooms may provide acceptable voice communication between those rooms.

4.5.12.5 Insectocutors should be placed strategically outside of cleanroom areas to reduce contamination risks from flying insects.

4.5.12.6 Power should be provided for electrically heated (bio-control) traps beneath sinks in Grade C environments, as an alternative to routine chemical sanitization. (Sinks are not permitted in Grade A aseptic processing rooms and are strongly discouraged in Grade B environments).

4.6 CONTROL AND INSTRUMENTATION

4.6.1 Control and Instrumentation (C&I) systems for sterile product manufacturing facilities provide focus on those facility and environment controls which affect patient safety and product quality. The objective is to provide design guidance, which results in cost-effective system designs, capable of being qualified.

4.6.2 C&I systems are used in many facility-related systems. They may be deemed to affect patient safety and product quality if they control, monitor, or record a critical process parameter or directly affect a critical quality attribute. Components of C&I systems may also be considered critical if they come into direct physical contact with the product.

4.6.3 The functions described may be combined within a single C&I system, or be performed by several independent systems.

4.6.4 Specific design advice has been given where possible, but it is stressed that each application will have different priorities and operational preferences that will influence the adopted solution.

4.6.5 It also is stressed that the designer should consider other relevant design criteria, such as safety, reliability, and design for maintenance.

4.6.6 CRITICAL PROCESS PARAMETERS – ENVIRONMENTAL

4.6.6.1 Environmental Conditions within the Production Area

4.6.6.1.1 The production of sterile products requires a clean classified work environment for open, exposed processes. Processes and products will vary greatly. It is likely that particular environmental parameters should be considered, specified, monitored, and recorded as discussed in Chapter 5 of this Guide.

4.6.6.1.2 A number of particulate and microbiological cleanliness requirements, DPs, and airflow requirements are required in the GMPs for particular typical process steps and unit operations. (These are discussed in Chapters 2 and 5 of this Guide).

4.6.6.1.3 If manufacture of several products is proposed, the designer should ensure that the design accommodates the most demanding product requirements.

4.6.6.2 MONITORING AND DOCUMENTING

4.6.6.2.1 Critical process parameters should be monitored and documented.

4.6.6.2.2 Monitoring means that a parameter is periodically (or continuously) measured to ensure it is within its defined limits. This can be accomplished with either permanently installed or portable instruments.

4.6.6.2.3 Documented means that the parameter value (or evidence that the value is within control limits) is recorded at some predefined frequency for future reference. The frequency should be based upon a written rationale that should reflect:

4.6.6.2.3.1 The consequences of manufacturing outside required (process) limits.

4.6.6.2.3.2 The probability and frequency of temporary parameter control loss.

4.6.6.2.3.3 The duration and frequency of activities such as process interventions.

4.6.6.2.4 It should be noted that the probability that a parameter will go out of control will depend largely upon the control system's reliability, complexity, dynamics, and whether it is an active or passive control system.

4.6.6.2.5 In this context, an active control system is deemed to have a control loop with direct feed-back or feed-forward, whereas a passive control system is where a condition is monitored and management action is implemented if needed to rectify the deviation in conditions.

4.6.6.2.6 When critical process parameters are monitored, the monitoring regime should, where possible, be established with alert and action limits. Alert limits provide early warning of a potential deviation enabling corrective or preventative measures to be taken prior to an action limit being reached. (See Section 8.2.3 of this Guide.)

Table 5 : Typical Environmental Parameters and How They are controlled

Critical Process Parameter	Active or Passive Control	Baseline Comments
Room temperature	Always active	Continuous recording recommended.
Room percent RH	Always active	Continuous recording recommended.
Room differential pressure	Active	Active control of pressure differences using actuated control dampers is not recommended by this Guide (see Chapter 5). Where this approach is taken, continuous recording of each pressure differential is recommended.
	Passive	Where pressure differences are passively controlled via proportional air volume balancing and room pressure relief dampers, these could be documented less frequently (i.e., less than continuously for ancillary aseptic processing area rooms). Excursions should be recorded.
Particle count	Passive	Particle count is controlled passively, through such means as filters, low leakage ductwork, personnel control, air change rates. Continuous recording may not be necessary. In addition, see 8.7.3.
Temperature of process environment	Always active	Continuous recording recommended.
Relative humidity of process environment	Specifically controlled or limited by the HVAC psychometrics	Continuous recording recommended.
Room/enclosure pressure differential	Both active control and passive (static air balancing) techniques can be deployed.	Where the pressure differential is an essential part of separation of spaces of different cleanliness class or contamination risk, the pressure differential should be continuously monitored, recorded, and suitable alarms installed. The frequency of monitoring can be related to the criticality of the controlled space; e.g., aseptic processing areas are considered more important than clean preparation or formulation areas, and therefore should be continuously monitored and recorded. Passive (locked damper) control with continuous monitoring is considered to be the technical baseline for room pressure differentials.

4.6.6.3 ALERT AND ACTION ALARMS

4.6.6.3.1 Critical process parameters should remain within specified values. Where monitoring and documenting is necessary, the monitoring system should provide:

4.6.6.3.1.1 An Alert alarm to indicate that the parameter has deviated from the normal operating range (i.e., outside the normal operating conditions – a possible control problem).

4.6.6.3.1.2 An Action alarm to indicate that the parameter has deviated from process limits (i.e., a product quality issue).

4.6.6.3.2 Alarms should "latch" and not be self-canceling (i.e., the alarm remains active even after the condition has been corrected) until acknowledged by a user, or operator. Alarms affecting the quality of the product must be documented.

4.6.6.3.3 Where momentary parameter deviation outside specified limits is acceptable, appropriate time delay intervals can be incorporated into the alarm logic. These should be thoroughly tested and the rationale documented as part of the system qualification.

4.6.6.4 PROCESS LIMITS, DESIGN LIMITS, AND NORMAL OPERATING CONDITIONS

4.6.6.4.1 Process limits are the upper and lower limits demanded by the production process(es).1 Design limits are used to calculate HVAC plant or utility capacity, and are based upon a number of factors, such as:

4.6.6.4.1.1 Operator comfort

4.6.6.4.1.2 Energy conservation

4.6.6.4.1.3 Regulatory requirements

4.6.6.4.1.4 Process limits

4.6.6.4.1.5 What is technically and practically possible

4.6.6.4.2 Normal operating conditions usually are within design limits and become apparent during operation; the extremes of these conditions are defined by the alert limits.

4.6.6.4.3 For example, let us consider a case where the process limits are 22°C ±4°C (71.6°F ±7.2°F). The HVAC system plant is designed to provide 22°C ±2°C (71.6°F ±3.6°F); however, control to within 22°C ±1°C (71.6°F ±1.8°F) is usual. Alert limits can be set at 23°C (71.4°F) and 21°C (69.8°F), as deviation outside these conditions indicates a situation worthy of investigation.

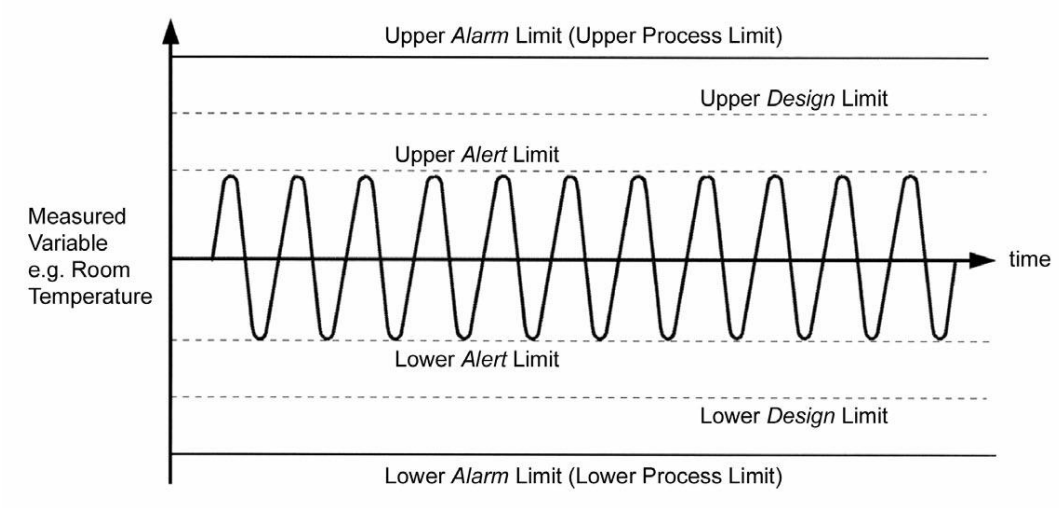


Figure 4
Alert and Alarm Limits

4.6.7 PRODUCTION PROCESS PARAMETERS

4.6.7.1 The number and diversity of production processes that can be used in sterile product manufacturing facilities are such that a comprehensive discussion of their parameters is not practical within the scope of this Guide.

4.6.7.2 Detailed knowledge of the production process in question and application of rigorous design and operation review methods are necessary to identify systems which affect patient safety and product quality and related parameters or conditions.

4.6.8 INSTRUMENTATION

4.6.8.1 PHYSICAL DESIGN

4.6.8.1.1 Instruments in process areas should be located to allow cleaning and sanitization of exposed surfaces and should be designed and installed to prevent accumulation of particulate matter. Computer screens and keyboards located in processing areas should be cleanable, such as utilizing touch membrane technology

4.6.8.1.2 Instruments in direct contact with the product, its components, or associated with a critical manufacturing process should be designed and installed to:

4.6.8.1.2.1 Prevent accumulation of any matter (including product).

4.6.8.1.2.2 Withstand required cleaning/sanitization processes and agents without degradation.

4.6.8.1.2.3 Not present a contamination risk to the product or its components.

4.6.8.1.2.4 Not be degraded (physically or in performance) by contact with the product, its components, or the processes to which it is subjected.

4.6.8.1.2.5 Instruments directly in contact with the product are selected on basis of the following :

- ❖ Instrument technology type.
- ❖ Surface design and finish (internal and external).
- ❖ Metallic alloy selection (corrosion resistance).
- ❖ Non-metallic composition and surface finishes (internal and external).
- ❖ Wetted versus external surfaces.
- ❖ Placement and mounting of instrumentation.
- ❖ Temperature range requirements.
- ❖ Suitability for SIP, WIP, CIP
- ❖ Gaskets, seals, and welds.
- ❖ Smart versus traditional instruments.
- ❖ Need for redundancy.

4.6.8.1.3 Many instruments have sensing elements remote from their data processing components. The use of such instruments allows isolation, separation, or remote location of the processing components. This may simplify cleaning and reduce contamination risk.

4.6.8.2 PERFORMANCE ACCURACY

4.6.8.2.1 Instrument performance is defined using such terms as:

4.6.8.2.1.1 Accuracy

4.6.8.2.1.2 Uncertainty

4.6.8.2.1.3 Resolution

4.6.8.2.1.4 Repeatability

4.6.8.2.1.5 Hysteresis

4.6.8.2.1.6 Response time

4.6.8.2.1.7 Stability

4.6.8.2.2 When assessing an instrument's accuracy, several factors should be considered:

4.6.8.2.2.1 Fitness for purpose.

4.6.8.2.2.2 By how much does the instrument cost increase with accuracy.

4.6.8.2.2.3 How misleading can the instrument be without threatening product quality.

4.6.8.2.2.4 The impact of higher accuracy instruments on the reduction of the risk of manufacture under unsuitable conditions as a result of instrument drift.

4.6.8.2.3 For each critical process parameter, there usually are process limits within which a product should be produced or a process operate. These limits should be defined in pharmacopeias, product registration documents, company standards, or process validation documents.

4.6.8.2.4 C&I systems should be designed to control conditions to a set-point within the process limits, usually with a margin of safety or reserve; these are the normal operating conditions.

4.6.8.2.5 An instrument's indicated value will be subject to uncertainty2 (i.e., subject to the instrument accuracy). For the true condition to remain within process limits, at the indicated extremes of the alert limits, the instrument's accuracy should give a measurement whose uncertainty is no greater than the difference between the process and alert limits. This difference defines the instrument's minimum accuracy requirement, and is the Instrument Permitted Limit.

4.6.8.2.6 Using an instrument with an accuracy greater than the instrument permitted limit allows instrument drift, while remaining within process limits.

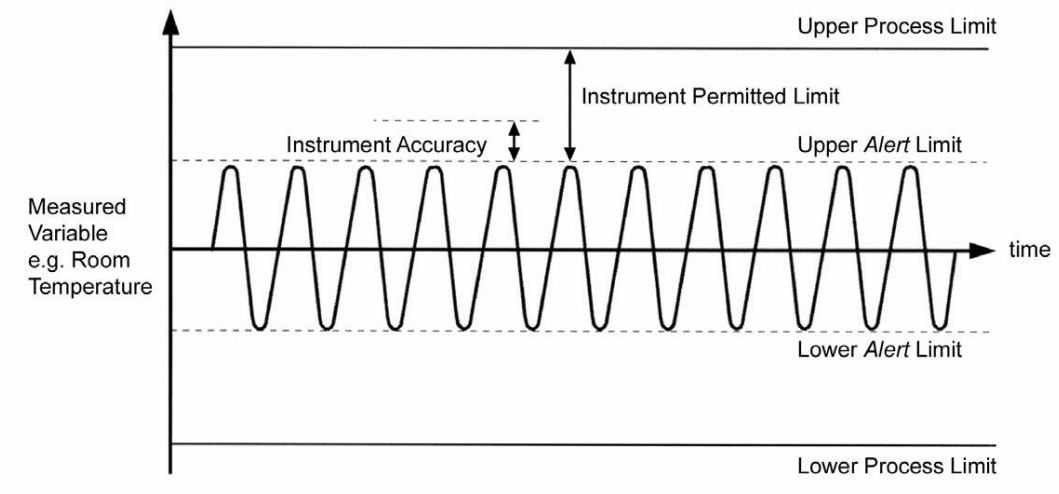


Figure 5
Instrument Permitted Limits

4.6.8.2.7 As an example,, let us consider a temperature control loop associated with a production process. The process limits are 22°C ±2°C (71.6°F ±3.6°F), and alert limits are 22°C ±1°C (71.6°F ±1.8°F).

4.6.8.2.8 To guarantee that the temperature remains within the process limits, at the extremes of the alert limits, the instrument measuring temperature should be accurate to at least ±1°C (±1.8°F). If the instrument drifts outside this accuracy level, production outside process limits could occur.

4.6.8.2.9 If a temperature measuring instrument with accuracy of ±0.5°C (±0.9°F) is used, the instrument can drift by 0.5°C (±0.9°F), and still guarantee manufacture within process limits.

4.6.8.2.10 Using the minimum (i.e., poorest) accuracy instrumentation will require checking of calibration more frequently, or, accepting a higher risk of operating outside the process limits and, consequently, risking product quality. Both options have cost implications that often justify using a more accurate instrument.

4.6.8.2.11 The instrument manufacturer's performance claims should be verified. In general, selecting commonly used instruments from internationally known suppliers should provide a satisfactory confidence level.

4.6.8.3 LOCATION

4.6.8.3.1 Instrument sensors measuring the critical process or environmental parameter(s) for a product or component should be located at a point representative of the condition to be measured.

4.6.8.3.2 Where separate sensors are used to control and monitor the same critical process parameter, they should be collocated to ensure the parameter is equally measured.

4.6.8.3.3 Sanitation and the need for cleanliness also vary within the range of basic pharmaceutical requirements, but typically sensitivity to manufacturing parameters and contamination go hand-in-hand.

4.6.8.4 CALIBRATION

4.6.8.4.1 The calibration method and its cost should be considered when selecting any instrument. Instrument suppliers should be asked to provide comprehensive calibration guidance for their instruments before one is chosen.

Calibration determines how accurate an instrument or sensor is performing. Despite the fact that the vast majority of instruments today are highly accurate, regulatory bodies still need to know the exact extent of an instrument's inaccuracies, measured against specified tolerance levels.

Vast quantity of instruments requiring regular calibration, a process that can be a time-consuming and costly process. Large amounts of calibration data are produced and archived, which must be easily accessible, particularly in the event of an audit.

Calibration management software can make locating records, and verifying that systems work, a more streamlined and automated process entirely. Not only does plant efficiency improve as a result, but unforeseen instrument failures can also be minimized, thus reducing the likelihood of expensive periods of downtime.

Traceability is also an important factor in calibrations. Some instruments need to be measured against the relevant corresponding national standard. The appropriate monitoring and measurements, and required measuring devices, are determined by the organizations themselves to provide evidence of a product’s conformity to standards.

Measurements and monitoring practices are consistent with measurement and monitoring requirements. Using documenting calibrators, results can be automatically stored in the calibrator’s memory and then automatically transferred to a database. The absence of manual inputting leads to a much faster and cheaper process. Analyzing instrument history trend reports based on the stored calibration records helps to inform the optimal calibration interval for a certain instrument.

4.6.9 ELECTRICAL INSTALLATION

4.6.9.1 Wiring and wiring containment system requirements associated with instrumentation are defined in Chapter 7 of this Guide.

4.6.10 GENERAL DESIGN ISSUES

4.6.10.1 Computerized system life cycle activities, such as specification, design, and verification should be scaled according to:

4.6.10.1.1 System impact on patient safety, product quality, and data integrity (risk assessment).

4.6.10.1.2 System complexity and novelty (architecture and categorization of system components).

4.6.10.1.3 Outcome of supplier assessment (supplier capability).

4.6.10.2 The following sections will discuss cost-effective separation of system functions (i.e., monitoring and control) and system choice in the context of typical supplier capabilities.

4.6.11 HVAC

4.6.11.1 CONTROLS SYSTEM CHOICE

4.6.11.1.1 There are three basic configurations.

4.6.11.1.2 Commercially available BMS systems are acceptable.

4.6.11.1.3 There may be some safety-critical systems that should utilize DCs and SCADA.

4.6.11.1.4 HVAC may be monitored and controlled using several control system types. Those designed specifically for HVAC include:

4.6.11.1.4.1 Conventional controllers (typically single-loop controls).

4.6.11.1.4.2 Building Management Systems (BMS).

4.6.11.1.5 Other control systems that can be used, but primarily are aimed at controlling processes, include:

4.6.11.1.5.1 Programmable Logic Controllers (PLCs) with SCADA packages.

4.6.11.1.5.2 Distributed Control Systems (DCSs).

4.6.11.1.6 When specifying systems to control HVAC, the following should be considered:

4.6.11.1.6.1 HVAC's industrial nature in cleanroom applications may not justify use of PLC or DCS-based solutions; however, personnel safety issues may justify their use.

4.6.11.1.6.2 Pharmaceutical HVAC can be controlled satisfactorily using HVAC industry control systems.

4.6.11.1.7 Where control (only) is required for a few simple systems, conventional controls may provide a marginal cost advantage. This advantage is offset by the fact that conventional controls cannot be integrated readily into any future BMS demanded by site development.

4.6.11.1.8 As the application's scale, complexity, and remote monitoring demands increase, the use of BMSs rapidly becomes more cost-effective.

4.6.11.1.9 Monitoring of critical environmental parameters can be accomplished via the process control system, which should be qualified. The qualification of the BMS may then become simpler. (See "Use of Building Management Systems and Environmental Monitoring Systems in Regulated Environments," Pharmaceutical Engineering, September/October 2005 (Reference 15, Appendix 3).

Note : For more details on HVAC Control System, refer Chapter 2.3 Guidance on Building Management System (BMS) Design for Pharma

4.6.11.2 AIRBORNE PARTICLE COUNTING

4.6.11.2.1 It is essential to differentiate between the act of classification of a space environment, and monitoring that environment in operation. The method for formal classification is specified in ISO 14644-1 (Reference 11, Appendix 3). This standard defines the minimum number of sample locations, the minimum sample size at each location, the class limits, and the method for evaluation of the data in order to define the class achieved. It should be noted that in the context of sterile product manufacture, Annex 1 of the EU GMP sets some class limits that are different from those found in FDA's September 2004 Aseptic Processing Guidance and ISO 14644-1:1999 (References 7 and 11, Appendix 3). Monitoring may use similar instrumentation, but in this case certain critical or most important locations are determined from investigation and studies, and these are monitored to demonstrate the performance of critical parts of the controlled environment.

4.6.11.2.2 Particle counting instruments measure the airborne non-viable particle concentration operate by taking a sample of the air in the space and measuring the particle concentration by evaluation of scattered light in a special optical chamber. Such Instruments can measure both number and size of particles in the size range 0.1 to 5.0 µm. Particle counting systems can be configured in different ways:

4.6.11.2.2.1 A single portable instrument, usually located close to the environment being classified or monitored. These instruments can be used for both classification and monitoring. Instruments of this sort are suitable for evaluating particles in the size range 0.1 to 5.0 µm.

4.6.11.2.2.2 A single fixed instrument, connected to multiple sample locations by way of tubing arrays and a manifold system. Each location is sampled in turn. The particle counter is connected to a data acquisition system. These systems are used only for monitoring. Instruments of this sort are suitable for evaluating particles only in the size range 0.1 to 0.5 µm due to the potential drop-out of larger particle in the transport tubing.

4.6.11.2.2.3 Multiple miniature point-of-use particle counters, each located close to a location that is to be monitored, and connected to a data acquisition system. These systems are used for monitoring particles only in the size range 0.1 to 5.0 µm.

4.6.11.2.3 Key points to consider when evaluating particle monitoring systems include:

4.6.11.2.3.1 The difficulty of correlation of data from the relatively small number of sample points of a monitoring system, compared to the larger number of data points used to carry out classification in the "at rest" or "in operation" states.

4.6.11.2.3.2 Identifying the room's "worst case" points and relating them to overall room conditions.

4.6.11.2.3.3 Determination of appropriate sampling frequency for monitoring systems.

4.6.11.2.3.4 Management and interpretation of potentially large amounts of data acquired from automated monitoring systems to identify problems.

4.6.11.2.3.5 Determination of alert and action levels.

4.6.11.2.3.6 Procedures to be followed in the event of excursion beyond alert and action levels.

4.6.11.2.4 Where particle concentrations are very low, monitoring system alert and action levels may be better expressed using frequency (pattern) of seeing low counts rather than trying to discriminate between very low numbers.

4.6.11.2.5 The FDA's 2004 Guidance (Reference 5, Appendix 3) says "Regular monitoring should be performed during each production shift. We recommend conducting nonviable particle monitoring with a remote counting system. These systems are capable of collecting more comprehensive data and are generally less invasive than portable particle counters."

4.7 BARRIER AND ISOLATOR TECHNOLOGY

4.7.1 For new and renovated aseptic processing facilities, barrier technologies such as Restricted Access Barrier Systems (RABS) and isolators represent systems of choice for optimizing product integrity and as such they are being used increasingly for aseptic filling. These technologies can be applied to batches of all sizes, from small-scale filling of clinical trial materials, up to and including large, automated, high-speed processing lines. Isolators have a valuable role to play in protecting the operator and the surrounding environment when the product is hazardous. While these technologies have been in use for more than ten years, they are still developing, and some aspects will continue to change over time.

4.7.2 People are the greatest source of contamination in the manufacture of sterile products. Over the past decade, substantial progress has been made in separating the operator from the critical areas within the aseptic manufacturing suite. Isolators, RABS, blow-fill-seal, conventional barriers, and the increasing use of robotics in these systems have increased personnel separation from the critical areas. Many of the advantages of these technologies, however, can be negated by poor design, lack of knowledge concerning their operation, and ineffective operator training. Absolutely basic to the design concept are the ergonomic aspects of the production operation to be undertaken. This should be considered in conjunction with mechanical movement, and appropriate material and equipment transfers, sterilizability, and an appropriate background environment in which the system is to be operated. These decisions should be made on a case-by-case approach, depending upon the application and specific system design.

4.7.3 SYSTEM DEFINITIONS

4.7.3.1 It is important to understand the, at times, subtle differences and distinctions among the various types of isolator and barrier systems used in pharmaceutical aseptic processing. Further, there is overlap in the degrees of separation and operator protection among these systems; however, isolators, RABS, and barrier systems can be broadly classified according to the type of separation they provide and the assurance of maintaining that separation.

4.7.3.2 ISO 14644-7 (Reference 11, Appendix 3) shows increasing levels of separation assurance moving from purely aerodynamic separation (as in a unidirectional airflow hood) to complete physical separation (as in a closed isolator).

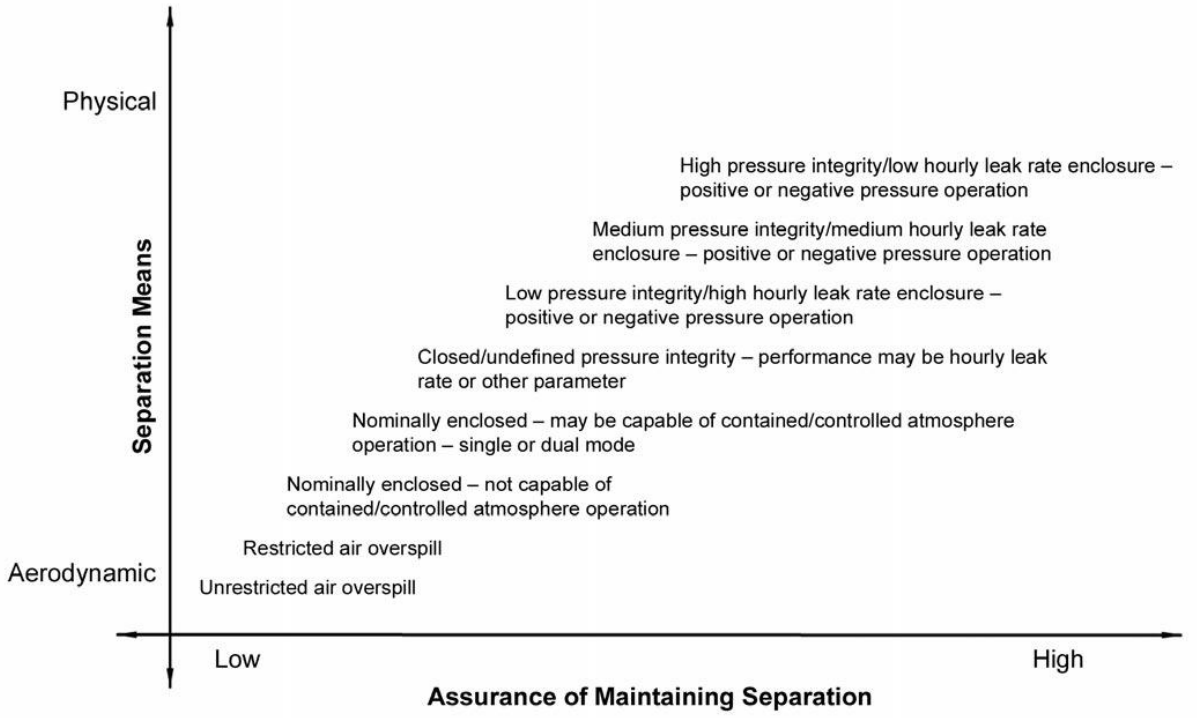


Figure 6
Increasing Levels of Separation Assurance

4.7.3.3 Along this continuum, barrier systems tend to utilize physical separation and air overspill to separate personnel from the aseptic processing critical areas, while isolators tend to rely on strict physical separation and positive pressure differentials (or sometimes negative pressure differentials for hazardous processes) to provide the necessary level of separation and protection.

4.7.4 ISOLATORS: An isolator is defined as "a decontaminated unit meeting Grade A conditions that provides uncompromised, continuous isolation of its interior from the surrounding environment."

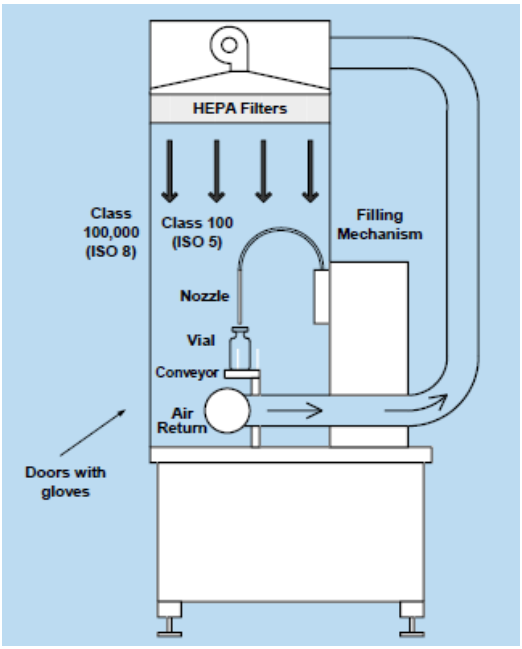


Figure 7
Isolator

4.7.4.1 Isolators can be either "open" or "closed" depending upon their operational state and may operate at positive, neutral, or negative pressures with respect to the surrounding environment. When "closed," isolators may exchange air with the surrounding environment only through microbially retentive filters. When "open," isolators may transfer air directly to the surrounding environment through openings (e.g., "mouse holes") that preclude the ingress of bio-contamination.

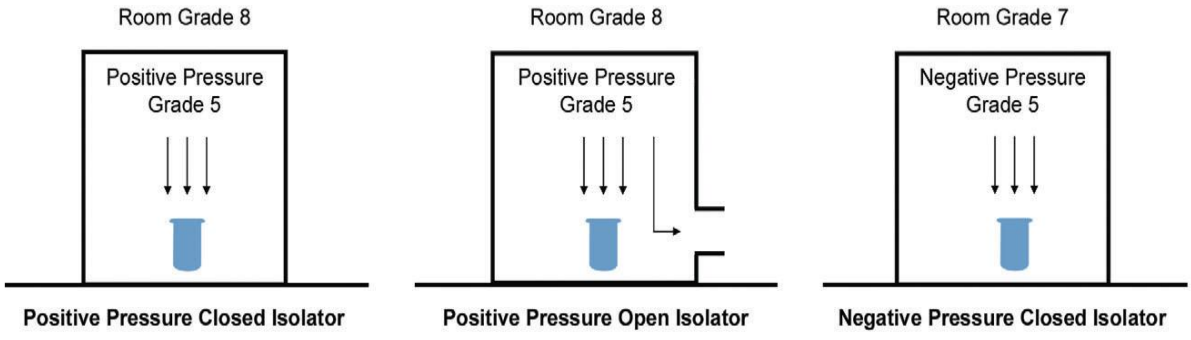


Figure 8
Isolator Types and Surrounding Environment Classifications

4.7.5 BARRIER SYSTEMS: A barrier system is defined as "a system of physical partitions that affords Grade A protection by partially separating its interior from the surrounding environment utilizing airflow."

4.7.5.1 Barrier systems, especially the more recent designs termed RABS, provide some of the same advantages as isolators while eliminating some aspects of isolator design. RABS systems improve upon the basic performance of simple barrier designs.

4.7.5.2 RABS is defined as "an aseptic processing system that provides an enclosed, but not closed, environment meeting Grade A conditions utilizing a rigid-wall enclosure and air overspill to separate its interior from the surrounding environment."

4.7.5.3 RABS designs are flexible to take into account existing and new facilities and processes. The two general classes of RABS are active and passive.

4.7.5.3.1 Active RABS use an integral HEPA-filtered air supply to the critical area and manual high-level disinfection, using sporicidal agents to achieve appropriate, reproducible, and significant logarithmic reduction. Gloves and transfer ports are used for manipulation and commodity addition.

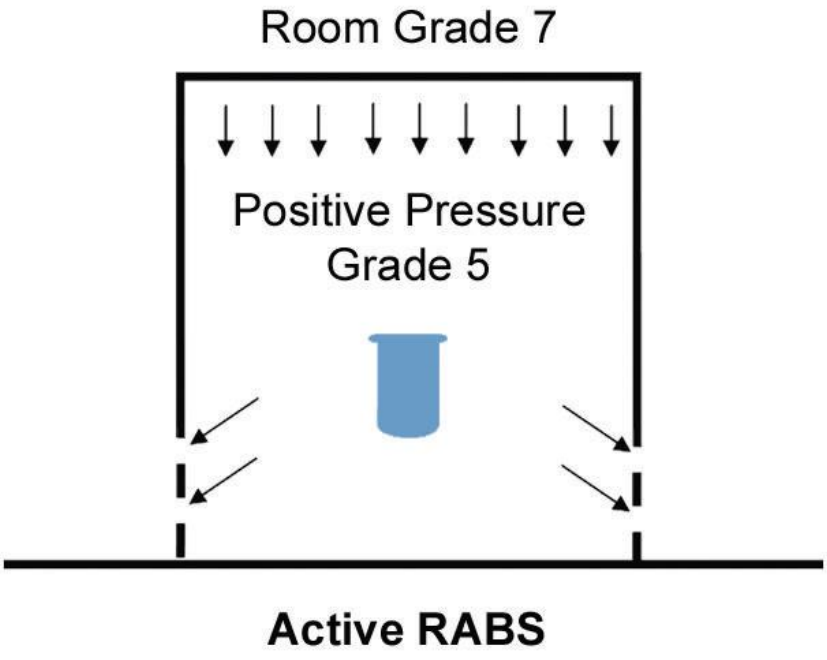


Figure 9
Active RABS and Surrounding Environment Classification

4.7.5.3.2 In passive RABS, the airflow to the critical area is provided by ceiling-mounted HEPA filters and the bottom of the enclosure is open to provide for airflow through the system. It is important that the HEPA-filtered air supply extend laterally outside of the enclosure to prevent ingestion into the critical area of viable and non-viable particulates from the surrounding environment. Passive RABS utilize the same type of glove and transfer ports and high-level disinfection procedures as active RABS.

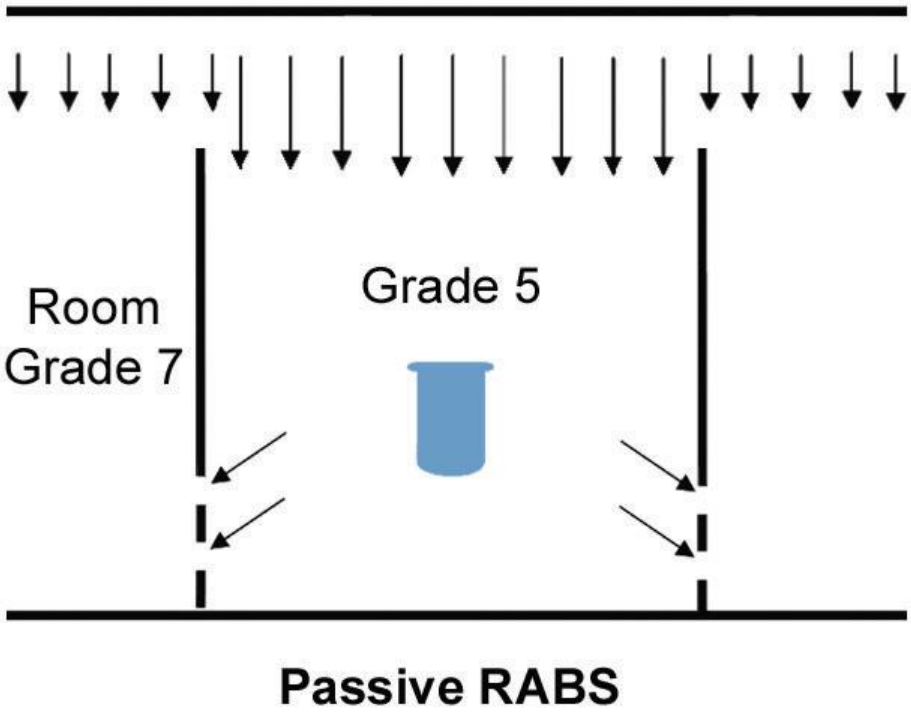


Figure 10
Passive RABS and Surrounding Environment Classification

4.7.5.4 While there is no single design model for a RABS, these systems share the following common “quality by design” characteristics :

4.7.5.4.1 Rigid wall enclosure that provides full physical separation of the aseptic processing operations from operators.

4.7.5.4.2 Unidirectional airflow systems providing a Grade A environment to the critical area(s).

4.7.5.4.3 Glove port(s), half-suit(s), and/or automation are used to access all areas of the enclosure which need to be reached by an operator during filling operations.

4.7.5.4.4 Gloves and gauntlets attached to glove ports are sterile when installed; thereafter, gloves should be disinfected or changed as appropriate to minimize the risk of bio-contamination.

4.7.5.4.5 Sterilization-in-Place (SIP) should be used for contact parts such as fluid pathways. Where this cannot be achieved, such parts should be sterilized in an autoclave, transferred to the RABS via a suitable procedure, such as introduction through an RTP, and aseptically assembled before processing.

4.7.5.4.6 Entry of material such as environmental monitoring materials, consumables, containers, and closures is via a transfer system that prevents exposure of sterile surfaces to non-Grade A environments and to personnel.

4.7.5.4.7 “High-level disinfection” of all non-product contact surfaces within the RABS with an appropriate sporicidal agent before batch manufacture.

4.7.5.4.8 Surrounding room classification should be minimum Grade B in operation.

4.7.5.4.9 Some processes may include rare open-door interventions. In these cases, because of the inherently increased risk to product, the following are required to maintain the RABS protection concept:

4.7.5.4.9.1 Provision for appropriate high-level disinfection of non-product contact surfaces following a door open intervention.

4.7.5.4.9.2 Locked door access or interlocked door access with recorded intervention alarms (and/or other satisfactory means of documentation) and mandated appropriate line clearance.

4.7.5.4.9.3 Positive airflow from the enclosure to the exterior environment while the door is opened. Qualification studies should demonstrate that in the event of a necessary pre-defined intervention, no contamination can enter the critical area(s).

4.7.5.4.9.4 Appropriate Grade A classification areas may be necessary immediately adjacent to outside of enclosure to always assure Grade A conditions inside the RABS. Examples of such situations are: Setup of sterile equipment that requires unwrapping of autoclave packaging outside of the RABS. Any machine sections that require open door interventions (such as certain powder filling applications)

4.7.6 SYSTEM COMPARISONS

4.7.6.1 In traditional, conventional aseptic filling operations, the filling equipment and gowned personnel operate together in a cleanroom environment. There is limited defined separation (sometimes in the form of flexible plastic curtains) between the personnel and the production environment, and the product and product contact exposure areas are locally protected in a Grade A environment.

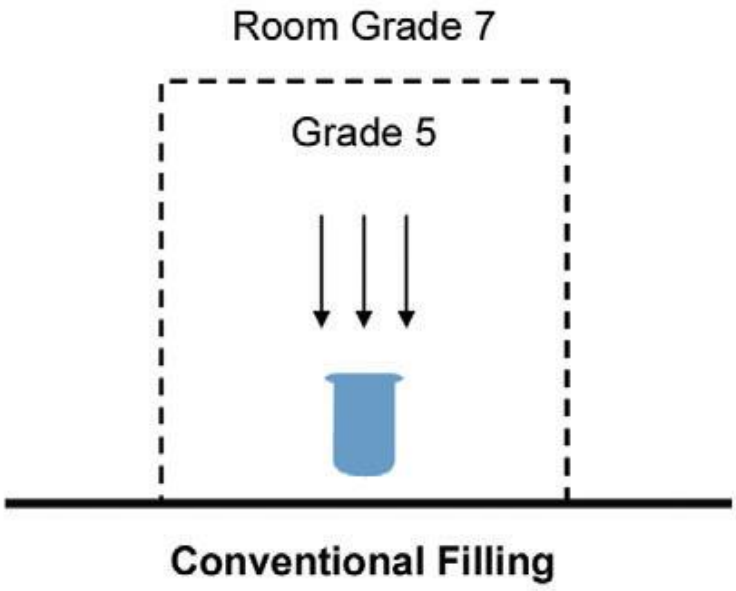


Figure 11
Conventional Filling and Surrounding Environment Classification

4.7.6.2 Isolators and RABS utilize physical or aerodynamic methods (or both) to achieve separation from the surrounding environment. There are two primary differences between isolators and RABS:

4.7.6.2.1 Decontamination: Isolators are reproducibly decontaminated using an automated system (such as H2O2) while RABS usually are manually high-level disinfected.

4.7.6.2.2 Pressure differentials: Isolators operate at an established pressure differential with respect to the surrounding environment, while RABS utilize air overspill without a defined pressure differential to achieve aerodynamic separation.

4.7.6.3 The table below contains points to be considered and highlights areas of differences among traditional cleanrooms, advanced barriers, and isolator designs. Each system should be considered in terms of its intended and the specific circumstances related to that use.

Table 6 : Points to Consider for Traditional Cleanrooms, Advanced Barrier, and Isolator Designs

Issue	Traditional Cleanroom (Unidirectional Airflow Systems and Curtains)	Restricted Access Barrier Systems (RABS)	Isolator Systems
Degree of separation	Separation provided by room pressure differentials and cleanroom clothing systems.	Superior to cleanrooms.	Superior to other technologies.
Initial facility	Point of reference costs.	Costs may be higher than traditional cleanroom. More equipment related costs. Large footprint of higher classified environments in passive systems.	Isolator equipment may be more expensive. Facility capital and operational costs can be significantly lower.
Facility lead time	Point of reference.	▪ Building infrastructure time consuming. Facility activities more complex. ▪ More project elements and vendors involved.	Equipment more complex. Footprint of the facility significantly reduced (do not need gowning rooms, etc).
Qualification obstacles	Point of reference.	Issues well established and easy to resolve.	Issues well established and easy to resolve.
Qualification duration	6 to 9 months.	6 to 9 months typical but may be longer.	▪ 6 to 9 months typical but may be longer due to decontamination cycle ▪ development and validation. ▪ Longer periods are a reflection of intrinsic requirements rather than any insurmountable technical hurdle.
Operating cost	Point of reference.	May be slightly higher than traditional cleanroom.	▪ Approximately 75% less than cleanroom costs; mostly related to HVAC ▪ operating costs. ▪ Other savings in gowns, supplies, labor utilization, EM.
Operational hurdles	Largely personnel dependent	▪ Minimal changes to established technologies. ▪ Known entity. Easy adaptation from earlier operating modes. ▪ Easier to retrofit to existing lines than with isolator.	▪ Requires new elements. ▪ Changes to old paradigms necessary.
Environmental treatment	Decontamination performed by gowned personnel. Reproducibility and validation uncertain.	▪ High-level disinfection with sporicidal agent performed by gowned personnel. ▪ Reproducibility and validation uncertain.	▪ Reproducible decontamination using automated cycles with a sporicidal agent. ▪ Can be validated.

Issue	Traditional Cleanroom (Unidirectional Airflow Systems and Curtains)	Restricted Access Barrier Systems (RABS)	Isolator Systems
Impact of personnel	Highly influenced by personnel.	▪ Environmental separation less effective than with isolators when open door intrusions are undertaken. ▪ Operator protection limited for hazardous compounds.	▪ More removed from critical area. ▪ Isolator enhances operator safety with hazardous compounds. ▪ Isolators present less risk than RABS.
Line operation	Risk of contamination dependent on cleanroom clothing and personnel behavior.	▪ Greatly reduced risk of contamination compared with traditional cleanroom technology. ▪ Isolator systems provide further reduced risk because of lack of defined pressure differential in RABS, but airflow overcomes this.	Lower risk of contamination due to complete and uninterrupted separation of environments.
Cleaning	Manual.	Difficult issue when handling hazardous compounds.	▪ Cleaning hazardous compound substantially safer. ▪ Complete CIP possible.
Complexity	Point of reference	▪ Systems generally are less complex than isolators. ▪ Can be retrofitted more easily to traditional cleanroom process equipment.	▪ More controls, equipment and instrumentation required. ▪ Decontamination adds extra elements. ▪ System and control integration issues can be significant.
Format changeover	Point of reference	▪ Size, component change easy. ▪ Product change requires internal cleaning. ▪ Greater risk of bio-contamination during changeover.	▪ Size, component change relatively easy. ▪ Product change requires internal cleaning.
Novelty	Point of reference.	Minimal	▪ Some firms have almost no isolators. ▪ Some firms have substantial experience. ▪ There is a definite learning curve which must be considered.

Issue	Traditional Cleanroom (Unidirectional Airflow Systems and Curtains)	Restricted Access Barrier Systems (RABS)	Isolator Systems
Intangibles	Point of reference.	▪ Easy to implement relative to isolators. ▪ Technology still evolving. ▪ Hazardous new products may create an advantage for isolators.	▪ More capable once fully operational. ▪ Newer technology, atill evolving. ▪ Hazardous new products may create an advantage for isolators.
Containment potential for hazardous products	None.	Limited.	Excellent.
Regulatory perspective	▪ Becoming increasingly unacceptable. ▪ No longer the design of choice.	▪ Recognized as a significant improvement over traditional cleanroom equipment, but not perceived to be equal to ▪ isolators in terms of product separation.	Considered superior.
Industry perspective	No longer the design of choice among major pharmaceutical companies.	▪ Largely proven technology with known limitations. ▪ Few uncertainties equal reduced risk.	▪ Gaining increasing acceptance and usage. ▪ Learning curve issues can lead to increased initial costs and start-up times.

4.7.7 FACTORS THAT MAY BE CONSIDERED WHEN CHOOSING AMONG THESE TECHNOLOGIES INCLUDE :

4.7.7.1 PERSONNEL INVOLVEMENT WITH THE ASEPTIC PROCESS: Isolator technology removes a major source of bio-contamination by eliminating direct operator intervention from the aseptic process, making it superior for aseptic/containment applications. RABS systems are superior to conventional manned cleanrooms for aseptic operation and can approach the superior separation provided by isolators if the doors remain closed.

4.7.7.2 LABOR EFFICIENCY GAINS: Isolators eliminate a confining gown, close-fitting hood, and face mask, leading to improved operator comfort and cost savings in laundry and cleanroom clothing sterilization (each operator can consume 4 to 5 gown sets per day). Isolator systems can allow the same operator to serve several different functions on the same line without regowning, affording greater labor utilization and significantly reducing gowning costs. In general, access to the aseptic processing area is no longer restricted by sterile gowning and degowning procedures, thereby permitting controlled, multiple access routes. These advantages, however, can be lost if the isolator is not designed ergonomically for easy operator interaction. RABS do not offer these advantages as the operators must wear full aseptic garb and are largely restricted to a single location/function.

4.7.7.3 CONTAINMENT OF TOXIC MATERIALS: Isolators can be particularly useful for processing of hazardous powders or biologically hazardous material when operated as closed systems. RABS provide the better separation than conventional cleanrooms but are not suitable if containment of toxic materials is required.

4.7.7.4 SET-UP TIME AND FACILITY START-UP: Containment of the process within an isolator means that some early construction and pre-delivery testing can be performed off-site, prior to installation, while the surrounding environmental room is being constructed. Modular construction of the room means that the user has the flexibility to modify the room without major reconstruction of the building. Maximum benefit can be gained from a simple, ergonomically-designed process layout. RABS start-up periods are closer to those for conventional cleanrooms as critical facility environmental systems are required and control systems are less complex than they are for isolators. Since isolators are independent units, the control systems can be designed integrally and placed into operation with the isolator, potentially shortening facility start-up time.

4.7.7.5 OPERATING COSTS: For most applications, the scaled down size of the aseptic process and associated air handling equipment, combined with the lower environmental class of the background room and reduced gowning and environmental monitoring requirements, results in reduced operating costs for isolator systems. Operating costs for RABS designs are comparable to those for manned cleanrooms.

4.7.7.6 CAPITAL COSTS: Isolator equipment cost usually is higher than conventional equipment and may offset initial capital cost savings gained by improved space utilization, compared to a conventional facility. RABS and associated processing considerations are somewhat more expensive than conventional cleanrooms but, generally, are less expensive than isolators. Isolators may be the cheapest option for new construction. Individual cost analyses should be performed for RABS versus isolators, and consideration should be given to operational as well as capital costs, including the facility.

4.7.7.7 MAINTENANCE ACCESS: Good maintenance access (from outside the critical environment) should be designed in at the start and is possible with both RABS and isolator designs. Given the free-standing nature of isolators, access may be superior and gowning requirements minimal.

4.7.7.8 INFLEXIBILITY OF THE EQUIPMENT: Sometimes, it is difficult to change equipment (RABS or isolator, or its process) to accommodate product changes, etc.

4.7.7.9 INTEGRITY OF ISOLATOR BETWEEN TECHNICAL AREA AND ASEPTIC ENVIRONMENT SIDE: Care should be taken in design, especially for machine drives, to ensure that the aseptic interior of the isolator is not compromised. The heat load in an isolator should be carefully considered during design and start-up to avoid out-of range temperatures. Similarly, ensuring gloves or half-suits do not become damaged is considered a critical activity in the management of both RABS and isolators.

4.7.7.10 CLEANING AND SURFACE DECONTAMINATION: Design and validation of cleaning/decontamination requirements for isolators will affect ergonomics and material selection, as the sterilizing vapor can be aggressive to some materials (e.g., hydrogen peroxide attacks certain plastics), and some materials (e.g., lubricants) can inactivate hydrogen peroxide. Nevertheless, these systems can be reproducibly validated to perform the desired treatment. RABS rely on manual cleaning/high-level disinfection, which may be a less reliable and reproducible treatment than automated decontamination systems (e.g., vapor-phase hydrogen peroxide, chlorine dioxide) used for isolators. Although surface decontamination is performed on the isolator and high-level disinfection in the RABS, the sterile product contact parts should preferably be sterilized in situ (SIP) or autoclaved. Where those parts cannot be sterilized in an autoclave, the vapor phase hydrogen peroxide decontamination system can be utilized if the process can be validated to achieve a six-log reduction of an appropriate challenge organism.

4.7.7.11 ERGONOMICS: The position of the glove ports, half-suits, and interfaces with the operator is crucial as the aseptic method may suffer if the operator is uncomfortable. The designer should develop the most efficient layout, as poor layouts cannot be easily changed later. This is an important consideration for RABS and isolators.

4.7.7.12 TRANSFER SYSTEMS: Transfer systems, e.g., Rapid Transfer Ports (RTPs), should ensure that the design and operating procedures are correct, and that during transfers, the aseptic core remains intact. Particular care should be taken to maintain integrity of rapid transfer ports.

4.7.7.13 AIRFLOW WITHIN THE EQUIPMENT: Airflow within the RABS should be unidirectional at the product, container, or closure exposure points. In closed isolator applications, it may not be necessary to have unidirectional airflow where there is no requirement to protect one part of the internal space from another. During isolator decontamination with vapor, effective vapor distribution is required to ensure good distribution, and turbulent airflow can help ensure rapid and complete aeration of all parts of the isolator. Optimum gas distribution and airflow performance should be determined. The heat load in an isolator needs to be carefully considered during design and start-up to avoid out-of-range temperatures.

4.7.7.14 PRESSURE DIFFERENTIAL: Isolators are maintained at positive pressure relative to their surroundings in order to prevent ingress of any contamination from the external environment and during hand removal from gloves. Excessive overpressure can be a problem with air balancing in continuous process systems utilizing dehydrogenation tunnels. RABS designs do not have a defined pressure differential between the internal and external environments..

Note: Air Overpressure: a positive pressure isolator is maintained at an overpressure relative to its surrounding environment in order to meet the design requirement of separating the inner isolator environment from the external environment. Use of high overpressure is intended to form what amounts to an invisible wall with the external environment at any openings in the isolator. The overpressure specification should incorporate a safety margin to preclude any ingress of contamination from the surrounding environment.

In general, an open isolator is designed to include an egress hole maintained at a minimum overpressure above 12.5 Pa (0.05 inches water gauge)), relative to the surroundings. A preferred overpressure is 20 Pa or higher. For example, isolator designs have often used a set point in the area of 24.884Pa (0.1inchwatergauge) or more. Whatever overpressure specification is used, it should be supported by data and qualified. The egress hole should be protected, e.g., through the use of an additional UF unit, to preclude microbial ingress.
There should be design provisions to prevent induction of contamination from the external environment.

4.7.8 RABS/ISOLATOR TYPE

4.7.8.1 RABS and isolators are intended to improve the sterility assurance level for aseptic processing operations. Interfaces and transfers for hazardous/toxic products may require special features to protect the operator (e.g., personal protective equipment) and surrounding background (e.g., buffer airlock leading into the surrounding area).

4.7.8.2 Rigid wall construction has been found to be more reliable and durable, and offers greater airflow/direction control that may be of benefit in removing particulates generated by the production process. Flexible-walled designs may offer less reliability due to the potential for failures in the materials creating leakage including pin holes that might not be detected. Flexibility of the sidewalls can result in turbulence at the sidewalls, which can result in bio-contamination of the critical zone. The flexible walls can outgas the sterilant or decontaminating agent causing destruction of some biological products.

4.7.8.3 All systems typically utilize stainless steel body construction, glazed with rigid plastic or safety glass.

4.7.8.4 Air handling systems are HEPA-filtered, and may recirculate the air. Recirculated air is passed through ducts, or double skin walls and windows, to be returned to the system fan. Air may be supplied uni-directionally over the critical areas (e.g., filling and stoppering zones) via HEPA filters to optimize air quality. In isolator systems, a large percentage of the air is typically recirculated internally within the isolator. RABS returns the air to the fan-HEPA system through the surrounding classified environment.

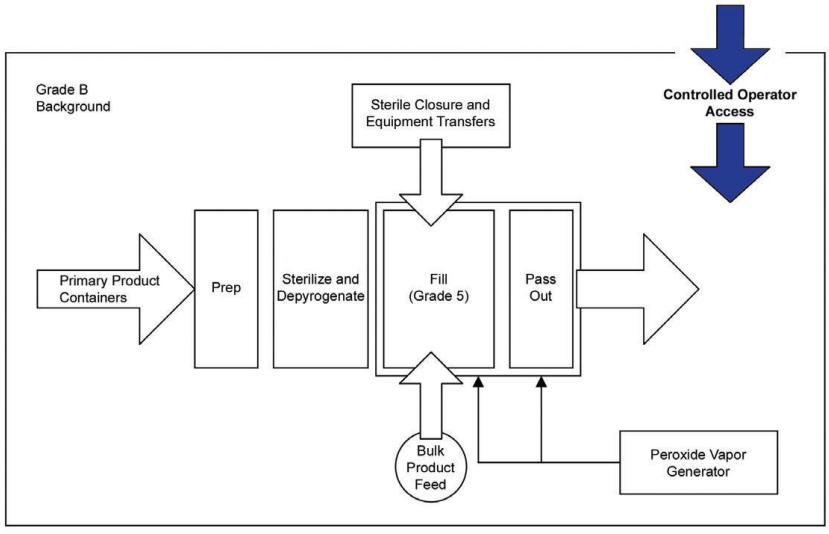


Figure 12
Example – Arrangement for an Isolator Facility

4.7.9 EQUIPMENT DESIGN

4.7.9.1 Ergonomic design is fundamental to a successful system design. The equipment can be designed to minimize sterile volume, by limiting the overall footprint (i.e., plan area). This will minimize air handling and airflow requirements.

4.7.9.2 The following points should also be noted:

4.7.9.2.1 Equipment should be designed with the ergonomics of operating through glove-ports or half-suits in mind. This means all points for adjustment and manual interaction should be positioned well within the operator's reach from outside the enclosure.

4.7.9.2.2 For positive pressure isolators, the equipment interface with the isolator system should be sealed to maintain the required DP and isolator integrity. A similar design concept is appropriate for RABS designs even though a pressure differential may not be present.

4.7.9.2.3 For isolator systems that are sterilized by gassing, equipment materials should be resistant to attack and degradation by the decontaminating agent.

4.7.9.2.4 Maintainable parts should be designed so as to be external to the environment.

4.7.9.2.5 The use of automated equipment should be considered, whenever feasible, in order to minimize human involvement within the controlled environment.

4.7.9.3 While a half-suit may help operators' access equipment, it should have a good ergonomic design.

4.7.9.4 Machine design for aseptic filling equipment should incorporate features which ensure that size changes can be accomplished simply and quickly, with the minimum number of size parts. Use of electromagnetic couplings and automated servo motor actuated adjustments may be incorporated.

4.7.9.5 To the extent possible, the machinery (e.g., mechanical drives) should be sited outside the enclosure. This allows the unit to seal to the working top of the machine and reduces the possibility of contaminants being entrained from the machinery drive mechanism to the aseptic filling zone. An effective seal, however, is difficult to achieve, and particular attention should be paid to the movement of drive shafts, connecting rods, and cable wire entries. An efficient, vapor tight seal should be maintained to contain toxic decontaminant gas or disinfecting agents and ensure that reciprocating parts are adequately protected to prevent entrainment of contamination from outside the enclosure through the machine plate.

4.7.9.6 In the less desirable situation where the enclosure has to surround the entire machine, the possibility of contaminants being entrained from the drive mechanism may be controlled by greatly increased airflows and pressure regimes arranged to protect the aseptic filling zone. Caution is required, however, as decontamination may be very difficult to achieve reproducibly.

4.7.9.7 Further ergonomic advantage may be achievable by eliminating the traditional mechanical filling pump system. Alternatives are time, pressure, and inductive flow filling mechanisms that eliminate the need for mechanical pumps and drives, or mounting filling mechanisms external to the enclosure. The aim is to simplify the ergonomic requirements of filling machine setup by removing unnecessary mechanical items from inside the enclosure.

4.7.9.8 The control system for the filling equipment should be configured so as to permit dry cycling during decontamination of the isolator, in order to expose all the equipment surfaces to the sterilizing vapor. Ergonomic design should allow access for all surfaces to be cleaned effectively, prior to gaseous surface decontamination. Before a decontamination cycle begins, the isolator should be mechanically clean (and dry, depending on the decontaminating agent). This may necessitate a drying step prior to decontamination.

4.7.9.9 Equipment should be designed to allow effective aeration following the decontaminating process.

4.7.9.10 COMPONENT AND EQUIPMENT TRANSFERS

4.7.9.10.1 The mechanisms chosen for the various transfer operations are crucial to protect the aseptic processing area. It is generally considered ideal to provide a direct interface with the autoclave, depyrogenation oven, and/or sterilizing transfer device, as part of the overall design.

4.7.9.10.2 For sterile applications, the transfer mechanism should be capable of protecting the interior from bio-contamination.

4.7.9.10.3 The major consideration is the ability to sterilize the contents of the transfer device before allowing access to the controlled workspace.

4.7.9.10.4 A common technique for passing items into the enclosure is via a RTP. In this case, items are sterilized in a separate canister, which is designed to be docked onto the transfer door of the enclosure. The docking process seals the outer face of the transfer door to the lid of the canister in an air tight manner. Air tightness is ensured by the use of multiple-lip seal gaskets. The action of locking the canister to the enclosure simultaneously releases the lid from the canister and locks it onto the transfer door of the enclosure which can then be opened from inside using the glove access. The seals should be sterilizable and frequently high-level disinfected. The number of times RTPs are used should be minimized, as each use increases the probability of contamination. Where an RTP is not practical, the interface should be sterilizable.

4.7.9.10.5 Maintenance of the RTP port and multiple-lip seal gaskets is critical to preclude contamination.

4.7.9.10.6 Design should permit passage of items to and from the enclosure without opening it to the surrounding area. In the cases where the transfer system for the enclosure has to be open to the surrounding room, e.g., mouse-hole exits, or where it is integral with a dry heat tunnel sterilizer for the transfer of components, the direction of airflow must ensure that contaminants will not pass into the enclosure, and that appropriate DPs are maintained and local protection afforded.

4.7.9.11 GLOVE SYSTEMS, GAUNTLETS, AND HALF-SUITS

4.7.9.11.1 A gauntlet, glove sleeve, or half-suit system on an enclosure can develop a leak. Automation of the process can minimize operator interventions that necessitate the use of gloves and half-suits. The impact of any leakage requires thorough investigation and evaluation. Occurrences of leakages can be reduced by the use of robust materials, appropriate maintenance and inspection regimes, and by operators having trimmed finger nails. The use of a thin sterile glove liner as part of a gowning regime, worn by the operator, coupled with hand disinfection may protect the glove from bio-contamination and reduce the risk of damage.

4.7.9.11.2 Physical and visual examinations of glove seams and seals for gross defects (holes and splits of 2 to 3 mm) should be undertaken before and after a working session.

4.7.9.11.3 Several commercially available glove leak test kits are available, but they do not provide a guarantee of glove integrity. The choice will depend on the required sensitivity to detect a leak resulting from a hole not easily visible. The apparatus should inflate the glove to expand holes that otherwise remain partially sealed and undetectable. A high test pressure reduces the hold period required to detect pressure decay to a few minutes, which, in turn, minimizes the influence of ambient temperature, room air, and pressure variations.

4.7.9.12 GAUNTLETS

4.7.9.12.1 Gauntlets are one-piece, full, arm-length gloves. They usually are thicker than the standard surgical latex glove, but they do not fit particularly well and may reduce the operator's sensitivity. Gauntlets are available in a range of polymers with varying resistance and degradation.

4.7.9.13 GLOVE/SLEEVES

4.7.9.13.1 This consists of a sleeve, terminating in a cuff piece, to which the glove is attached.

4.7.9.13.2 Clean glove replacement without subsequent decontamination is not recommended, as it may jeopardize the integrity of the system. If it is provided, the changeover technique should be validated and the operator fully trained to avoid jeopardizing the enclosure integrity. Operators should be made aware of risks posed to gloves used in an aseptic environment, and, in particular, such things as fingernail length and the wearing of jewelry should be restricted.

4.7.9.14 HALF-SUITS

4.7.9.14.1 An isolator half-suit is a flexible sealed suit usually constructed from a durable vinyl/PVC polymer which physically separates the operator from the isolator environment. It is fitted with a light semi-rigid clear hood to permit good all-round visibility. The suit extends down to the waist of the operator and is usually attached and sealed to the isolator via an oval flange or other locking mechanism located in the working height base tray of the isolator unit. The suit is fed with its own air supply for both breathing and operator comfort and the arms are fitted with cuff pieces and gloves as described in Section 9.3.4. While offering much better access within the isolator, half-suits provide a larger surface area challenge for sanitization/sterilization and potential for in-use damage especially around the waist region. As such, they should be regularly inspected for deterioration and subjected to pressure leakage testing to confirm their integrity especially at the start and end of processing campaigns and following installation.

4.7.9.15 BACKGROUND ENVIRONMENT

4.7.9.15.1 The classification of the background environment in which the enclosure is located should be based on a risk assessment considering the design choice and operational characteristics of the chosen system and its associated transfer mechanisms and discharge ports (e.g., mouse holes).

4.7.9.15.2 Current practice is to set an acceptable standard for the isolator background, at least at Grade C (in operation). Although specific applications of isolator technology are viewed on an individual basis, the background is expected to be a classified area, supplied with a HEPA-filtered positive pressure air system, and a controlled air change rate. An adjoining area should be provided for changing overalls, hair and beard covers, as well as shoe covers, to comply with classified room requirements.

4.7.9.15.3 RABS designs require an aseptic processing environment external to the enclosure, as the absence of DP between the interior and exterior of the enclosure mandates that all personnel wear full aseptic garb. The surrounding environment is typically Grade B. An adjoining area should be provided for changing into full aseptic garb to comply with classified room requirements. This changing routine emphasizes the key nature of operations performed in the immediate environment of the RABS system.

4.7.9.16 BACKGROUND MONITORING

4.7.9.16.1 The extent of background monitoring will vary with the design choice. Background environments to isolators need not be monitored as frequently as the internal environment. As the surrounding environment to a RABS is an aseptic zone and can pose significant contamination risks, frequent monitoring is required. Provision should be made, however, for the assessment of particulate and bio-burden challenges to the enclosure. Installed gloves and half-suits should be assessed in accordance with a predetermined program.

4.7.9.17 ENCLOSURE CLASSIFICATION

4.7.9.17.1 The inner environment must meet Grade A or better.

4.7.10 DECONTAMINATION CYCLE DEVELOPMENT (ISOLATORS)

4.7.10.1 Prior to beginning decontamination, the isolator should be mechanically cleaned to remove contamination that may otherwise interfere with the effectiveness of the surface decontaminant. Both the cleaning technique and cleaning process must be validated, so engineers should consider the ergonomics of access, via the glove ports, or half-suit, to all surfaces within the isolator if the isolator is to be cleaned while closed. The use of extension tools for cleaning some internal surface areas may be required.

4.7.10.2 A properly designed and validated vapor treatment to decontaminate the isolator should be implemented. It should be noted that only surface decontamination is accomplished by the various treatments that may be used. Surfaces must be exposed sufficiently to the agent in order to achieve isolator decontamination. The isolator decontamination cycle should be validated to ensure its effectiveness throughout the isolator.

4.7.10.3 The necessary level of decontamination should be determined on the basis of risk assessment and analysis.

4.7.10.4 DECONTAMINATION SYSTEMS

4.7.10.4.1 There are several types of decontamination systems available for use with isolators. These include hydrogen peroxide-based systems and systems based on the use of chlorine dioxide. Undoubtedly, other decontamination systems will be developed. Manufacturers' recommendations should be used as the basis for developing and validating cleaning, conditioning, sterilization cycle, and aeration cycles for these systems. Considerations pertinent to hydrogen peroxide-based systems in this section are applicable for the most part to other types of gaseous and vapor-phase decontamination systems.

4.7.10.4.2 Precautions should be taken at the design stage to define load volume, configuration, and packing materials.

4.7.10.4.3 Particular attention should be paid to areas where there is poor vapor circulation (e.g., masked surfaces, such as beneath bottles, component packs, and dead ends, caused by the presence of sensors, pipework, etc.).

4.7.10.4.4 It is important that any loose items, that can be autoclaved, are autoclaved.

4.7.10.5 SURFACE FINISHES

4.7.10.5.1 Passivation may be required to prevent corrosion of ferrous metals contaminated by vapor-phase hydrogen peroxide gases.

4.7.10.5.2 The isolator surface should be finished to a uniform dull polish, generally No. 4 (240 grit) or better. All chamber joints should be fully welded, with hygienic construction, crack- and crevice-free with generously radiused corners for easy cleaning.

4.7.10.6 REMOVAL OF THE DECONTAMINANT – AERATION

4.7.10.6.1 Some hydrogen peroxide generators use internal catalytic converters to remove breakdown products of peroxide during decontamination, replenishing it with fresh vapor to maintain the decontamination process. This catalyst also is used to remove residual hydrogen peroxide from the isolator at the end of the cycle. In larger systems, this converter can be external to increase aeration capacity.

Note: Catalytic converters may not be required or needed in all cases.

4.7.10.6.2 Peroxide vapor should be removed from the chamber at the end of the cycle to prevent it from venting into the workplace or contaminating the product. The normal return air breakdown from the generator may be supplemented by additional air handling to purge the isolator. This purge air exhaust is normally protected by a catalytic converter (usually platinum on alumina). Partial aeration of the isolator, using the catalyst in the generator, may be an alternative prior to venting the isolator to the atmosphere. Local environmental regulations, however, should be considered before exhausting peroxide from a partially aerated isolator to the atmosphere.

4.7.10.6.3 Verification of the effectiveness of purge vapor catalysts is generally assessed by sampling the downstream airflow for absence of vapor, using commercially available vapor detection tubes.

4.7.10.6.4 Aeration times should compensate for absorption of the vapor on the surfaces, e.g., vinyl, PVC of gloves and half-suits, and into packing materials, e.g., the TyvekTM paper of equipment wraps, also glazing gaskets, product tubing, and HEPA filter media. The aeration time is prolonged in these instances. The use of suit supports or glove extenders will reduce folds where vapor can be trapped. After aeration to levels below 1 ppm residual vapor-phase hydrogen peroxide, it is possible that continued desorption from polymers will contribute to airborne vapor levels.

4.7.10.6.5 Upon completion of the surface decontamination phase, and during the aeration phase, it is vital to design the air handling to maintain DP up to, and including, the point that normal airflows are re-established.

4.7.10.7 AIRFLOW MODELING

4.7.10.7.1 The air handling system is crucial to the performance of the decontamination process. The use of prototypes or mockups to verify a proposed isolator design is highly desirable, both to investigate airflows within all areas of the isolator and verify the ergonomic design of the process.

4.7.10.7.2 This simulation model can be used to conduct smoke test experiments to provide a useful basis for systematic location of biological indicators at the most vulnerable areas with a consequent saving in validation time and effort. Titanium oxide/oxychloride smoke is a peroxide catalyst and should never be used in a recirculation system intended for peroxide decontamination. Modifications to the final installation to optimize airflows can be expensive, technically difficult, and unpredictable

4.7.10.7.3 A sophisticated modeling system, such as three-dimensional ultrasonic anemometer airflow patterning or a computational fluid dynamics software package, can be a useful development tool. Velocity conditions can be different for various phases of the process (e.g., sterilization, aeration, and normal operation).

4.7.10.7.4 Changes to the airflows may be imposed by ergonomic considerations, loading configurations, etc. Modeling will greatly add to the understanding of the isolator, reducing cost and time required at validation. Optimization of the airflows will result in reductions in air handling system cost and time required to decontaminate the equipment. Changes to the in-use airflow may be required for the isolator decontamination process to ensure that all surfaces are properly contacted by the gaseous decontaminant. In such cases, additional fans may be required to be installed for this purpose.

4.7.10.7.5 In considering areas liable to be shadowed from the decontaminant vapor, design should give particular attention to half-suits, gauntlets, wrist collars, and gloves. Frames inserted into the suit or gauntlet will ensure the garment is fully deployed. Gauntlets, wrist collars, and gloves, including fingers, should be fully extended and separated, not mask any surface, and not be telescoped into the cuff during decontamination. Where used, internal suspension systems, such as stainless steel chains, should be sterilizable and non-shedding.

4.7.10.8 VAPOR AND MATERIAL COMPATIBILITY

4.7.10.8.1 Common sterilizing vapors used in isolator technology to decontaminate the internal surfaces of the isolator are known to attack certain lubricants, gaskets, materials (such as polycarbonate), metals, and bearings. Material compatibility with the agent, therefore, should be considered from the outset. In addition to the titanium oxide/oxychloride smoke source mentioned above (see section 9.4.4) some materials considered for installation and use in the device, e.g., certain lubricants, may have a detrimental effect on the agent(s) used for decontamination.

4.7.10.8.2 Seals, joints, gaskets, etc., should be inspected, and the isolator tested for leakage on a regular basis.

4.7.11 HIGH-LEVEL DISINFECTION (RABS AND OTHER BARRIER DESIGNS)

4.7.11.1 Barrier systems should be subjected to periodic high-level disinfection with sporicidal agents. This is ordinarily a labor intensive exercise that must be carefully conducted to ensure that all portions of the system/facility are properly disinfected in the prescribed order; the process may be done with the doors closed if the system is equipped with glove and gauntlet systems and is ergonomically designed for the process. The methods and practices for the high level disinfection activities should be defined in written procedures.

4.7.11.2 When the high-level disinfection is performed on an opened unit, the individuals performing this activity should wear full aseptic garb and have passed gowning qualification. Additional personal protective equipment may be necessary to assure operator safety.

4.7.12 ENVIRONMENTAL MONITORING

4.7.12.1 Environmental monitoring schedules for barrier systems and isolators are similar to those for a classified cleanroom. (Note: The exposure of settle plates may be limited by possible dehydration of the surface due to the high air change rate within the enclosure.) Special attention must be paid to the aseptic quality of the sampling apparatus in order to avoid false contamination of the sample. Non-invasive sampling is preferred, e.g., impingement sampling with equipment located outside the wall, or using equipment exposed to the same decontamination regime as the isolator. Use of such equipment should be validated to ensure the results are comparable to those obtained by local sampling because of the potential for microorganism capture in the sampling tubing. In addition, swab samples and contact plates will provide useful data.

4.7.12.2 The transfer of materials and liquids to and from the enclosure presents a major challenge to the sterility of the system together with the background challenge of the surrounding environment.

4.7.12.3 Additionally, the special requirements of glove systems should be considered, especially as a number of operators will use the same gloves with a consequent challenge to the hygiene of the glove system.

4.7.13 LEAK DETECTION (ISOLATORS)

4.7.13.1 The type of isolator and its design will determine leakage characteristics (e.g., number of windows, glove ports, and transfer ports). Isolator leakage is of concern where there is potential for loss of decontaminant gas or toxic product, or where it may allow the air from the surrounding environment to enter via induction during glove and half-suit entries and exits.

4.7.13.2 The leak test is designed to ensure that the isolator continues to be operated within its original design characteristics. Although gas leakage can be detected, small leaks may not be detected. The method of leak testing should be defined at the design stage and an acceptable leak rate should be established between the manufacturer and the user. A number of different leak test methods are possible :

4.7.13.2.1 Leak test by pressure drop.

4.7.13.2.2 Leak test by maintaining a constant pressure with a known flow rate.

4.7.13.2.3 Leak test using a tracer vapor.

4.7.13.2.4 Ultrasonic, etc.

4.7.13.3 Alternative tests could be developed which may be equally appropriate for a particular design. A relevant leak test specification should be established as part of the maintenance program.

4.7.13.4 LEAK TEST BY PRESSURE DROP

4.7.13.4.1 The isolator is completely sealed and pressure increased to greater than normal working pressure. The pressure source is isolated, and pressure and temperature documented every two minutes, for up to 30 minutes to allow the pressure to equilibrate. The test should be performed under conditions of constant temperature and background room pressure. The test can be used only to indicate gross leakage due to the effects of temperature and barometric pressure change. It is a useful safety precaution and integrity check prior to decontamination.

4.7.13.5 LEAK TEST BY MAINTAINING A CONSTANT PRESSURE WITH A KNOWN FLOW RATE

4.7.13.5.1 The isolator is completely sealed and pressurized to the test pressure, and it is then held at the test pressure by injecting air, at a known flow rate, to compensate for leaks.

4.7.13.5.2 In this case, the pressure and leak rate remain constant, and there is no change in volume during the test. To give meaningful results, a high precision flow meter is required and the temperature and pressure are accurately documented and compensated for in the calculation.

4.7.13.6 LEAK TEST USING A TRACER VAPOR

4.7.13.6.1 The tracer vapor cylinder (helium or ammonia) is placed inside the isolator which is then completely sealed.

4.7.13.6.2 The isolator is pressurized using the tracer vapor and a vapor detector is used to scan all seals, gaskets, sleeves, etc.

4.7.13.6.3 Some method of circulating the air inside the isolator should be employed.

4.7.13.7 OTHER TEST METHODS

4.7.13.7.1 Ultrasonic (results are difficult to interpret due to different materials and wall thicknesses).

4.7.13.7.2 Soap solution may be applied to seals and gaskets joints when the isolator is under pressure.

4.7.13.7.3 Smoke testing with dispersed particulate, pressurized within the isolator and a particle count system applied around the seals and joints; an oil-free smoke substitute should be used that does not inhibit decontamination or support microbiological growth.

4.7.13.7.4 **Note:** Titanium oxide smoke sticks should not be used for airflow testing as a deposit forms on the surfaces which is not easily cleaned, and is a catalyst to the breakdown of hydrogen peroxide.

4.7.13.7.5 Precautions should be taken to protect in-situ particle count apparatus.

4.7.13.8 LEAK TESTING FREQUENCY

4.7.13.8.1 Leak tests should be performed on a regular basis for both safety and verification of enclosure integrity. Frequency depends on whether the system is a pressure/vacuum (containment) system. The decision on leak testing frequency should be based on a risk assessment and depend upon the following:

4.7.13.8.1.1 Isolator system application

4.7.13.8.1.2 Operator and background environment hazards

4.7.13.8.1.3 Background environment quality

4.7.13.8.1.4 Isolator design

4.7.13.8.1.5 Preventative maintenance needs

4.7.13.8.2 This decision also should consider the effect of vibration from fans, filling equipment, etc., on joints, HEPA filter clamping systems, or rubber gaskets that may become brittle over a period of time, due to exposure to sanitizing vapor.

4.7.14 AIR SYSTEM TESTING

4.7.14.1 The air circulating system is tested in a similar way to any traditional classified area. Test specifications will normally include:

4.7.14.1.1 Overpressures, monitored continuously.

4.7.14.1.2 Air change rates or airflow volume.

4.7.14.1.3 Pressure drops across HEPA filters.

4.7.14.1.4 HEPA leak test.

4.7.14.1.5 Airflow video with oil free smoke or water vapor.

4.7.14.1.6 Air velocities at various critical locations.

4.7.14.1.7 Particulate counting.

4.7.14.1.8 Temperature.

4.7.14.1.9 Relative humidity.

4.7.14.2 The design of the air-handling control system should enable those physical parameters that characterize the performance of the system to be easily documented. This automated system will be subject to the requirements of GMP as applied to software development and validation.

4.7.14.3 If this is the case and, if over a period of time, it can be demonstrated that the control environment conditions are maintained, the level of microbiological monitoring may be reduced.

4.7.14.4 Of these physical parameters, the DP throughout the system and the non-viable particle count should be monitored continuously at predetermined critical points.

4.7.15 MAINTENANCE

4.7.15.1 Improperly maintained RABS and isolators can negatively impact sterility assurance, so an adequate, condition based, preventative maintenance program is critical. Poor maintenance and inadequate attention to operating procedures are the usual causes of failure.

4.7.15.2 Ergonomic modeling must consider the requirements of maintenance personnel who perform ongoing running adjustments to machinery. In this respect, the design should consider the maintenance aspects of the enclosure, its support services, and the equipment contained therein. Provision of maintenance access panels is a crucial aspect of the design.

4.7.15.3 In addition to filters, gaskets, and seals, maintenance must consider items peculiar to the enclosure, such as door seals, transfer port gaskets, and the attachment of glove rings to glazing panels. Among other components in the maintenance program, HEPA filters and gloves should be replaced on a regularly scheduled basis.

4.7.15.4 Since monitoring of physical parameters is crucial to the overall confidence of an aseptic environment, protocols should be developed for the calibration of sensors on an ongoing basis. Particular consideration should be given to providing test equipment to calibrate dedicated probes, such as combined temperature and humidity sensors, or pressure transducers.

4.7.15.5 The maintenance schedule should also encompass any sensors, HEPA filters, or calibrated equipment related to decontaminant vapor generation equipment.

4.7.15.6 TRAINING

4.7.15.6.1 The selection, training, and motivation of personnel are vital to Good Manufacturing Practice. Exclusive reliance on the enclosure to preserve the aseptic processing environment will not be enough and may give a false sense of security. Operators should be given a thorough understanding of how to operate the control system and perform the aseptic operation within it. The operator is required to have knowledge of the transfer devices and decontamination system and their inter-relationship with the overall aseptic process. As always, operators should adhere to aseptic techniques in performing manipulations for any aseptic process. Operator procedures should not permit inappropriate manipulation by gloves or gauntlets in the critical zone and should stress the use of sterile tools during aseptic operations. Training should consist of both theoretical and practical aspects, concluding with a formal, documented assessment and authorization to work with the system.

4.8 GENERAL CONSIDERATIONS

4.8.1 This chapter covers other considerations that may have an effect on the CGMP issues outlined in this Baseline® Guide. These include key non-GMP regulatory/compliance design issues, such as environmental, health, and safety, etc., that should be considered for successful facility design, and which may otherwise indirectly affect CGMP.

4.8.2 It is assumed that the reader of this Guide understands and applies the principles of Good Engineering Practice (GEP); it is not the intention of this section to offer GEP guidance or to list the vast array of regulations with which engineers work.

4.8.3 Specific country or region regulations may apply that are not covered within this chapter. It should be noted that a facility must adhere to the legislative requirements of the country in which it is based, even if the product will be exported to another country, e.g., some legislation in the country of manufacture may be more stringent than the country into which the pharmaceutical product is being imported.

4.8.4 The following is not intended to be a comprehensive reference source or to cover all relevant regulatory or other aspects.

4.8.5 ENVIRONMENTAL – GENERAL

4.8.5.1 The environmental impact of the processing should be considered

4.8.5.2 There is significant pressure, both statutory and voluntary, on the pharmaceutical industry to reduce the environmental load from processes, including energy usage. All areas of the product supply chain and product life cycle should be considered, e.g.:

4.8.5.2.1 Processing waste.

4.8.5.2.2 Environmentally friendly packaging.

4.8.5.2.3 Facility energy usage.

4.8.5.2.4 Emissions such as greenhouse gases or acidic gases.

4.8.5.2.5 Facility water usage.

4.8.5.2.6 Non-processing waste.

4.8.5.2.7 Facility and equipment disposal.

4.8.5.3 Sterile processes may be completely CGMP compliant, but may still not be completely within other regulations if the environmental impacts are not considered during the design process (product, process, and facility). Likewise, there may be instances where the requirements of GEP in this area conflict or contradict CGMPs.

4.8.5.4 The engineering solution should consider both issues: GEP and CGMP. Note: Although the above is written from a GEP perspective, there is an FDA expectation that processes will not violate other regulatory requirements.

4.8.6 PARTICULATE EMISSIONS – AIR

4.8.6.1 At-source containment of solid materials is recommended as the best means of controlling particulate emissions. Where this is not possible and high airborne concentrations are unavoidable, regulations often require efficient exhaust filtration. In addition, high efficiency air filtration may be required before discharge in to the atmosphere. Permissible emission levels for pharmaceutical dusts are particularly low in most regulations.

4.8.7 VOLATILE ORGANIC COMPOUNDS (VOCS), ODORS, AND COMBUSTION PRODUCTS

4.8.7.1 Typically, sterile facilities do not generate large quantities of these substances. More often, they can arise from cleaning, disinfection, and fumigation activities. Disposal or removal of fumigants (liquid or airborne) is a particular challenge in this respect. Storage of combustible materials may require control zones within a facility with maximum quantities per control zone. Relevant regulatory requirements should be taken into account in this area of plant design. Permits and waste recovery may be required.

4.8.8 OZONE DEPLETERS

4.8.8.1 HVAC cooling systems, freeze dryers, and other process equipment may contain refrigerants that affect atmospheric ozone. Local regulations may require certified repair and service personnel.

4.8.9 ENVIRONMENTAL – WASTE WATER

4.8.9.1 Waste water discharges are regulated in most countries. Design should address the control of discharges and consider the assimilative capacity of receiving waters. Use of solvents to clean process equipment increases the risk of solvent losses from the plant and, potentially, into the environment. There may be a local requirement to recycle solvent. This introduces cross contamination issues into the processes, which could have a CGMP impact and should be addressed. (See Chapter 4 of this Guide.) Water treatment, cleaning, and washing operations can generate significant volumes of waste water from sterile facilities, and in some instances, water conservation measures may be appropriate.

4.8.9.2 SPILL PREVENTION

4.8.9.2.1 Regulatory authorities may require measures for spill prevention or containment within manufacturing and storage areas.

4.8.9.3 FIRE WATER RETENTION FACILITIES

4.8.9.3.1 Retention facilities (ponds, dikes) may be required to avoid storm water or surface water contamination in the event of fire.

4.8.9.4 EFFLUENT TREATMENT

4.8.9.4.1 Effluent treatment may be required, depending upon projected loads and local discharge standards. Treatment steps may be chemical, biological, or combinations of both. The location of treatment facilities, in relation to plant air/HVAC intakes, should be given careful consideration.

4.8.9.5 WASTE WATER SEGREGATION

4.8.9.5.1 Varying levels or types of contamination from different operations may require segregation of waste water streams within manufacturing and utilities areas. Hydraulic loadings on treatment facilities should be minimized and special arrangements made for handling lightly contaminated aqueous streams.

4.8.9.6 RECYCLING/WASTE MINIMIZATION

4.8.9.6.1 Authorities may seek application of the principles of clean manufacturing and resource conservation. In sterile facilities, these principles, initially, may conflict with GMP requirements. These potential conflicts should be reconciled during the design stage.

4.8.10 ENVIRONMENTAL NOISE

4.8.10.1 EXTERNAL NOISE

4.8.10.1.1 Due to their large air handling requirements, sterile facilities may be a source of objectionable noise outside the building. Fans, compressors, and other utilities equipment can generate unacceptable noise levels, in terms of both volume and frequency. Local regulations should be checked so as to ensure that boundary noise does not exceed acceptable levels. Suitable attenuation techniques should be employed to comply with the appropriate levels.

4.8.10.2 NOISE SENSITIVE AREAS

4.8.10.2.1 In addition to regulatory requirements, sensitivity of the surrounding community to noise should be assessed at site selection and early design stage. Existing and potential residential developments should be considered, and surrounding topography should be assessed for rural sites.

4.8.10.3 NOISE IN WORKING ENVIRONMENT

4.8.10.3.1 Strict standards are applied by health and safety bodies in respect to noise in the working environment. Manufacturing and utilities equipment specifications must comply with the appropriate standards, and localized attenuation implemented where needed. It is not unusual for processing equipment to be the major source of noise in the workplace, especially where glassware is handled.

4.8.10.4 NOISE REDUCTION

4.8.10.4.1 If possible, noise generating equipment should be located remote from work areas. As sound attenuation usually contains soft material, cleanable non-shedding materials may be used as noise reduction measures in the facility or in HVAC. Typical clean area finishes offer little sound absorption potential, so noise is addressed in equipment specifications (e.g., larger fans running at lower speeds in the HVAC air handler). If noise cannot be controlled in other ways, sound attenuation materials in air handling systems should provide optimum cleanability and not harbor bio-burden. Product and process requirements should be taken into account when designing noise attenuation systems.

4.8.11 ENVIRONMENTAL-SOLID AND CONCENTRATED WASTES

4.8.11.1 RESPONSIBILITY

4.8.11.1.1 Off-site disposal of some wastes from sterile facilities may be necessary. In general, plant site operators remain responsible for downstream environmental and safety hazards arising from offsite disposal. Disposal contractors should be controlled carefully, and, in some instances, licensed. Disposal operations may require certification.

4.8.11.2 LANDFILL SITES

4.8.11.2.1 Landfill sites are subject to an increasing level of control by authorities, and their location, suitability, and management should be assessed. In some areas, even innocuous solid wastes from pharmaceutical operations are subject to strict control.

4.8.11.3 SHIPMENTS OF WASTES

4.8.11.3.1 EU and US regulations apply strict controls for both internal and trans-border shipments of hazardous materials. These should be taken into account in logistics planning of facility operation.

4.8.11.4 INCINERATION

4.8.11.4.1 Incineration may be essential for disposal of toxic, or potent, solids or liquids, and may be located on or off-site. On site incineration can raise particularly sensitive environmental issues, and disposal in this manner often requires an increased level of licensing and certification.

4.8.12 HEALTH AND SAFETY

4.8.12.1 HAZARD IDENTIFICATION

4.8.12.1.1 Safety should be built in to the facility and equipment design, and should not be excessively reliant on compliance by operators to procedures. A robust "what if" scenario analysis or a Hazard and Operability Study (HAZOP)/Hazard Identification (HAZID)/Hazard Analysis (HAZAN) process should be used to identify potential processing safety issues. A mitigation plan should be developed to address areas of risk.

4.8.12.1.2 The engineering solution should consider both GEP and CGMP. Processes may be completely CGMP compliant, but may not be completely within current legislation, if safety issues are not considered during design of facility and process.

4.8.12.2 TRAINING AND SAFE BEHAVIORS

4.8.12.2.1 Training is a regulatory requirement under CGMP. An essential element of safe behaviors is driven by attitude and a core value that safety can never be compromised. Operator safety during normal operations and mishaps also should be reviewed. Training also should be evaluated f or manual and material handling operations, including potential operational exposure, knowledge of universal precautions, and the use of personal protective equipment. All personnel involved with the design and operation of a facility should consider the hazardous nature of the solvents or chemicals in use for each process.

4.8.12.2.2 A construction safety training program should complement the safe design of a facility.

4.8.12.3 POTENT AND TOXIC PRODUCTS

4.8.12.3.1 Potent and toxic products require special design considerations. Containment considerations may conflict with cleanroom design principles, such as positive pressure cascades, and require special attention to HVAC and building design. Operator exposure limits should be established for the material being handled, and should form the basis for design of containment or isolation measures.

4.8.12.4 CLEANING AND DISINFECTANT MATERIALS

4.8.12.4.1 Many materials used for these purposes are hazardous chemicals, and safe handling methods should be incorporated in the design and operating procedures. As cleaning and sanitizing dilutions should be made up fresh daily, there is potential for personnel to have frequent exposure to these chemicals.

4.8.12.5 MATERIALS HANDLING

4.8.12.5.1 Mechanical handling methods help avoid unsafe lifting practices. These should be addressed in early design phases as they may affect building layout and structure. Local and national requirements should be applied to certification of lifting devices, etc.

4.8.12.5.2 Techniques for dust minimization at transfer points for solid materials should be included in the design.

4.8.12.6 SURFACES AND SAFE ACCESS

4.8.12.6.1 Cleanability and sanitizability requirements should be combined with non-slip properties when specifying floor surfaces.

4.8.12.6.2 Dedicated access routes for operation and maintenance of equipment should be incorporated in building layouts.

4.8.12.7 FIRE PREVENTION

4.8.12.7.1 The requirements for fire protection (e.g., sprinklers) in clean areas may conflict with the CGMP needs of that clean area, i.e., the inclusion of fire protection equipment can add additional potential contaminants to the clean environment. Sprinkler systems create cleaning and air pressure leakage problems in clean areas, so alternative fire prevention methods may be specified. Building specifications can require fire resistant construction, addressing flame spread properties, and avoiding combustible materials.

4.8.12.8 MEANS OF ESCAPE

4.8.12.8.1 The requirements for exiting a facility in an emergency may conflict with CGMP considerations when considering the philosophy of protecting the product in open processing. Design of sterile facilities should overcome the conflict between complex entry and exit routines to preserve air pressure cascades and fire escape routes to get people safely out of the facility. An emergency exit should avoid conflict with clean area requirements. Door interlocks should be overridden when emergency exit is necessary.

4.8.12.9 PROTECTION OF MACHINERY

4.8.12.9.1 Operators should be protected from moving components in manufacturing and utility equipment. Adequate guarding, interlocking, and safe maintenance access should be provided. Sharp edges on equipment and transfer systems should be avoided. Equipment design should address particularly potential hand injuries.

4.8.12.10 ELECTRICAL SAFETY

4.8.12.10.1 Most electrical design codes incorporate adequate electrical safety, which should be incorporated in facility design. IEEE or harmonized European Standards for electrical equipment, particularly in hazardous areas, should be addressed where appropriate.

4.8.12.11 SAFETY OF PRESSURIZED SYSTEMS

4.8.12.11.1 Recognized standards must be implemented in specifying boilers, pressure vessels, piping systems, etc. Although US and international codes have general acceptability, local requirements should also be incorporated in system design.

4.8.12.12 DUST EXPLOSION AND STATIC HAZARDS

4.8.12.12.1 Dust explosion and static hazards should be addressed carefully when solid materials are being handled in powder form. Explosion risks should be assessed for significant solids transfer operations, including dispensing, size reduction, dust collection, etc. Adequate explosion venting to atmosphere should be provided where appropriate. In some instances, explosion containing systems are required for particularly hazardous operations. Process inerting may be required.

4.8.13 SITE SELECTION AND LOCATION

4.8.13.1 AMBIENT AIR QUALITY

4.8.13.1.1 This is a primary requirement in site selection for a sterile facility. If the facility is located in an industrial or agricultural area, the impact of activities in those areas should be considered. Air sampling and analysis for the presence of objectionable levels of chemicals and dust may be appropriate prior to site selection.

4.8.13.2 WATER SUPPLY

4.8.13.2.1 A reliable supply of good quality water is important for pharmaceutical facilities. Local water sources should be assessed prior to site selection, noting that the quality may be subject to seasonal variation. If municipal water is available, in addition to quality, the level of its pretreatment should be assessed. Excessive chlorination may cause difficulties in water treatment and purification for sterile products.

4.8.13.3 ENVIRONMENTAL SENSITIVITY

4.8.13.3.1 Site selection should address the potential environmental sensitivity of the selected area. The existence of recreational areas, nature preserves, watersheds, flood plains, endangered species, etc., may require investigation.

4.8.13.4 OTHER SELECTION CONSIDERATIONS

4.8.13.4.1 Other considerations in selection of sites for sterile facilities should include:

4.8.13.4.1.1 Climatic conditions.

4.8.13.4.1.2 Local geographic conditions.

4.8.13.4.1.3 Suitability of site for building foundations.

4.8.13.4.1.4 Requirements for special structural or seismic design.

4.8.13.4.2 Communities and industrial parks may require adherence to specific architectural standards.

4.8.13.5 LOCAL CODE OFFICIALS

4.8.13.5.1 Depending on the geographical location of the sterile product manufacturing facility, the learning curve of local officials may be quite steep. Local code officials may not have the knowledge or the experience to understand the scope of work, or how to apply the current codes, standards, and regulation to the permitting, inspection, and approval of these facilities. It helps to develop a relationship with local code officials early in the programming and conceptual design stage of the project to build trust and alignment. The officials may need to be educated about the business, the facility design, its processes, and the project schedule. Discussions should cover the execution plans for the facility fit-out and qualification activities. If possible, local officials may visit other similar facilities to gain a greater level of understanding prior to the permitting, inspection, and approval process.

4.8.14 ENERGY SOURCES

4.8.14.1 NATURAL GAS

4.8.14.1.1 A nearby natural gas source is an advantage and should be assessed as a part of the initial site selection. Oil or other energy sources are normally transportable and should be easily accessible on the site.

4.8.14.2 FUEL STORAGE

4.8.14.2.1 Storage facilities should be specified on the basis of incoming supply usage and reliability. Storage facilities should be designed in accordance with recognized standards and provide adequate environmental protection against spillage.

4.8.14.3 ELECTRICAL SUPPLIES AND CHARACTERISTICS

4.8.14.3.1 The key requirement for electrical power supplied to a sterile facility is reliability. The consequences of power failures are serious (especially if frequent or extended), and should be evaluated prior to site selection. Characteristics of the available supply should be checked. Misunderstandings can occur due to specification of incorrect voltages and frequencies. In addition to nominal values, the tolerance range for local supplies should be evaluated.

4.8.14.4 ENERGY CONSERVATION

4.8.14.4.1 It is prudent to incorporate a level of energy conservation within the facility design, in anticipation of increasing regulatory requirements and economic pressure in this respect. Non-contaminating heat recovery arrangements and combined heat and power (cogeneration) systems should be considered for installation in the future.

4.8.14.4.2 Facilities in Europe should consider workplace access to a window to the outdoors. This can be an energy saving feature, but usually is driven by operator health and safety requirements.

4.8.15 AUDITING, MONITORING, AND REPORTING

4.8.15.1 FREEDOM OF ACCESS TO INFORMATION

4.8.15.1.1 The US and European regulations incorporate legal requirements for freedom of access to information. These should be addressed at the design stage, and procedures developed to comply with their operational requirements.

4.8.15.2 ENVIRONMENTAL IMPACT STATEMENTS

4.8.15.2.1 Both US and European regulations require Environmental Impact Assessments (EIA) prior to proceeding with industrial developments. These requirements, and the time for processing the information and procuring permits, should be allowed for in design schedules.

4.8.15.3 EMERGENCY PLANNING

4.8.15.3.1 For regulatory reasons and good operating practice, emergency response plans should be prepared for the facility.

4.8.15.4 ENVIRONMENTAL MANAGEMENT SYSTEMS

4.8.15.4.1 Most authorities require some level of management system for an environmental program. This requirement should be addressed at the design stage.

4.8.15.5 EMISSIONS REGISTER

4.8.15.5.1 The regulatory standards of a country may require comprehensive records for monitoring of ongoing emissions, as well as documenting and explaining deviations from accepted standards.

4.8.15.6 DOCUMENTATION

4.8.15.6.1 It is good engineering practice to document both the design and the operation of a facility.

4.8.15.6.2 In order to comply with GEP, specific documentation may be required, in addition to that required by CGMP; for instance, pressure vessel regulations require significant documentation to show that all pressure systems are designed with due regard to safety regulations.

4.8.15.6.3 Commissioning documents should reflect adherence to non-GMP regulations, as described in the user requirements documentation created at the start of the project.

4.8.16 SECURITY

4.8.16.1 CONTROLLED SUBSTANCES

4.8.16.1.1 Where appropriate, secure storage areas should be provided for controlled narcotics and other listed dangerous substances.

4.8.16.2 DOCUMENT STORAGE

4.8.16.2.1 Consideration should be given to secure fireproof storage for hard copy manufacturing documents. Backup procedures and off-site storage may be necessary for electronically stored data. Refer to US FDA 21 CFR Part 11 (electronic records and electronic signature regulation) and EU GMP Chapter 4 and Annex 11 for more information on requirements for integrity of records maintained electronically.

4.8.16.3 LOGICAL SECURITY

4.8.16.3.1 In addition to providing physical security for a sterile pharmaceutical facility, logical security should also be considered. The appropriate safeguards for information and automation systems should be part of the facility design. Safeguards may include information network firewalls, use of usernames and passwords to log into computer systems, and controls for downloading and changing process recipes. Systems should provide a means to change usernames and passwords on a periodic basis. Systems should be designed to provide data acquisition and enable periodic back up of data.

4.8.16.4 LABEL STORAGE

4.8.16.4.1 Secure facilities are required for labels and printed packaging materials. In addition to internal accountability, storage of labels and printed packaging materials should be secured against external interference.

5.0 : ATTACHMENTS/ASSOCIATED FORMS

ATTACHMENT NO.	ATTACHMENT TITLE
Attachment – 1	Multiple guidance requirements for building & facilities (for reference only).

******* End of Document*******

Attachment 1

Multiple Guidance Requirements for Building & Facilities

USFDA - Sterile Drugs Products Produced by Aseptic Processing, Sep-2004, Sec. IV, Building and facilities	Annex 1, EU Manufacture Sterile Medicinal Products Guidelines - November 25, 2008	WHO GMP Guidelines Annex 6	PIC/S PI032-02 Annex 1 Guideline Interpretations
"The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination." As provided for in the regulations, separate or defined areas of operation in an aseptic processing facility should be appropriately controlled to attain different degrees of air quality depending on the nature of the operation. Design of a given area involves satisfying microbiological and particle criteria as defined by the equipment, components, and products exposed, as well as the operational activities conducted in the area. Clean area control parameters include microbiological and particulate data. Initial qualification includes an assessment of air quality under static conditions and dynamic conditions. Aseptic processing facility monitoring program assess conformance with specified clean area classifications under dynamic conditions on a routine basis. Two clean areas are of particular importance to sterile drug product quality: the critical area, and the supporting clean areas associated with it.	3. Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risks of particulate or microbial contamination of the product or materials being handled. Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products. 2. The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are divided into two categories; firstly, those where the product is terminally sterilized, and secondly those which are conducted aseptically at some or all stages. 4. Clean rooms and clean air devices should be classified in accordance with EN ISO 14644-1. 7. "In operation" classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this. EN ISO 14644-2 provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.	7.2 The operating conditions should be such as to prevent microbial contamination. 1.2 The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilization should be carried out in separate areas within the clean area. These areas are classified into four grades. 1.3 Manufacturing operations are divided here into two categories: • first, those where the product is terminally sterilized; and second, those which are conducted aseptically at some or all stages 4.1 Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate level of environmental cleanliness in the operational state to minimize the risks of particulate or microbial contamination of the product or materials being handled. 4.3 For the manufacture of sterile pharmaceutical preparations, four grades of clean areas are distinguished as follows:	4.1 Clean room/clean air device classification. Section 3 defines at rest and in operation states, which are not new. However, it should be noted that the company needs SOPs to define at rest and in operation states, which might be specifically required for each production room. These SOPs should include a definition of equipment to be installed and running, number of operators to be present, etc. 4.2 Clean room/clean air device monitoring Section 15: New text: The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended "clean up period" should be attained. Interpretation: The number of sampling points and the sampling frequency are to be determined by at least a risk assessment, including risk identification, risk analysis and risk evaluation (see also GMP Annex 20). There is no need for a continuous monitoring. However, the frequency should be higher than that of ReQualification of these areas.

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A critical area is one in which the sterilized drug product, containers, and closures are exposed to environmental conditions that must be designed to maintain product sterility (§ 211.42(c) (10)). Activities conducted in such areas include manipulations (e.g., aseptic connections, sterile ingredient additions) of sterile materials prior to and during filling and closing operations. This area is critical because an exposed product is vulnerable to contamination and will not be subsequently sterilized in its immediate container. To maintain product sterility, it is essential that the environment in which aseptic operations (e.g., equipment setup, filling) are conducted be controlled and maintained at an appropriate quality. One aspect of environmental quality is the particle content of the air. Particles are significant because they can enter a product as an extraneous contaminant, and can also contaminate it biologically by acting as a vehicle for microorganisms (Ref. 2). Appropriately designed air handling systems minimize particle content of a critical area.	15. The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended “clean up period” should be attained. 5. For classification purposes in Grade A zones, a minimum sample volume of 1m3 should be taken per sample location. For Grade A the airborne particle classification is ISO 4.8 dictated by the limit for particles ≥5.0 um. For Grade B (at rest) the airborne particle classification is ISO 5 for both considered particle sizes. For Grade C (at rest & in operation) the airborne particle classification is ISO 7 and ISO 8 respectively. For Grade D (at rest) the airborne particle classification is ISO 8. For classification purposes EN/ISO 14644-1 methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size and the method of evaluation of the data collected.	• Grade A: The local zone for high-risk operations, e.g. filling and making aseptic connections. Normally such conditions are achieved by using a unidirectional airflow workstation. Unidirectional airflow systems should provide a homogeneous air speed of 0.36–0.54 m/s (guidance value) at a defined test position 15–30 cm below the terminal filter or air distributor system. The velocity at working level should not be less than 0.36 m/s. The uniformity and effectiveness of the unidirectional airflow should be demonstrated by undertaking airflow visualization tests; • Grade B: In aseptic preparation and filling, this is the background environment for the grade A zone; • Grades C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products or carrying out activities during which the product is not directly exposed (i.e. aseptic connection with aseptic connectors and operations in a closed system). A unidirectional airflow and lower velocities may be used in closed isolators and glove boxes. 4.6.2 For classification purposes in Grade A zones, a minimum sample volume of 1 m^3 should be taken per sample location.	4.1 Clean room / clean air device classification A formal risk analysis study based on experiments and analysis of the monitoring data (over at least 6 months of operation) should provide a basis for the determination of frequencies and limits. Frequencies and limits should be process based and the results of the initial qualification and ongoing monitoring should be taken into account when setting operational alert and action limits. These limits and sample locations should be periodically reviewed for on-going validity of the risks initially considered. Those frequencies and limits should be process-based and the results of the qualification should be taken into account. 4.2 Clean room/clean air device monitoring Section 8: New text: Clean rooms and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.

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Air in the immediate proximity of exposed sterilized containers/closures and filling/closing operations would be of appropriate particle quality when it has a per-cubic-meter particle count of no more than 3520 in a size range of 0.5 µm and larger when counted at representative locations normally not more than 1 foot away from the work site, within the airflow, and during filling/closing operations. This level of air cleanliness is also known as Class 100 (ISO 5). We recommend that measurements to confirm air cleanliness in critical areas be taken at sites where there is most potential risk to the exposed sterilized product, containers, and closures. The particle counting probe should be placed in an orientation demonstrated to obtain a meaningful sample. Regular monitoring should be performed during each production shift. We recommend conducting nonviable particle monitoring with a remote counting system. These systems are capable of collecting more comprehensive data and are generally less invasive than portable particle counters. Some operations can generate high levels of product (e.g., powder) particles that, by their nature, do not pose a risk of product contamination.	1. The manufacture of sterile products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency. 6. Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of precipitation of particles ≥5.0um in remote sampling systems with long lengths of tubing. Isokinetic sample heads shall be used in unidirectional airflow systems.	4.7.1 For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, for example, live organisms and radiological hazards. In such cases monitoring during routine equipment set-up operations should be undertaken before exposure to the risk. Monitoring during simulated operations should also be performed. The Grade A zone should be monitored at a frequency and sample size such that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of ≥ 5.0 µm particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself. 4.9 Levels of detection of microbial contamination should be established for the purpose of setting alert and action limits and for monitoring the trends in environmental cleanliness in the facility. Limits expressed in colony-forming units (CFU) for the microbiological monitoring of clean areas in operation.	Interpretation: Frequency, location and number of monitoring locations should be based on a formal risk assessment and not on ISO 14644-1. Data obtained during classification and previous monitoring data should be considered. Critical locations should be covered. 4.2 Clean room / clean air device monitoring Section 15: New text: The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended “clean up period” should be attained. Interpretation: The number of sampling points and the sampling frequency are to be determined by at least a risk assessment, including risk identification, risk analysis and risk evaluation (see also GMP Annex 20). There is no need for a continuous monitoring. However, the frequency should be higher than that of re-qualification of these areas.

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It may not, in these cases, be feasible to measure air quality within the one-foot distance and still differentiate background levels of particles from air contaminants. In these instances, air can be sampled in a manner that, to the extent possible, characterizes the true level of extrinsic particle contamination to which the product is exposed. Initial qualification of the area under dynamic conditions without the actual filling function provides some baseline information on the non-product particle generation of the operation. HEPA (High Efficiency Particulate Air) filtered air should be supplied in critical areas at a velocity sufficient to sweep particles away from the filling/closing area and maintain unidirectional airflow during operations. The velocity parameters established for each processing line should be justified and appropriate to maintain unidirectional airflow and air quality under dynamic conditions within the critical area (Ref. 3). (A velocity of 0.45 meters/second (90 feet per minute) has generally been established, with a range of plus or minus 20 percent around the set point. Higher velocities may be appropriate in operations generating high levels of particulates.)	9. For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g., live organisms and radiological hazards. In such cases monitoring during routine equipment set up operations should be undertaken prior to exposure to the risk. Monitoring during simulated operations should also be performed. The Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events, and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of ≥5.0um particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.	1.1 The production of sterile preparations should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency. 4.6.1.1 Classification should be clearly differentiated from operational process environmental monitoring. 11.9 A filtered air supply should be used to maintain a positive pressure and an airflow relative to surrounding areas of a lower grade under all operational conditions; it should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of approximately 10–15 Pascal (guidance value). Particular attention should be paid to the protection of the zone of greatest risk, i.e. the immediate environment to which the product and the cleaned components in contact with it are exposed. The recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain certain materials, e.g. pathogenic, highly toxic, radioactive, or live viral or bacterial materials or products.	4.1.3 It should be considered that inert gases will prevent the growth of aerobic microorganisms. Therefore, for process simulations sterile filtered air should be used instead of inert gases, also for breaking a vacuum. Where anaerobes are detected in the environmental monitoring or sterility testing, the use of an inert gas should be considered for a process simulation, as inert gas is supporting the growth of anaerobes. 4.1.4 Before enumerating the different process simulation test procedures some preliminary explanations are necessary for the preparation of liquid media as it is used for the majority of the process simulation tests. Where a liquid nutrient medium is used, it should be prepared in a similar manner to the product.

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Proper design and control prevents turbulence and stagnant air in the critical area. Once relevant parameters are established, it is crucial that airflow patterns be evaluated for turbulence or eddy currents that can act as a channel or reservoir for air contaminants (e.g., from an adjoining lower classified area). In situ air pattern analysis should be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions. The studies should be well documented with written conclusions, and include evaluation of the impact of aseptic manipulations (e.g., interventions) and equipment design. Videotape or other recording mechanisms have been found to be useful aides in assessing airflow initially as well as facilitating evaluation of subsequent equipment configuration changes. It is important to note that even successfully qualified systems can be compromised by poor operational, maintenance, or personnel practices.	10. It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. The importance of the particle monitoring system should be determined by the effectiveness of the segregation between the adjacent Grade A and B zones. The Grade B zone should be monitored at such a frequency and with suitable sample size that changes in levels of contamination and any system deterioration would be captured and alarms triggered if alert limits are exceeded. 8. Clean rooms and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices. 54. It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle¬ generating person, operation or machine to a zone of higher product risk.	The decontamination of the facilities and the treatment of air leaving a clean area may be necessary for some operations. 11.10 It should be demonstrated that airflow patterns do not present a contamination risk; for example, care should be taken to ensure that particles from a particle-generating person, operation or machine are not conveyed to a zone of higher product risk. 11.8 Airlock doors should not be opened simultaneously. An interlocking system and a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time. 11.11 A warning system should be operated to indicate failure in the air supply. Indicators of pressure differentials should be fitted between areas where this difference is important, and the pressure differentials should be regularly recorded and failure alarmed. 4.4 In order to reach the B, C and D air grades the number of air changes should be appropriate for the size of the room and the equipment and personnel present in it.	The medium should be dissolved in Water for Injection in a standard manufacturing vessel. If heat is required to dissolve it then only minimal heat should be used. The pH of the medium should be measured and, if necessary, adjusted to bring it into the required range. The medium should be aseptically filtered into an aseptic holding vessel using the normal production filter and processing procedure. In justified cases it may be also acceptable to sterilize the media. All aseptic holding vessels should be covered by a process simulation test on a regular basis unless a validated, pressure hold or vacuum hold test is routinely performed. 9.7.1 Aseptic holding and filling vessels should be subject to routine planned preventive maintenance. Gaskets and O-rings should be checked regularly. Sight-glass gaskets are rarely checked routinely, and, after a number of autoclave cycles, may become brittle and allow bypass of room air. All vessels should be subject to regular leak testing (pressure hold or vacuum hold). Where glass vessels are used, an alternative leak test method should be advised.

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Air monitoring samples of critical areas should normally yield no microbiological contaminants. We recommend affording appropriate investigative attention to contamination occurrences in this environment. Supporting clean areas can have various classifications and functions. Many support areas function as zones in which non-sterile components, formulated products, in-process materials, equipment, and container/closures are prepared, held, or transferred. These environments are soundly designed when they minimize the level of particle contaminants in the final product and control the microbiological content (bio-burden) of articles and components that are subsequently sterilized. The nature of the activities conducted in a supporting clean area determines its classification. FDA recommends that the area immediately adjacent to the aseptic processing line meet, at a minimum, Class 10,000 (ISO 7) standards under dynamic conditions. Manufacturers can also classify this area as Class 1,000 (ISO 6) or maintain the entire aseptic filling room at Class 100 (ISO 5).	13. In Grade A and B zones, the monitoring of the ≥5.0um particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure. The occasional indication of ≥5.0um particle counts may be false counts due to electronic noise, stray light, coincidence, etc. However, consecutive or regular counting of low levels is an indicator of a possible contamination event and should be investigated. Such events may indicate early failure of the HVAC system, filling equipment failure or may also be diagnostic of poor practices during machine set-up and routine operation. 18. Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air, and surface sampling (e.g., swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitization.	4.37 Components, bulk-product containers, equipment, and any other articles required in a clean area where aseptic work is in progress, should be sterilized and wherever possible passed into the area through double-ended sterilizers sealed into the wall. Other procedures that prevent the introduction of contamination may be acceptable in some circumstances. 4.35 Any gas that is used to purge a solution or blanket a product should be passed through a sterilizing filter. 7.7 The integrity of the sterilized filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from these during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals. Consideration should be given to	9.6.1 It is important that the integrity of critical gas and air vent filters is confirmed immediately after the filling and if it fails, the disposition of the batch determined. In practice vent filters fail the integrity test more frequently than product filters as generally they are less robust and more sensitive to pressure differentials during steam sterilization.

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An area classified at a Class 100,000 (ISO 8) air cleanliness level is appropriate for less critical activities (e.g., equipment cleaning). An essential part of contamination prevention is the adequate separation of areas of operation. To maintain air quality, it is important to achieve a proper airflow from areas of higher cleanliness to adjacent less clean areas. It is vital for rooms of higher air cleanliness to have a substantial positive pressure differential relative to adjacent rooms of lower air cleanliness. For example, a positive pressure differential of at least 10-15 Pascal (Pa) (equal to 0.04-0.06 inches of water gauge) should be maintained between adjacent rooms of differing classification (with doors closed). When doors are open, outward airflow should be sufficient to minimize ingress of contamination, and it is critical that the time a door can remain ajar be strictly controlled (Ref. 4).	19. Recommended limits for microbiological monitoring of clean areas during operation: (See table) 46. In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used. 47. To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards, and equipment. Doors should be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason. 48. False ceilings should be sealed to prevent contamination from the space above them. 49. Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean. 64. Precautions to minimize contamination should be taken during all processing stages including the stages before sterilization.	increase monitoring of filter integrity in processes that involve harsh conditions, e.g. the circulation of high-temperature air. 7.4 Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size 0.22 micron (or less), or with at least equivalent microorganism-retaining properties, into a previously sterilized container. Such filters can remove bacteria and molds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment. Filtration alone is not considered sufficient when sterilization in the final container is possible. Of the methods currently available, steam sterilization is preferred. 7.5 Owing to the potential additional risks of the filtration method as compared with other sterilization processes, a double-filter layer or second filtration through a further sterilized microorganism-retaining filter immediately prior to filling may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.	

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In some cases, the aseptic processing room and adjacent cleanrooms have the same classification. Maintaining a pressure differential (with doors closed) between the aseptic processing room and these adjacent rooms can provide beneficial separation. In any facility designed with an unclassified room adjacent to the aseptic processing room, a substantial overpressure (e.g., at least 12.5 Pa) from the aseptic processing room should be maintained at all times to prevent contamination. If this pressure differential drops below the minimum limit, it is important that the environmental quality of the aseptic processing room be restored and confirmed. The Agency recommends that pressure differentials between cleanrooms be monitored continuously throughout each shift and frequently recorded. All alarms should be documented and deviations from established limits should be investigated.	53. A filtered air supply should maintain a positive pressure and an air flow relative to surrounding Areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10 - 15 Pascal (guidance values). Particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g., pathogenic, highly toxic, radioactive, or live viral or bacterial materials or products. Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations. 55. A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.	7.6 The fiber-shedding characteristics of filters should be minimal (virtually zero). Asbestos-containing filters should not be used under any circumstances. 4.5 High-efficiency particulate air (HEPA) filters should be subjected to an installed filter leakage test in accordance with ISO 14644-3 (3) at a recommended interval of every 6 months, but not exceeding 12 months. The purpose of performing regular leak tests is to ensure the filter media, filter frame and filter seal are free from leaks. The aerosol selected for HEPA leak testing should not support microbial growth and should be composed of a sufficient number or mass of particles. HEPA filter patching is allowed at the filter manufacturer and in situ operation provided that the patch sizes and procedures follow the recommendations of ISO 1822-4 (4). 6.7 Sterilization by dry heat may be suitable for non-aqueous liquids or dry-powder products. The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. If air is supplied it should be passed through a microorganism-retaining filter (e.g., a HEPA filter). Where sterilization by dry heat is also intended to remove pyrogens,	

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Air change rate is another important cleanroom design parameter. For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically acceptable. Significantly higher air change rates are normally needed for Class 10,000 and Class 100 areas. A suitable facility monitoring system will rapidly detect atypical changes that can compromise the facility's environment. An effective system facilitates restoration of operating conditions to established, qualified levels before reaching action levels. For example, pressure differential specifications should enable prompt detection (i.e., alarms) of an emerging low pressure problem to preclude ingress of unclassified air into a classified room. A compressed gas should be of appropriate purity (e.g., free from oil) and it's microbiological and particle quality after filtration should be equal to or better than that of the air in the environment into which the gas is introduced. Compressed gases such as air, nitrogen, and carbon dioxide are often used in cleanrooms and are frequently employed in purging or overlaying.	81. Components, containers, equipment, and any other article required in a clean area where aseptic work takes place should be sterilized and passed into the area through double-ended sterilizers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination. Non-combustible gases should be passed through micro-organism retentive filters. 93. After the high temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling fluid or gas in contact with the product should be sterilized unless it can be shown that any leaking container would not be approved for use.	challenge tests using endotoxins are required as part of the validation. 12.5 All equipment such as sterilizers, air-handling and filtration systems, air vent and gas filters, water treatment, generation, storage, and distribution systems should be subject to validation and planned maintenance; their return to use should be approved. 12.4 When equipment maintenance is carried out within a clean area, clean instruments and tools should be used and the area should be cleaned and disinfected again, where appropriate, before processing recommences, if the required standards of cleanliness and/or asepsis have not been maintained during the maintenance work. 10.1 Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes. As far as possible, inspections and controls should be conducted from outside such areas. 11.1 All premises should as far as possible be designed to avoid the unnecessary entry of supervisory or control personnel. Grade A and B areas should be designed so that all operations can be observed from outside.	

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Membrane filters can be used to filter a compressed gas to meet an appropriate high-quality standard. These filters are often used to produce a sterile compressed gas to conduct operations involving sterile materials, such as components and equipment. For example, we recommend that sterile membrane filters be used for autoclave air lines, lyophilizer vacuum breaks, and tanks containing sterilized materials. Sterilized holding tanks and any contained liquids should be held under positive pressure or appropriately sealed to prevent microbial contamination. Safeguards should be in place to prevent a pressure change that can result in contamination due to back flow of non-sterile air or liquid. Gas filters (including vent filters) should be dry. Condensate on a gas filter can cause blockage during use or allow for the growth of microorganisms. Use of hydrophobic filters, as well as application of heat to these filters, where appropriate, prevents problematic moisture residues.	113. The integrity of the sterilized filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure to be used across the filter should be determined during validation and any significant differences from this during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals. 50. Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture. In other areas, air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent backflow.	11.12 Consideration should be given to restricting unnecessary access to critical filling areas, e.g., grade A filling zones, by means of a physical barrier. 12.1 A conveyor belt should not pass through a partition between a grade A or B clean area and a processing area of lower air cleanliness, unless the belt itself is continuously sterilized (e.g. in a sterilizing tunnel). 11.7 Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand-washing facilities should be provided only in the first stage of the changing rooms. There should not be a change of more than one grade between airlocks or passages and changing rooms, i.e. a grade D passage can lead to a grade C airlock, which leads to a grade B changing room, which	

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We recommend that filters that serve as sterile boundaries or supply sterile gases that can affect product be integrity tested upon installation and periodically thereafter (e.g., end of use). Integrity tests are also recommended after activities that may damage the filter. Integrity test failures should be investigated, and filters should be replaced at appropriate, defined intervals. HEPA filter integrity should be maintained to ensure aseptic conditions. (The same broad principles can be applied to ULPA filters). Leak testing should be performed at installation to detect integrity breaches around the sealing gaskets, through the frames, or through various points on the filter media. Thereafter, leak tests should be performed at suitable time intervals for HEPA filters in the aseptic processing facility. For example, such testing should be performed twice a year for the aseptic processing room. Additional testing may be appropriate when air quality is found to be unacceptable, facility renovations might be the cause of disturbances to ceiling or wall structures, or as part of an investigation into a media fill or drug product sterility failure.	110. Filtration alone is not considered sufficient when sterilization in the final container is possible. With regard to methods currently available, steam sterilization is to be preferred. If the product cannot be sterilized in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilized container. Such filters can remove most bacteria and molds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment. 111. Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration via a further sterilized micro-organism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point. 112. Fiber-shedding characteristics of filters should be minimal.	leads to a grade B clean room. Changing rooms should be of a sufficient size to allow for ease of changing. Changing rooms should be equipped with mirrors so that personnel can confirm the correct fit of garments before leaving the changing room. 13.2 The container closure system for aseptically filled vials is not fully integral until the aluminum cap has been crimped into place on the stoppered vial. Crimping of the cap should, therefore, be performed as soon as possible after stopper insertion. 13.7 Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, predetermined period. 11.2 In clean areas all exposed surfaces should be smooth, impervious, and unbroken to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.	

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Among the filters that should be leak tested are those installed in dry heat Depyrogenation tunnels and ovens commonly used to depyrogenate glass vials. Where justified, alternate methods can be used to test HEPA filters in the hot zones of these tunnels and ovens. Any aerosol used for challenging a HEPA filter should meet specifications for critical physicochemical attributes such as viscosity. Dioctylphthalate (DOP) and poly-alpha-olefin (PAO) are examples of appropriate leak testing aerosols. Some aerosols are problematic because they pose the risk of microbial contamination of the environment being tested. Accordingly, the evaluation of any alternative aerosol involves ensuring it does not promote microbial growth. There is a major difference between filter leak testing and efficiency testing. An efficiency test is a general test used to determine the rating of the filter. (The efficiency test uses a mono-dispersed aerosol of 0.3 micron sized particles and assesses filter media. Downstream readings represent an average over the entire filter surface. Efficiency tests are not intended to test for filter leaks.)	97. The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation. 60. All equipment such as sterilizers, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems should be subject to validation and planned maintenance; their return to use should be approved. 51. Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand washing facilities should be provided only in the first stage of the changing rooms.	11.3 To reduce the accumulation of dust and to facilitate cleaning, there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards, and equipment. Doors should be carefully designed to avoid uncleanable recesses; sliding doors may be undesirable for this reason. Swing doors should open to the high-pressure side and be provided with self-closers. Exceptions are permitted based on egress and site environmental, health and safety containment requirements. 11.4 False ceilings should be sealed to prevent contamination from the void space above them. 11.5 Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean. Sanitary pipes and fittings should be used and threaded pipe connections should be avoided.	

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An intact HEPA filter should be capable of retaining at least 99.97 percent of particulates greater than 0.3 µm in diameter. The purpose of performing regularly scheduled leak tests, on the other hand, is to detect leaks from the filter media, filter frame, or seal. The challenge involves use of a poly-dispersed aerosol usually composed of particles with a light-scattering mean droplet diameter in the submicron size range, including a sufficient number of particles at approximately 0.3 µm. (Although the mean is normally less than one micron, it is greater than 0.3 µm.) Performing a leak test without introducing a sufficient upstream challenge of particles of known size upstream of the filter is ineffective for detecting leaks. It is important to introduce an aerosol upstream of the filter in a concentration that is appropriate for the accuracy of the aerosol photometer. The leak test should be done in place, and the filter face scanned on the downstream side with an appropriate photometer probe, at a sampling rate of at least one cubic foot per minute. The downstream leakage measured by the probe should then be calculated as a percent of the upstream challenge	52. Both airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time. 34. Prior to the completion of stoppering, transfer of partially closed containers, as used in freeze drying should be done either in a grade A environment with grade B background or in sealed transfer trays in a grade B environment.	11.6 Sinks and drains should be avoided wherever possible and should be excluded from grade A and B areas where aseptic operations are carried out. Where installed they should be designed, located and maintained so as to minimize the risks of microbial contamination; they should be fitted with effective, easily cleanable traps and with air breaks to prevent backflow. Any floor channels should be open and easily cleanable and be connected to drains outside the area in a manner that prevents the ingress of microbial contaminants. 12.2 Whenever possible, equipment used for processing sterile products should be chosen so that it can be effectively sterilized by steam or dry heat or other methods. 12.3 As far as possible, equipment fittings and services should be designed and installed so that operations, maintenance, and repairs can be carried out outside the clean area. Equipment that has to be taken apart for maintenance should be re-sterilized after complete reassembly, wherever possible.	

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An appropriate scan should be conducted on the entire filter face and frame, at a position about one to two inches from the face of the filter. This comprehensive scanning of HEPA filters should be fully documented. A single probe reading equivalent to 0.01 percent of the upstream challenge would be considered as indicative of a significant leak and calls for replacement of the HEPA filter or, when appropriate, repair in a limited area. A subsequent confirmatory retest should be performed in the area of any repair. HEPA filter leak testing alone is insufficient to monitor filter performance. It is important to conduct periodic monitoring of filter attributes such as uniformity of velocity across the filter (and relative to adjacent filters). Variations in velocity can cause turbulence that increases the possibility of contamination. Velocities of unidirectional air should be measured 6 inches from the filter face and at a defined distance proximal to the work surface for HEPA filters in the critical area. Velocity monitoring at suitable intervals can provide useful data on the critical area in which aseptic processing is performed.			

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The measurements should correlate to the velocity range established at the time of in situ air pattern analysis studies. HEPA filters should be replaced when non-uniformity of air velocity across an area of the filter is detected or airflow patterns may be adversely affected. Although contractors often provide these services, drug manufacturers are responsible for ensuring that equipment specifications, test methods, and acceptance criteria are defined, and that these essential certification activities are conducted satisfactorily. Note: The design concepts discussed within this section are not intended to be exhaustive. Other appropriate technologies that achieve increased sterility assurance are also encouraged. Aseptic processes are designed to minimize exposure of sterile articles to the potential contamination hazards of the manufacturing operation. Limiting the duration of exposure of sterile product elements, providing the highest possible environmental control, optimizing process flow, and designing equipment to prevent entrainment of lower quality air into the Class 100 (ISO 5) clean area are essential to achieving high assurance of sterility (Ref. 4).			

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Both personnel and material flow should be optimized to prevent unnecessary activities that could increase the potential for introducing contaminants to exposed product, container-closures, or the surrounding environment. The layout of equipment should provide for ergonomics that optimize comfort and movement of operators. The number of personnel in an aseptic processing room should be minimized. The flow of personnel should be designed to limit the frequency with which entries and exits are made to and from an aseptic processing room and, most significant, its critical area. Regarding the latter, the number of transfers into the critical area of a traditional cleanroom, or an isolator, should be minimized. To prevent changes in air currents that introduce lower quality air, movement adjacent to the critical area should be appropriately restricted.			

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Any intervention or stoppage during an aseptic process can increase the risk of contamination. The design of equipment used in aseptic processing should limit the number and complexity of aseptic interventions by personnel. For example, personnel intervention can be reduced by integrating an on-line weight check device, thus eliminating a repeated manual activity within the critical area. Rather than performing an aseptic connection, sterilizing the preassembled connection using sterilize-in-place (SIP) technology also can eliminate a significant aseptic manipulation. Automation of other process steps, including the use of technologies such as robotics, can further reduce risk to the product. Products should be transferred under appropriate cleanroom conditions. For example, lyophilization processes include transfer of aseptically filled product in partially sealed containers. To prevent contamination, a partially closed sterile product should be transferred only in critical areas.			

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(Appropriately designed transfer equipment provides these conditions and can be qualified for this purpose.) Facility design should ensure that the area between a filling line and the lyophilizer provide for Class 100 (ISO 5) protection. Transport and loading procedures should afford the same protection. The sterile drug product and its container-closures should be protected by equipment of suitable design. Carefully designed curtains and rigid plastic shields are among the barriers that can be used in appropriate locations to achieve segregation of the aseptic processing line. Use of an isolator system further enhances product protection (see Appendix 1). Due to the interdependence of the various rooms that make up an aseptic processing facility, it is essential to carefully define and control the dynamic interactions permitted between cleanrooms. Use of a double-door or integrated sterilizer helps ensure direct product flow, often from a lower to a higher classified area. Airlocks and interlocking doors will facilitate better control of air balance throughout the aseptic processing facility.			

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Airlocks should be installed between the aseptic manufacturing area entrance and the adjoining unclassified area. Other interfaces such as personnel transitions or material staging areas are appropriate locations for air locks. It is critical to adequately control material (e.g., in-process supplies, equipment, utensils) as it transfers from lesser to higher classified clean areas to prevent the influx of contaminants. For example, written procedures should address how materials are to be introduced into the aseptic processing room to ensure that room conditions remain uncompromised. In this regard, materials should be disinfected according to appropriate procedures or, when used in critical areas, rendered sterile by a suitable method. If stoppered vials exit an aseptic processing zone or room prior to capping, appropriate assurances should be in place to safeguard the product, such as local protection until completion of the crimping step. Use of devices for on-line detection of improperly seated stoppers can provide additional assurance.			

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Cleanrooms are normally designed as functional units with specific purposes. The materials of construction of cleanrooms ensure ease of cleaning and sanitizing. Examples of adequate design features include seamless and rounded floor to wall junctions as well as readily accessible corners. Floors, walls, and ceilings should be constructed of smooth, hard surfaces that can be easily cleaned. Ceilings and associated HEPA filter banks should be designed to protect sterile materials from contamination. Cleanrooms also should not contain unnecessary equipment, fixtures, or materials. Processing equipment and systems should be equipped with sanitary fittings and valves. With rare exceptions, drains are considered inappropriate for classified areas of the aseptic processing facility other than Class 100,000 (ISO 8) areas. It is essential that any drain installed in an aseptic processing facility be of suitable design.			

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Equipment should be appropriately designed (§ 211.63) to facilitate ease of sterilization. It is also important to ensure ease of installation to facilitate aseptic setup. The effect of equipment design on the cleanroom environment should be addressed. Horizontal surfaces or ledges that accumulate particles should be avoided. Equipment should not obstruct airflow and, in critical areas, its design should not disturb unidirectional airflow. Deviation or change control systems should address atypical conditions posed by shutdown of air handling systems or other utilities, and the impact of construction activities on facility control. Written procedures should address returning a facility to operating conditions following a shutdown.			

HVAC Design for OSD Plant

CONTENTS

HVAC Design for OSD Plant Guideline

1. PURPOSE

The Purpose Of This Document Is To Provide Guidance For HVAC Design For OSD Manufacturing Facility

2. SCOPE

This Procedure Is Applicable To Provide Design Guidance For The Following :

2.1 Buildings And Facilities

2.2 Process Equipment Considerations

2.3 Heating, Ventilation, And Air Conditioning (HVAC)

2.4 Utility Systems

2.5 Electrical Services

2.6 Control And Instrumentation

3. RESPONSIBILITY

- Engineering Department

4. DEFINITIONS

- **Acceptance Criteria** : Measurable Terms Under Which A Test Result Will Be Considered Acceptable.

- **Action Limit** : The Action Limit Is Reached When The Acceptance Criteria Of A Critical Parameter Have Been Exceeded. Results Outside These Limits Will Require Specified Action And Investigation.

- **Air-handling Unit** : The Air-handling Unit Serves To Condition The Air And Provide The Required Airflow Within A Facility.

- **Airflow Protection Booth** : A Booth Or Chamber, Typically For Purposes Of Carrying Out Sampling Or Weighing, In Order To Provide Product Containment And Operator Protection.

- **Airlock** : An Enclosed Space With Two Or More Doors, Which Is Interposed Between Two Or More Rooms, E.G. Of Differing Classes Of Cleanliness, For The Purpose Of Controlling The Airflow Between Those Rooms When They Need To Be Entered. An Airlock Is Designed For Use By Either People Or Goods, And Are Referred To As Personnel Airlock (PAL), Or As Material Airlock (MAL).

- **As Built** : Condition Where The Installation Is Complete With All Services Connected And Functioning But With No Production Equipment, Materials, Or Personnel Present.

- **Atrest** : Condition Where The Installation Is Complete With Equipment Installed And Operating In A Manner Agreed Upon By The Customer And Supplier, But With No Personnel Present.

- **Clean Area (Cleanroom)** : An Area (Or Room Or Zone) With Defined Environmental Control Of Particulate And Microbial Contamination, Constructed And Used In Such A Way As To Reduce The Introduction, Generation, And Retention Of Contaminants Within The Area.

- **Contamination** : The Undesired Introduction Of Impurities Of A Chemical Or Microbial Nature, Or Of Foreign Matter, Into Or Onto A Starting Material Or Intermediate, During Production, Sampling, Packaging, Or Repackaging, Storage, Or Transport.

- **Controlled Area (Classified Area)**: An Area Within The Facility In Which Specific Procedures And Environmental Parameters, Including Viable And Non-viable Particles, Are Defined, Controlled And Monitored To Prevent Degradation, Contamination Or Cross- Contamination Of The Product.

- **Design Condition** : Design Condition Relates To The Specified Range Or Accuracy Of A Controlled Variable Used By The Designer As A Basis For Determining The Performance Requirements Of An Engineered System.

- **Design Qualification** : Design Qualification Is The Documented Check Of Planning Documents And Technical Specifications For Design Conformity With The Process, Manufacturing, Good Manufacturing Practices, And Regulatory Requirements.

- **Differential Pressure** : The difference in pressure between two points such as the pressure difference between an enclosed space and an independent reference point, or the pressure difference between two enclosed spaces.

- **Exfiltration** : Exfiltration is the egress of air from a controlled area to an external zone.

- **Extract Air** : Air leaving a space, which could be either return air or exhaust air. Return air means that the air is returned to the air-handling unit, and exhaust air means that the air is vented to atmosphere.

- **Facility** : The built environment within which the clean area installation and associated controlled environments operate together with their supporting infrastructure.

- **Good Engineering Practice (GEP)** : Established engineering methods and standards that are applied throughout the project life cycle to deliver appropriate, cost-effective solutions.

- **Hazardous Substance or Product** : A product or substance that may present a substantial risk of injury to health or to the environment.

5. PROCEDURE/BASIS OF HVAC DESIGN

The Primary Design Consideration In HVAC System Is For :

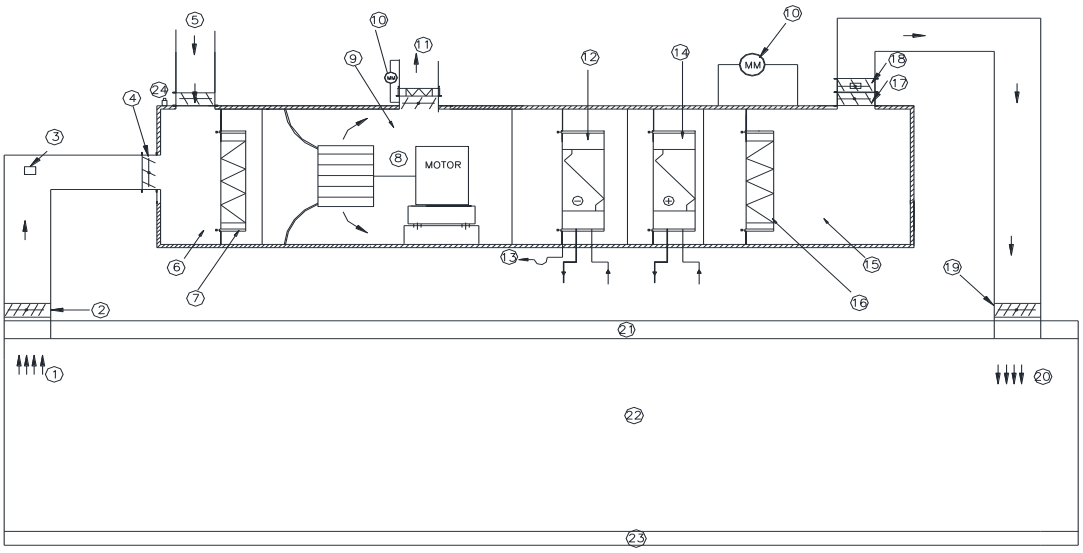
1. Product Protection And Avoidance Of Cross Contamination.
2. Personnel Protection And Comfort.
3. Environmental Protection And Compliance With Local Statutory Pollution Norms.

The Processing Areas Will Be Generally Designed, For Maintaining Temperature Of Nmt (Not More Than) 25°c And Relative Humidity Nmt 55 % Or 60 %, Unless Specifically Mentioned By User. The Relative Humidity Requirements Are Suggested By User As Per The Product Requirements.

The Control Of Temperature And Humidity Is Achieved By The Following:

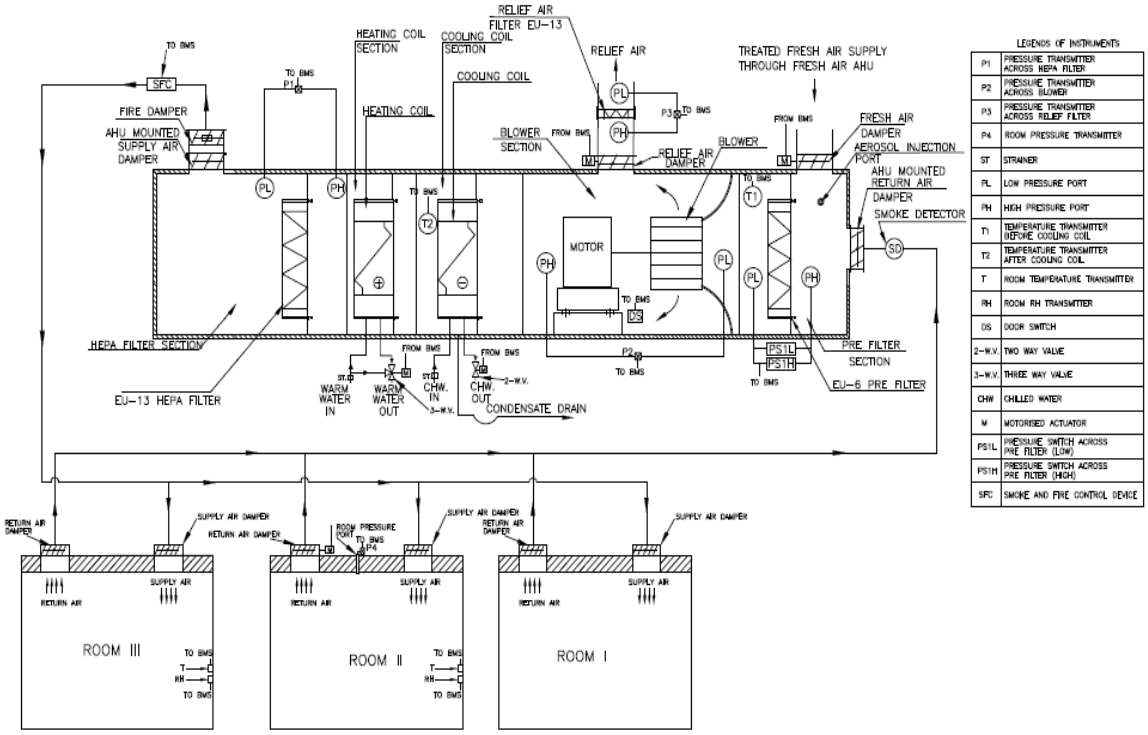
1. Chilling By Cooling Coil In AHU, To Achieve Temperature Control.
2. Heating By Using Warm Water Coil In Ahu, To Achieve Temperature Control In Winter, And Humidity Control In The Monsoons.

Schematic Diagram of Air Handling Unit
(with Basic Design)



1. Return air
2. Return air damper
3. Smoke detector
4. AHU mounted return air damper
5. Fresh air damper with EU-4 filter or treated fresh air supply through fresh air AHU
6. Pre-filter section
7. Pre-filter G4 /M5 / M6 / F7 (as applicable)
8. Blower
9. Blower section
10. Magnehelic manometer/differential pressure transmitter (as applicable)
11. Relief air with G4/E10/H14 filter (as applicable)
12. Cooling coil
13. Condensate drain
14. Warm water coil
15. Fine filter section
16. Fine filter M6/F8/E10/H14 (as applicable)
17. AHU mounted supply air damper
18. Fire damper
19. Supply damper
20. Supply air
21. Ceiling
22. Process cubicle
23. Floor
24. Test aerosol injection port

Common AHU
for Multiple Area



Remarks : Consider EN 799 and EN 1822 standards in place of Eurovent 4/5 rating :

Eurovent 4/5 Rating	EN 799 & EN 1822
EU4	G4
EU5	M5
EU6	M6
EU7	F7
EU8	F8
EU9	E10
EU13	H14

Sr. No.	Area	Classification	Design Temp	Design Humidity
1	Process Rooms (Dispensing, Sampling, Manufacturing, Sifting, Blending, Compression, Coating, Inspection, Primary Packing, Day & In-process store	ISO-8 at Rest	19 to 25°C	40% to 55%
2	Process Corridor	ISO-8 at Rest	19 to 25°C	40% to 55%
3	RM, PM, SPM	Controlled Unclassified	15 to 25°C	30% to 60%
4	TPM	Controlled Unclassified	15 to 25°C	40% to 75%
5	F.G. Store	Controlled Unclassified	15 to 25°C	30% to 75%
6	Packing Hall	Controlled Unclassified	15 to 25°C	30% to 75%
7	Qc	Controlled Unclassified	15 to 25°C	30% to 75%
8	Micro Supporting Area	ISO-8 at Rest	19 to 25°C	40% to 60%

1. As per regulatory guidelines and industry practices for oral solid dosage manufacturing facility, we propose to follow Class “D” classification (ISO 8 at rest) for all core process areas.

2. The HVAC system is designed to handle multiple product manufacturing, or it can be designed for single product manufacturing.

3. Final filter as HEPA for all ISO 8 and above classified area (preferably terminal or at least in plenum), and for other area as fine dust controls F5/F7/ F9.

AHU GROUPING

- AHU grouping is conceptualized based on activities to be performed in the process rooms & classifications.
- Dedicated AHUs are proposed for each process area.
- Quarantine and store areas (if the areas are nearby to each other), will be clubbed together as this system will be in operation for 24 hrs., either on On-Off or sleep mode as per ACPH requirement.
- Clean equipment store area will have dedicated AHU (or will be clubbed with other clean equipment area if the areas are nearby), as system will be in operation for 24hrs either on On-Off or sleep mode as per ACPH requirement.
- Dedicated AHUs for the process corridor are proposed. The AHUs will be selected with 20 % buffer in handling fresh air quantity to give additional flexibility in achieving pressure gradients.
- Solvent staging, service/technical area, and toilet will have ventilation supply and exhaust unit whichever are applicable.
- Service floor ventilation is provided for service floor area.
- All pass boxes will be considered as static or dynamic depending on the requirement of the respective area.

PRESSURE GRADIENT PHILOSOPHY

Pressure gradients are established to achieve the following GMP requirements :

1. Exfiltration from higher grade zone to lower grade zone.
2. General consideration of air movement from clean area to relatively unclean area.
3. Minimum pressure difference of 15 Pascal to be maintained and monitored between two rooms of different classifications.
4. Minimum 10 Pascal pressure difference to be maintained between two rooms of similar classification. Pressure gradient should be monitored in these areas.
5. Minimum 5 Pascal difference between two un-classified rooms.
6. If airlocks are used to segregate areas, bubble/cascade air locks can be used to segregate the areas for better controls and reduction of cross contamination. Lower DP up to 5 Pa can be acceptable with air locks with adequate validation.

DUST EXTRACTION PHILOSOPHY

- Dust extraction should be grouped as per AHU grouping. The design of extraction main header piping in such a way that it handle the single AHU as well as multiple AHUs.
- Dust collectors should be installed in the room, in order to remove dust particles that are generated while charging and discharging of powder in various machines.
- Dust collector discharge without scrubber should be taken out of the area from service floor cutout. The HEPA or fine filter assembly depending on product nature should be installed at the outlet of exhaust.
- SS 304 pipes are suggested for suction from walkable ceiling to dust collector inlet.
- Dust collector should have H14 of 0.3-micron HEPA filter with efficiency > 99.997%.
- The exhaust of the dust collector should be taken out through ducting to the atmosphere.

SOURCES OF PARTICLE CONTAMINATION

1. INTERNAL SOURCES

a) Non-viable particles may be dust, smoke, plastic, and metal debris from process or HVAC equipment, synthetic clothing fibers, etc.

b) Viable (living) organisms, such as spores, bacteria, and viruses.

c) HEPA filters can effectively remove more than 99.97% of these particles from the HVAC air supply.

d) Typical sources from inside the classified space include:
- Personnel.
- The process and its equipment.
- HVAC ductwork downstream of final HEPA filters.
- Contamination on items entering the cleanroom.
- Utilities serving the area.

2. PERSONNEL

a) People are the greatest source of particle contamination and the level of contamination they add depends on their level of gowning and associated comfort, and how they perform their tasks. Interventions can introduce particles where they are not wanted.

b) Particles can be non-viable (clothing) or viable (bacteria, mold).

3. PROCESS AND EQUIPMENT

a) Contaminants released from equipment are usually mostly non-viable if equipment is properly cleaned and stored. Cleaning activities may release large quantities of particles.

b) Spilled liquid material can become airborne if allowed to dry. Work surfaces should be kept clean where activity could dislodge deposited particles. Airflow patterns in the room can become critical if dislodged particles travel toward critical sites.

c) Airborne product itself may become a cross-contaminant of another product. High particle volumes from processes can be controlled by local exhaust, by airflow patterns, or by physical separation.

d) Particles generated within the HVAC system should be virtually eliminated by HEPA filters in the system. Location of the final HEPA filter in the HVAC system is important to assure the cleanest air supply to the room. Terminal filters (located at the point where air enters the room) are preferable and should be used for rooms classified as ISO 7 or cleaner. (NOTE: this is not related to OSD).

4. EXTERNAL SOURCES

a) A positive room DP helps to exclude external contaminants, reducing infiltration from more contaminated spaces through cracks in the room fabric and doors. Where rooms of different air quality classifications are joined by a doorway, an airlock should be used to assure that at least one door is in closed condition during transit.

b) Particles entering the HVAC system, such as from outdoor (fresh) air used for room pressurization and for operator health, are usually removed in the HVAC air filtration system, with the location and performance of the final HEPA filter being important to assuring removal. Pre-filters are often used to extend the life of the final (critical) air filter.

c) If a room is maintained at positive differential pressure, then airborne particles usually depend on the following variables:

d) Quantity of particles generated inside the room (internal sources) or carried into the room.

e) Quantity of dilution air supply (HVAC HEPA-filtered air).

f) Cleanliness of dilution air supply.

g) Degree of mixing with dilution air.

AIR CHANGES PER HOUR

- In process rooms such as blending, sifting, granulation, compression, coating, inspection, and primary packing ACPH will be maintained at minimum 20 ACPH, hence design will be done at 25 ACPH.
- In quarantine and other ancillary areas, ACPH will be maintained at minimum 10 ACPH, hence design will be done at 15 ACPH.
- The process corridor CFM will be designed as per the ex-filtration requirement to establish the pressure gradient. ACPH will be maintained at minimum 20 ACPH, hence design will be done at 25 ACPH.
- Warehouse will be designed for minimum 06 ACPH.
- The packing hall will be designed for minimum 06 ACPH.
- Main workmen change room (primary) will be designed for minimum 06 ACPH. Activated carbon filter will be used in the system serving the primary change room area.

FRESH AIR CFM CALCULATION IS BASED ON FOLLOWING:

1. Fresh air minimum 2 ACPH of the room volume.
   OR
2. 15 CFM per person.
   OR
3. 10% of air quantity supplied inside the room.
   OR
4. Required as per pressure gradient by virtue of infiltration, exfiltration and room exhaust (if any). The highest of the above four values will be considered for design.

For swing doors, door gaps of 5 mm at bottom and 1 mm at the periphery will be considered in establishing the infiltration/exfiltration from the door/room for pressure balancing during designing. For sliding doors, door gaps of 5 mm along the periphery will be considered for the same purpose.

AIR FLOW PATTERN

- Low level pick ups, i.e., risers, is proposed in core process rooms like granulation, blending, and compression, i.e., where density of powder generation is high. All risers will be provided without filters (wherever potent product manufacturing facility filters are provided)

- All other non-process rooms can have ceiling return.

- Location of the supply and return modules/risers should be planned to achieve the following:

    1. To generate sweeping effect in rooms with risers.

    2. Uniform air distribution to avoid stagnation points.

    3. Movement of air from a relatively clean zone to lesser clean zone within the room.

- The filter in return riser is recommended in order to reduce ducting contamination and carry-over of powders/choking of AHU pre filters and CHW coil. Also duct cleaning might be an issue in case there are no filters in return risers.

QUALIFICATION STRATEGY

- System is appropriately designed, located, installed, operated, and maintained to suit the intended purpose.

- Equipment is qualified prior to being brought into routine use.

- Qualification is done in accordance with predetermined and approved qualification protocols.

- The results of the qualification are recorded and reflected in qualification reports.

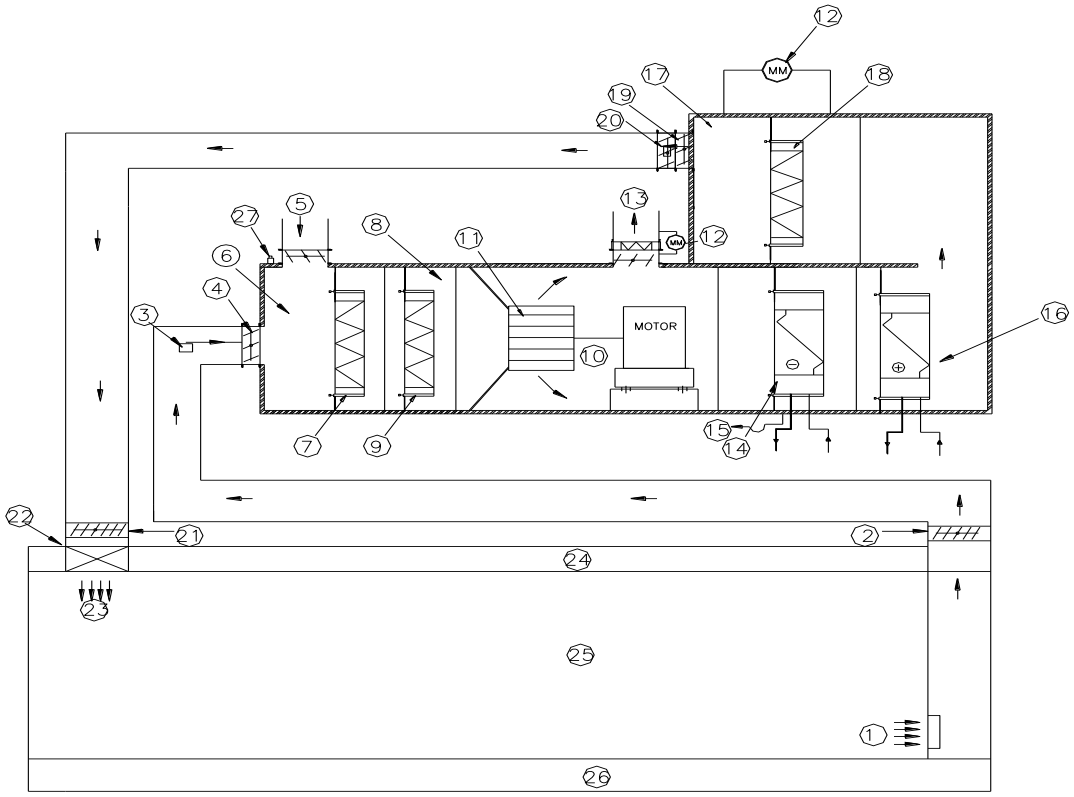
- Typical HVAC system parameters are qualified.

- New system shall be passed through all stages of qualification including URS, DQ, IQ, OQ and PQ as appropriate.

PPM checks of AHU

- Abnormal noise and vibrations.
- Air leakages and gaskets.
- Door hinges, locks, view lamps.
- Frequency monthly, and six-monthly.

Common AHU for Multiple Area

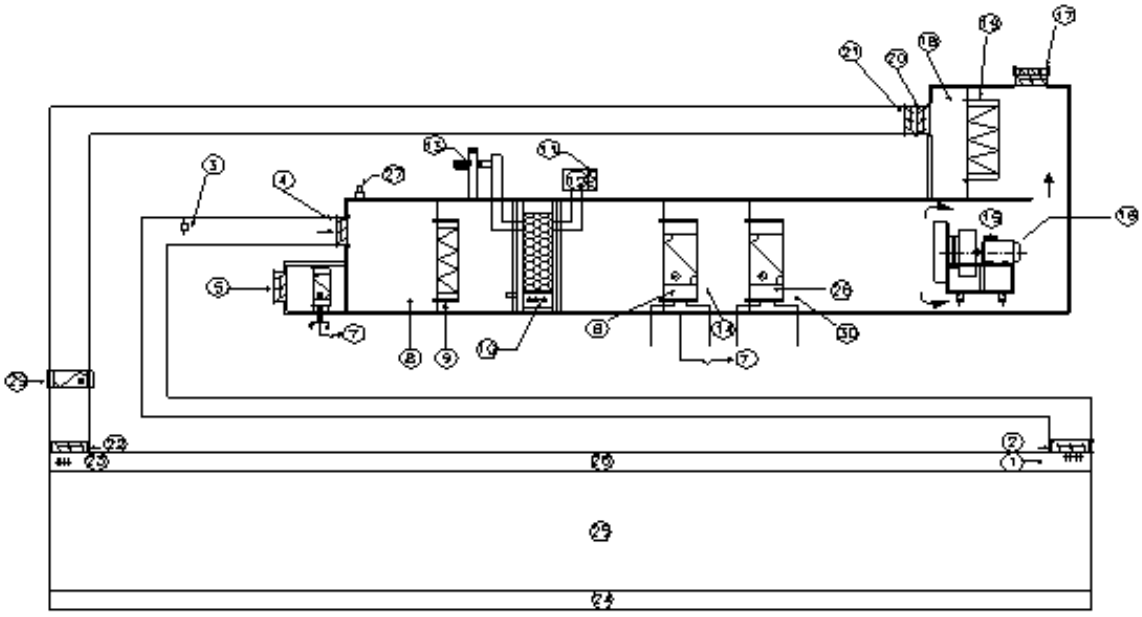


1. Return air through riser
2. Return air damper
3. Smoke detector
4. AHU mounted return air damper
5. Fresh air damper with EU-4 filter or treated fresh air supply through fresh air AHU
6. Pre-filter section
7. Pre-filter G4 /M5 / M6 / F7 (as applicable)
8. Intermediate filter section (if applicable)
9. Intermediate filter M6/F7/F8/E10 (as applicable)
10. Blower
11. Blower section
12. Magnehelic manometer/differential pressure transmitter (as applicable)
13. Relief air with G4/F9/H14 filter connected to exhaust unit (if applicable)
14. Cooling coil
15. Condensate drain
16. Warm water coil
17. Fine filter section
18. Fine filter F8/E10/H14 (as applicable)
19. AHU mounted supply air damper
20. Fire damper
21. Supply damper
22. Terminal HEPA H14/U15 (if applicable)
23. Supply air
24. Ceiling
25. Process cubicle
26. Floor
27. Test aerosol injection port

PPM CHECKS OF AHU-CUM-DEHUMIDIFIER

- Checking of bed motor, gaskets.
- Reactivation air temp setting, pressure switch.
- Blower reactivation.
- Safety interlocks, silica bed cleaning.
- Sequence of operation of dehumidifier.
- Sanitization and cleaning of coil.
- Frequency monthly and six-monthly.

Schematic Diagram of Air Handling Unit
(With Terminal HEPA, Intermediate filters & Riser)



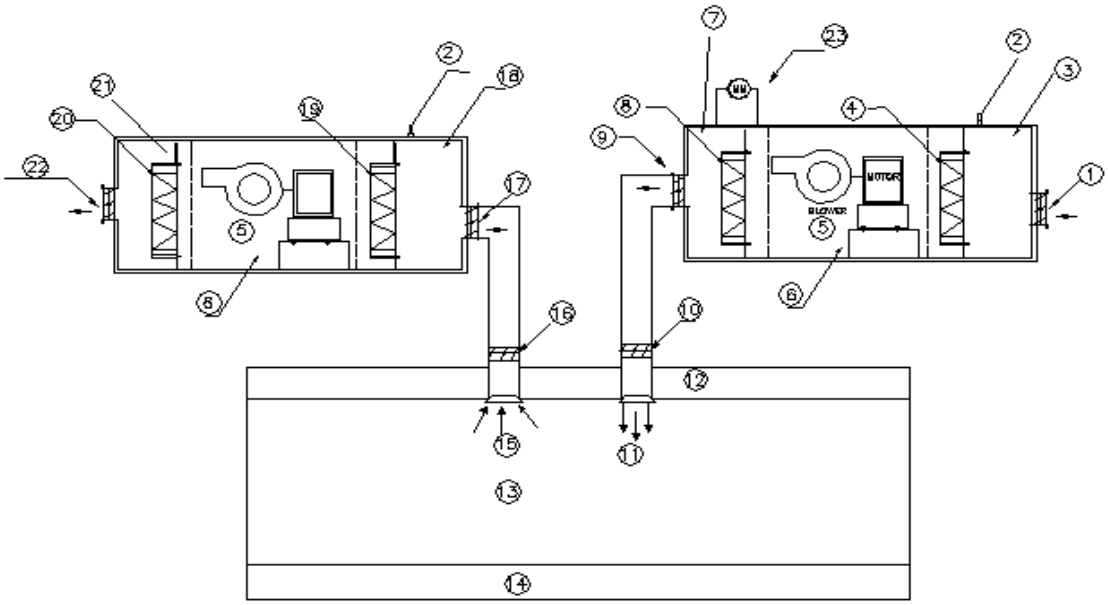
1. Return air through riser
2. Return air damper
3. Smoke detector
4. AHU mounted return air damper
5. Treated fresh air supply through fresh air AHU
6. Cooling Coil
7. Condensate drain
8. Pre-filter section
9. Pre-filter G4
10. Deceient wheel
11. Reactivation air filter G4
12. Heater box
13. Reactivation blower
14. Cooling coil section
15. Process blower
16. Process blower section
17. Relief air G4
18. Fine filter section
19. Fine filter H14
20. AHU mounted supply air damper
21. Fire damper
22. Supply air damper
23. Supply air
24. Floor

25. Process Cubicle
26. Ceiling
27. Test aerosol injection port
28. Heating Coil
29. Re heater
30. Heating Coil Section

PPM CHECKS OF VENTILATION SYSTEM

- Belt tension, alignment and condition.
- Balancing of blower, free movement of dampers.
- Frequency quarterly

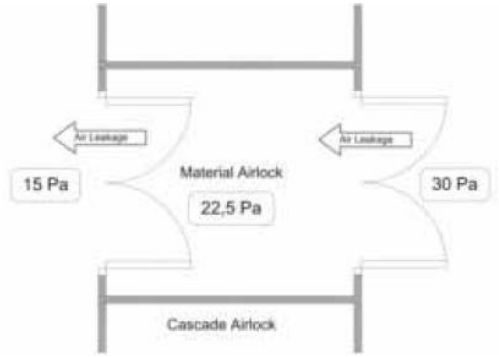
Schematic Diagram of Ventilation System (Once Through)



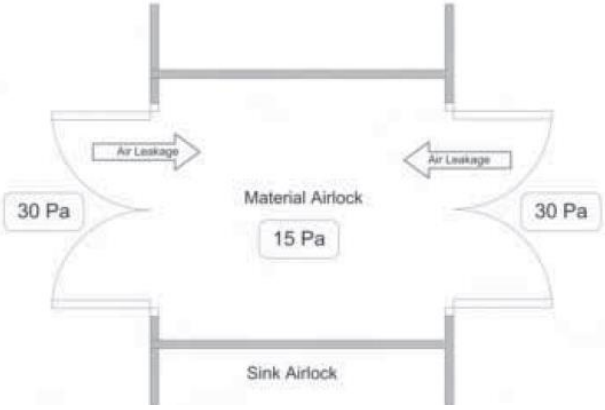
1. Fresh air damper
2. Test aerosol injection port (if applicable)
3. Pre-filter section.
4. Pre-filter (G4)/(M5) (as applicable)
5. Blower
6. Blower section
7. Fine filter section
8. Fine filter (M6/F7/F8/E10/ H14) (as applicable)
9. Ventilation Unit mounted supply air damper
10. Supply air damper
11. Supply air diffuser
12. Ceiling
13. Process cubicle
14. Floor
15. Return air diffuser
16. Return air damper
17. Ventilation unit mounted return air damper
18. Exhaust air pre filter section
19. Exhaust air pre filter (G4)/(M5) (as applicable)
20. Exhaust air fine filter (M6/F8/H14) (as applicable)
21. Exhaust air fine filter section (if applicable)
22. Exhaust air damper
23. Magnehelic manometer/differential pressure transmitter (as applicable)

DESIGN CONCEPTS ON PRESSURE GRADIENTS LINE

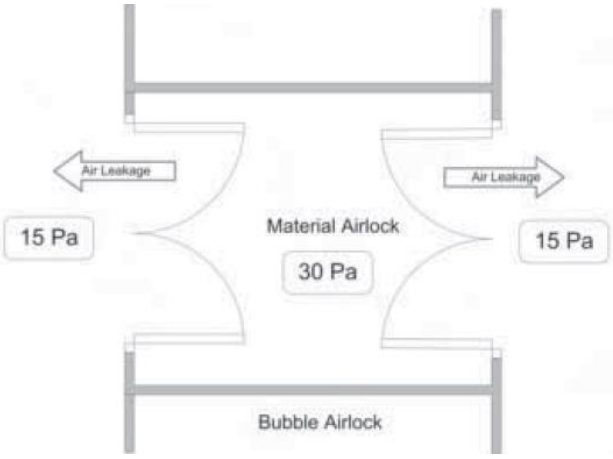
- Cascade Airlock



- Sink Airlock



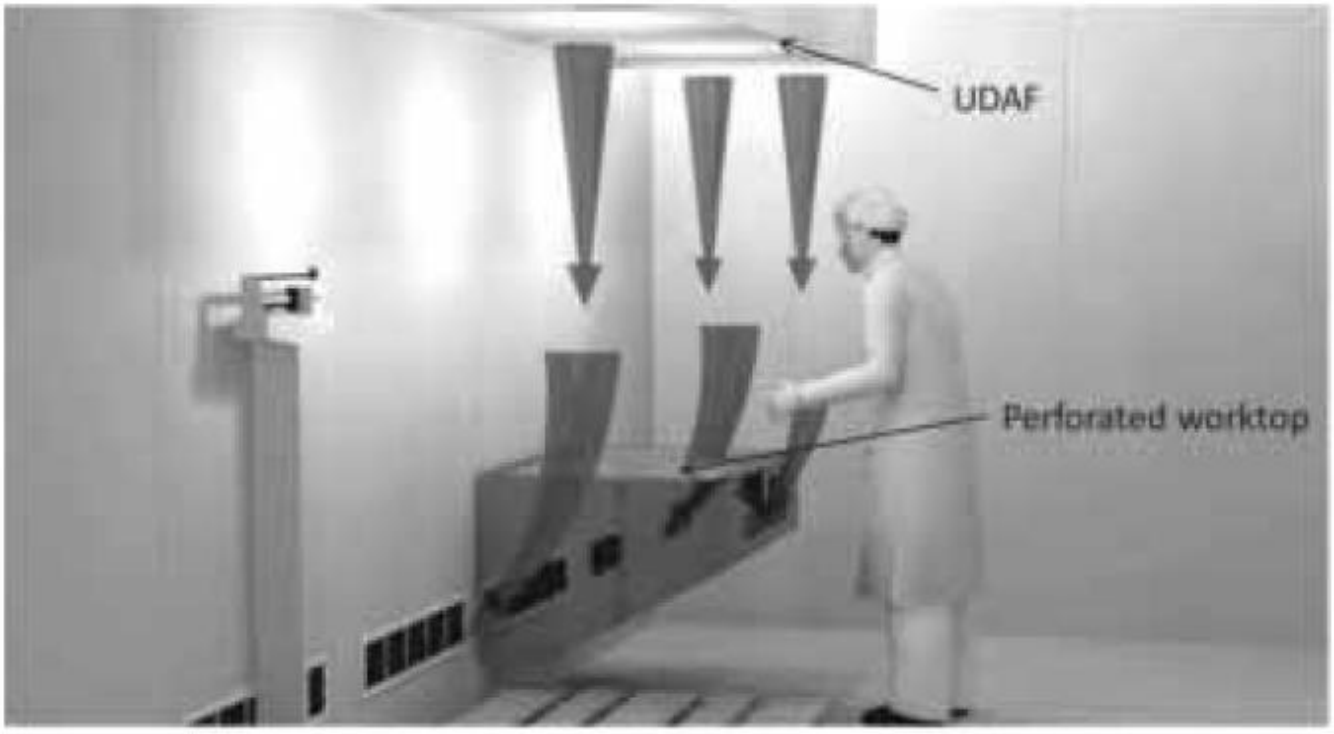
- Bubble Airlock



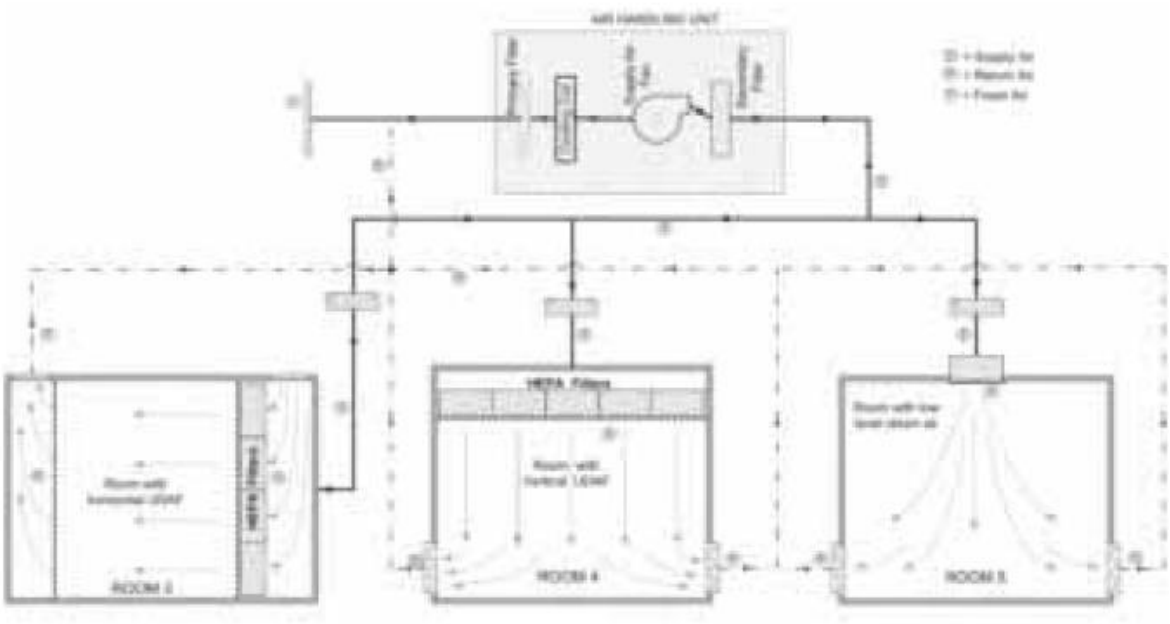
LAF CONCEPT

Unidirectional air flow is designed to provide Class 100 working environment at rest with built in scavenging system to ensure product, operator, and surrounding environment protection. The reverse laminar airflow bench finds major application in sampling and dispensing, frequently used for mixed airflow stream to control the hazardous emission of dust powder during dispensing or sampling process. This draws powder aerosols away from the operator and the operating environment, thereby protecting products and providing safe working conditions for personnel.

Reverse Laminar Air Flow Unit operates on a re-circulatory airflow principle providing containment by air movement. The pre-filters at the base of the rear wall capture the airborne contaminants generated. Intake velocity at pre-filters increases to ensure scavenging effect. A small percentage of air is discharged from the booth through the bleed exhaust HEPA filter to maintain the working space under negative pressure.
Reverse laminar air flow unit is available in a variety of standard dimensions, and cabinets can be custom engineered to any size. These units are available in powder coated mild steel, in SS 304/316/316L, or in a combination of both.



TYPICAL AIR FLOW DIAGRAM FOR DIFFERENT TYPES OF AREA



AHU DUCT CLEANING

1. Duct cleaning shall be performed only for return duct of HVAC system.

2. Area shall be identified which require duct cleaning.

3. Frequency:

    - Duct cleaning of areas shall be done once in two years
    - Duct cleaning shall not be applicable for sterile, aerosol and potent areas.

4. Area cleaning shall be carried out by user, on completion of the duct cleaning activity.

5. Duct cleaning by manual procedure:

    - Close the supply and return air dampers of the HVAC system, individual room dampers, or dust extraction system of which the ducting is to be cleaned.
    - Remove the duct attached to the HVAC system or dust extraction system of return side piece by piece.
    - Remove the gaskets attached to the ducting and dispose it to ETP.
    - Collect the powder accumulated in the return duct in a polythene bag and send it to ETP.
    - Clean the return and discharge duct internally and externally using vacuum cleaner and suitable solvent. Ensure effective cleaning of duct pieces through visual inspection.
    - All the powder collected during the individual duct cleaning should be sent to ETP.
    - Fix the ducting with new gasket and ensure sealing/soldering, and seal the joints with sealant as applicable.
    - Check all joints for any leakage and attend to the same if required.
    - Insulate the joints wherever applicable.

6. Duct cleaning procedure using automatic systems/robotic cleaning
   (to be carried out by external certified agency):

    - Close the supply and return air dampers of the HVAC system, individual room dampers or dust extraction system of which the ducting is to be cleaned.
    - Remove the manhole cover provided for ducting cleaning.
    - Carry out cleaning of the duct using the automatic systems of the external certified agency.
    - Confirm the cleaning activity visually by videography of the ducts.
    - Close the manhole and check all joints for any leakage and attend to the same if required.
    - All the powder collected during the individual duct cleaning should be sent to ETP.

FILTRATION LEVEL

Level	Condition	Example of area
Level 1	General	Area with normal housekeeping and maintenance where there is no potential for product contamination, e.g., warehousing.
Level 2	Protected	Area in which steps are taken to protect the pharmaceutical starting material or product from direct or indirect contamination or degradation, e.g., secondary packing, warehousing, first stage change rooms.
Level 3	Controlled	Area in which specific environmental conditions are defined, controlled, and monitored to prevent contamination or degradation of the pharmaceutical starting material or product, e.g., where product, starting materials and components are exposed to the room environment; plus, equipment wash and storage areas for equipment product contact parts.

FILTER CLEANING AND FILTER REPLACEMENT PROCEDURE

Procedure for cleaning of filters (without standby) for all cleanable air filters being used in Air Handling Unit (AHU), Forced Air Ventilation (FAV) system, Dehumidifier Units (DHU), AHU Cum Dehumidifier (ACDH), Laminar Air Flow units (LAF), garments, and Bio-Safety Cabinet (BSC)

- Start the filter cleaning activity with prior intimation to the respective user department.
- Put off the blower supply for AHU, FAV, DHU, ACPH, LAF, GC, MLAF, AS, FFU, DPB and BSC.
- Open the door of respective filter plenum of AHU or filter section of LAF/FAV/DHU/ACDH/GC/MLAF/AS/FFU/DPB/BSC by unscrewing the clamps provided at the sides or by removing the sealants from the slides (if applicable) or by sliding the filter from the sides.
- Remove the filter by loosening the wing nuts or clamps, and put it into a polythene bag. Tie the polythene bag.
- Clean the door, door corners, door gasket, and filter plenum using vacuum cleaner or duster.
- Vacuum cleaner should be used for equipment that are installed and used in powder generated areas.
- Close the door of filter plenum.

- Transfer the filters to filter cleaning room, and keep it in the pass box/pallet marked as uncleanable filters.
- All filters from each air handling system, FAV, DHU, ACDH, LAF, GC, MLAF, AS, FFU, DPB and BSC are to be cleaned together as a set.
- Remove the filter from polythene bag, and keep it in filter cleaning plenum of dust collector in the reverse direction to normal flow.
- Switch on the dust collector/scrubber.
- Open the compressed air valve and clean the filter with 0.01µ filtered compressed air at 3.0 to 4.0 bar pressure till it is visually clean.
- Close the compressed air valve.
- Remove the filter and put it in the direction of normal flow.
- After completion of cleaning of the filter as per schedule, switch off the dust collector/scrubber.
- Remove the filter and check visually for its integrity and any damage of the protective screen provided for media (if applicable), and replace the filter.
- The filter frame should be checked for dents or bends. Remove bends, if any.
- Check the rubber gasket for any damages and replace if required.
- Put the filter into fresh polythene bag keep it in the pass box/pallet marked as cleaned filters.
- Transfer the filters near the respective unit.
- Fix back the filter in the plenum.
- Close the door.
- Take the running trail of system and inspect to ensure no leakage. Ensure that the pressure drop across filter is within the specified range. Wherever possible, in case the pressure drop is not within the limit, clean the filter again and recheck the differential pressure; otherwise, replace filter with new filter and update filter code.

PROCEDURE FOR MONITORING & STORAGE OF HEPA FILTERS

- Since the filter media of HEPA filters are made from microfiber glass, these are very fragile. Hence, these should be handled carefully during storage, shifting, installation and testing.
- Filters shall not be lifted directly from the box; this may cause filter puncture. The storage box shall be opened from one end, the box turned upside down, and the filter lifted out the box of.
- If a filter is equipped with a removal strap, it shall be used carefully while removing the filter from the box, by holding the filter on the outside surface of the frame.
- Filter shall be stored in their individual cardboard package boxes until installation.
- Labelling of the filter shall content supplier name, filter size, filter rating, serial number and receipt date.
- Filter shall be stored in dry area, and shall not be exposed to extreme climatic conditions.
- Filters shall be stored in correct/upright position as referenced on packaging, by labelling it 'Right way Up' (the pleats should be vertical).
- Filters shall be marked "Fragile "and stored in a safe zone away from routine traffic activity.
- Pallets containing filters shall not be stacked on top of each other.
- Filters shall be stored as per manufacturers' recommendations.
- Rapid temperature fluctuations and corrosive environment adversely affects the filter condition.

REPLACEMENT POLICIES OF HEPA FILTERS

- Replacement of filters shall be done as per predefined schedule or whenever the following observations are made:
    - If the pressure drop across the filter bank is out of specified limit.
    - Filter loses its integrity.
    - Filter body or flange is found damaged.
    - Filter media is found damaged/soiled.
    - Sealing between filtration media and body is found damaged.
- Inform Quality Assurance and concerned department regarding the need for filter replacement.
- Before replacement of HEPA filters, filter integrity test shall be performed for old HEPA filters.

- Ensure the process activities are stopped, and cubicle is cleaned in case of final filter.
- Raise request and issue filter.
- Open the secondary packing of filter at the place of use just before fixing.
- Take filter close to the filter housing for which filter to be replaced.
- Ensure that AHU/LAF is switched off and fix the “UNDER MAINTENANCE BOARD.”
- Remove the old filter and put inside polythene bag.
- Wipe the plenum clean. Clean the filter housing and surrounding area.
- Clean the equipment plenum/duct/HEPA box and area with wet duster or vacuum cleaner as applicable.

DISPOSAL OF FILTERS

- Disposal of filter used for general products:
    - Collect the used filters in single polybag.
    - Damage the filters physically so that it cannot be reused, and put it in the scrap meant for disposal. Record the disposal.
- Disposal of filters used for sensitive products:
    - Collect the used filter in a double polybag.
    - Clean the used filter in filter washing/cleaning area.
    - Put the used filter in the container containing deactivating solution (if applicable).
    - After deactivation damage the filter and put it in scrap meant for disposal, and record disposal.

FOGGING AND DISINFECTION OF AHU DUCTING AND AHU DRAINS

- Ensure that the area is cleaned.
- Ensure that fogger is clean externally and status label should be fixed on the fogger.
- Spray the fogging agent as below:
    - Fogger should be used for spray fogging.
    - For fogging of area of 1000 ft3 volume, 1 Ltr of 20 % Virosil solution/7.4 % H_2O_2 should be calculated as follows:

Option I (for wet fogging): 20% Virosil solution XXXXX

For fogging of area of 1000 ft3 by volume, 1 ltr. of 20% Virosil solution should be calculated as follows:

Quantity (ltr.) of 20% Virosil solution (Q)= V/1000,

where,
V = Volume (ft3) of area to be fogged, i.e. length x width x height of space in ft3

Now calculate quantities of Virosil liquid and purified water to be prepare in 20% Virosil solution, as follows:

Quantity of Virosil liquid = Q in ltr. x 200
Quantity (ltr.) of purified water = Q in ltr. x 0.80

Option II (for dry fogging): 7.4% H_2O_2 solution

For fogging of area with 7.4% H_2O_2, the solution should be prepare as per following calculation:
7.4% H_2O_2 X 1000 / 35.0 % H_2O_2 = 211 ml. H_2O_2.

TEMPERATURE/RH MONITORING FREQUENCY AND RECORD

- Where appropriate, temperature and relative humidity should be controlled, monitored, and recorded, where relevant, in order to ensure compliance with requirements pertinent to the materials and products, and provide a comfortable environment for the operator where necessary.

- Maximum and minimum room temperatures and relative humidity should be appropriate. Alert and action limits on temperatures and humidities should be set, as appropriate.

- The operating band, or tolerance, between the acceptable minimum and maximum temperatures should not be made too close. Tight control tolerances may be difficult to achieve and can also add unnecessary installation and running costs.

- Cubicles, or suites, in which products requiring low relative humidity are processed, should have well-sealed walls and ceilings, and should also be separated from adjacent areas with higher relative humidity by means of suitable airlocks.

- Precautions should be taken to prevent moisture migration that increases the load on the HVAC system.

- Humidity control should be achieved by removing moisture from the air, or adding moisture to the air, as relevant.

- Dehumidification (moisture removal) may be achieved by means of either refrigerated dehumidifiers or chemical dehumidifiers.

- Appropriate cooling media for dehumidification, such as low temperature chilled water/glycol mixture or refrigerant, should be used.

- Humidifiers should be avoided if possible as they may become a source of contamination (e.g., microbiological growth). Where humidification is required, this should be achieved by appropriate means such as the injection of steam into the air stream. A product contamination assessment should be done to determine whether pure or clean steam is required for the purposes of humidification.

- Where steam humidifiers are used, chemicals such as corrosion inhibitors or chelating agents, which could have a detrimental effect on the product, should not be added to the boiler system. Only appropriate additives should be added to the boiler system.

- Humidification systems should be well drained. No condensate should accumulate in air handling systems.

- Other humidification appliances such as evaporative systems, atomizers, and water mist sprays, should not be used because of the potential risk of microbial contamination.

- Duct material in the vicinity of the humidifier should not add contaminants to air that will not be removed by filtration further downstream.

- Air filters should not be installed immediately downstream of humidifiers, as moisture on the filters could lead to bacterial growth.

TEMPERATURE MAPPING

There is an increasing awareness that storage areas need to be environmentally mapped to protect product quality and customer safety. A comprehensive temperature mapping study will ensure that the storage area is accurately monitored, properly maintained, and in compliance with all the applicable regulations.

Temperature mapping of the warehouse or storage area can be time consuming work, but external agency/vendors offers practical solutions to simplify the validation process in five steps to ensure that it is cost effective for your business while maintaining the highest standards of quality and reliability.

The following risks should be considered as part of the mapping plan:

- Goods stored close to the loading dock may be affected by drafts.

- Goods stored near the north facing wall and windows may be affected by solar heat.

- Lights can be a source of heat. Goods placed on high racking in close proximity to a light may be at risk.

- Goods movement and other activity in the more trafficable areas of the warehouse are likely to cause drafts.

- Goods stored on tall racking are likely to have a wide temperature variation between the top and the bottom racks.

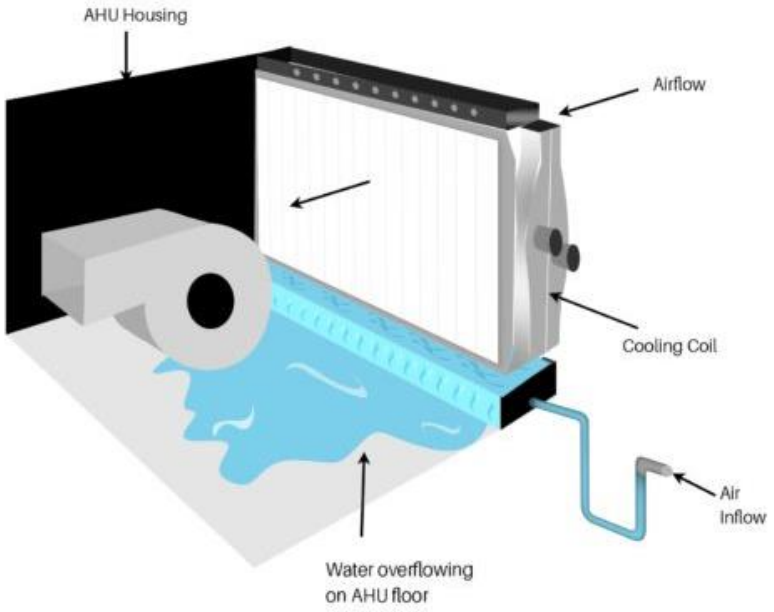


FIGURE 1: Drain Pan Flooding

One of the Example: Once fixed the trap was fixed, the problem went away. The cost of $2,000, including the cost of raising the AHU by 4 inches. However, the client was not happy about the change. There have been other cases where the AHU had to be raised, or condensate pumps had to be installed because the details were not thought through during design. The cost of these changes could be in the tens of thousands of dollars.

Ignoring coil condensate design makes engineers look incompetent. It can cause health issues because of mold and algae growth when not noticed early. Sizing the condensate trap is commonly overlooked, and there is no good literature that covers all aspects of design.

WHAT IS CONDENSATION?

When people think of condensation, it is common to think of water droplets accumulating on a glass of water with ice, or mist accumulating on a car windshield. Humid air condenses easily, which means condensation is much more common near the coast as compared to arid areas. An air conditioner that moves air at higher velocity produces condensate at a higher rate because condensate volume is proportional to the supply flow rate and the air density. Lower density air will result in a lower condensation rate. In engineering terms, condensation occurs when air hits a surface cooler than its dewpoint temperature. This is what happens at coil surfaces inside an AHU.

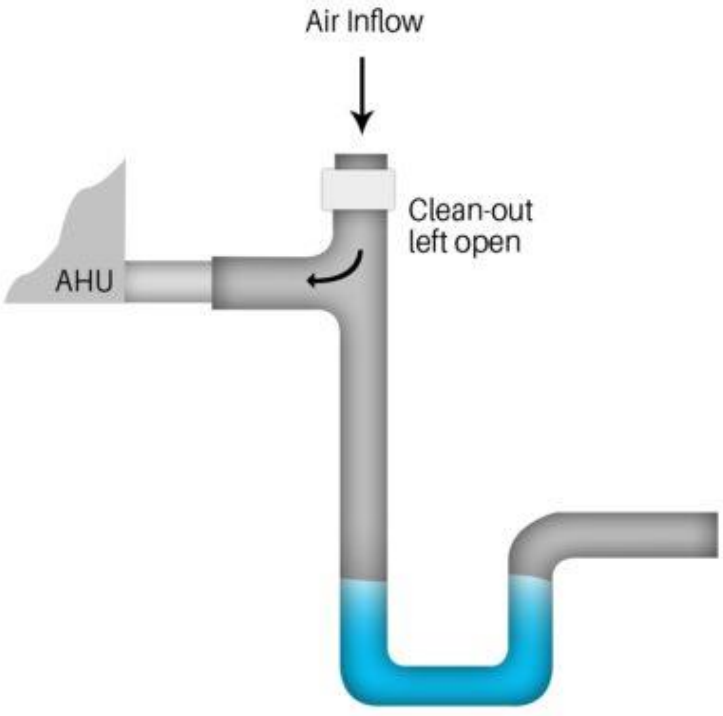


FIGURE 4A: CLEANOUT LEFT OPEN

STANDARD LIMITS FOR TEMPERATURE AND RELATIVE HUMIDITY

Sr. No.	Areas	Limit	
		Temp. ºC	RH %
1	All areas where environment is maintained under controlled condition with help of air handling unit, e.g., raw material storage, raw material quarantine, primary packing material store, secondary packing material store, LDPE granules transfer room, etc.	15-25	30-60
2	Empty capsule storage area	15-25	40-60
3	Stores (sampling area)/stores (dispensing area)	19-25	40-55
4	Raw material stores	15-25	30-50
5	Finished goods	15-25	30-75
6	Shipper store	15-40	30-75

6 COST CONSIDERATIONS

CAPITAL COSTS

HVAC systems for sterile manufacturing are expensive and represent a significant proportion of the total facility cost. The capital cost of a system can vary greatly and is dependent upon the decisions made throughout the design stages. The main factors that influence HVAC costs include:

1. Size of aseptic processing area: this should be optimized, without compromising material flow and product quality (HVAC size will be optimized accordingly).

2. A considered standby philosophy for the plant: it is not recommended to duplicate main HVAC plant items.

3. Simplicity of design: elaborate solutions are more expensive and can have a greater tendency to fail.

4. Integration of the HVAC design with other aspects of the facility: especially room layouts, process equipment, and other services.

5. The use of isolators can reduce room classification requirements, leading to smaller and lower cost HVAC systems, but are less flexible than RABS to modification once installed.

OPERATING COSTS

HVAC system design will affect the operating costs of the manufacturing facility, particularly as 24-hour operation is normally required.

The operating costs can be influenced by considering the following factors in the design process:

1. Optimum air change rates (ACPH).

2. Optimum recovery period to suit operating nature of facility.

3. Optimum differential pressure.

4. Air filtration arrangement to maximize life of HEPA filters.

5. Common sized HEPA filters utilized throughout the design to reduce spares inventory.

6. Use of re-circulation air or heat recovery use (if cross contamination issues permit).

7 ABBREVIATIONS

8 ANNEXURE

HVAC PARAMETER AND SPECIFICATION OOS

1. Air Handling Units

Parameters	Specification
1) Air quantity	M^3/Hr. (CFM)
2) Air velocity	M/Hr. (FPM)
3) Coil face area	M^2 (Ft^2)
4) Entering Air temperature (DB)	^0C
5) Entering Air temperature (WB)	^0C
6) Leaving Air Temperature (DB)	^0C
7) Leaving Air Temperature (WB)	^0C
8) Motor	
Rated horsepower	HP
Rated volts	Volts
Rated current	Amps
Actual current	Amps
Actual volts	Volts
Actual current	Amps
Actual power	KW

Parameters	Specification
Make:	
Model No:	
AHU TR:	
AHU CFM:	
Drain Pan MOC:	
Outer skin finish: plasticized/powder coated.	
Type of unit – horizontal or vertical:	
Inner skin MOC & gauge:	
Outer skin MOC & gauge:	
Overall dimension:	
Weight (kgs.):	
Noise level:	
Type of sections:	
Fan section, filter section:	
Coil sections:	
Cooling coil, heating coil:	

2. Centrifugal Fan

Parameters	Specification
Make & model no:	
Type of fan:	
Air quantity in cum./hr	
Fan speed RPM (normal/critical/maximum	
Fan motor HP (connected/consumed)	
Fan efficiency:	
Drive efficiency:	
Total efficiency:	
Outlet velocity in m/min:	
Fan dia. in mm.:	

Parameters	Specification
Balancing (static and or dynamic):	
Material of construction of vanes & SWG:	
Type of impeller blades:	
Static pressure in mm WG:	
Operating temperature 0C:	
Bearings (type/make):	
Bearing life:	
Performance curves with duty point duly marked:	

3. Filter Sections (PRE, FINE, HEPA.)

Parameters	Specification
Type:	
Make:	
Designation:	
Gross filter area M2:	
Velocity through filter in mts./min:	
Initial pressure in mm WG:	
Final pressure drops in mm WG:	
Maximum pressure drops in mm WG:	
Filter efficiency in (%):	
Particle retention capacity:	
Filter media:	
Filter framework MOC:	
Static load:	
Filter standards:	

4. Coil Sections

Parameters	Specification
Type:	
Make:	
Face area (M2):	

Parameters	Specification
Face velocity (mps):	
Sensible heat (kcal/hr):	
Latent heat (kcal/hr):	
Air quantity through coil (CMH):	
Water velocity through coil (mt./min):	
Water pressure drop across the coil:	
Air temperature, before coil (0C) dB & WB:	
Air temperature, after coil (0C) dB & WB:	
Row deep:	
Type of control:	
By pass factor:	
Max. cooling capacity available with offered coil:	
ADP (0C):	
Static load:	
Tube – material, OD x gauge, no. of rows:	
Fins – material, gauge, spacing:	
Hydro testing of coil:	

5. Heating Coil (Hot Water)

Parameters	Specification
Type:	
Make:	
Face area (M2):	
Face velocity (m/sec):	
Air quantity through coil (CMH)	
Water velocity through coil (m/min):	
Water pressure drop across the coil:	
Re circulating water quantity (ltr./min):	

Parameters	Specification
Air temperature, before coil (^{0}C) dB & WB:	
Air temperature, after coil (^{0}C) dB & WB:	
Row deep:	
Type of control:	
Bypass factor:	
Max. cooling capacity available with offered coil:	
Static load:	
Tube – material, OD x gauge, no. of rows:	
Fins – material, gauge, spacing:	
Hydro testing of coil:	

6. Piping

Parameters	Specification
Pipe: chilled water/hot water/drain:	
Make:	
Pipe type: ERW/seamless, etc.	
Class of pipe :	
Thickness of each pipe:	

7. Insulation

Parameters	Specification
Make:	
'K' value at 1000C	
Thickness:	
Density:	
Fire retardant property:	

8. Electrical Motors

Parameters	Specification
Type:	
Enclosure:	
Operating voltage:	
Output:	
No. of poles:	
Mounting:	
Shaft orientation:	
Bearing:	
Lubrication:	
Balancing:	
Coupling method:	
Type of coupling:	
Starter:	
Protection class:	
Insulation class:	
Rating/Test method:	
Performance test:	
Performance test certificate:	
Outdoor:	
Suitability:	

HVAC Design for Sterile Plant

CONTENTS

HVAC Design for Sterile Plant Guideline

1. PURPOSE

The Purpose Of This Standard Operating Procedure Is To Provide Guidance For Clean Room Design For Sterile Plants

2. SCOPE

This Procedure Is Applicable To Provide Design Guidance For Following :

2.1 Buildings And Facilities

2.2 Process Equipment Considerations

2.3 Heating, Ventilation, And Air Conditioning (HVAC)

2.4 Utility Systems

2.5 Electrical Services

2.6 Control And Instrumentation

2.7 Barrier And Isolator Technology

3. RESPONSIBILITY

- Engineering Department

4. DEFINITIONS

- **Acceptance Criteria :** Measurable Terms Under Which A Test Result Will Be Considered Acceptable.

- **Action Limit** : The Action Limit Is Reached When The Acceptance Criteria Of A Critical Parameter Have Been Exceeded. Results Outside These Limits Will Require Specified Action And Investigation.

- **Air-handling Unit** : The Air-handling Unit Serves To Condition The Air And Provide The Required Airflow Within A Facility.

- **Airflow Protection Booth** : A Booth Or Chamber, Typically For Purposes Of Carrying Out Sampling Or Weighing, In Order To Provide Product Containment And Operator Protection.

- **Airlock** : An Enclosed Space With Two Or More Doors, Which Is Interposed Between Two Or More Rooms, E.G., Of Differing Classes Of Cleanliness, For The Purpose Of Controlling The Airflow Between Those Rooms When They Need To Be Entered. An Airlock Is Designed For Use By Either People Or Goods: Personnel Airlock (PAL), Or Material Airlock (MAL).

- **As Built** : Condition Where The Installation Is Complete With All Services Connected And Functioning But With No Production Equipment, Materials, Or Personnel Present.

- **Atrest** : Condition Where The Installation Is Complete With Equipment Installed And Operating In A Manner Agreed Upon By The Customer And Supplier, But With No Personnel Present.

- **Clean Area (Cleanroom)** : An area (or room or zone) with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

- **Contamination** : The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or onto a starting material or intermediate, during production, sampling, packaging or repackaging, storage or transport.

- **Controlled Area (Classified Area)** : An area within the facility in which specific procedures and environmental parameters, including viable and non-viable particles, are defined, controlled, and monitored to prevent degradation, contamination or cross-contamination of the product.

- **Design Condition** : Design condition relates to the specified range or accuracy of a controlled variable used by the designer as a basis for determining the performance requirements of an engineered system.

- **Design Qualification** : Design qualification is the documented check of planning documents and technical specifications for design conformity with the process, manufacturing, good manufacturing practices and regulatory requirements.

- **Differential Pressure** : The difference in pressure between two points such as the pressure difference between an enclosed space and an independent reference point, or the pressure difference between two enclosed spaces.

- **Exfiltration** : Exfiltration Is The Egress Of Air From A Controlled Area To An External Zone.

- **Extract Air** : Air Leaving A Space, Which Could Be Either Return Air Or Exhaust Air. Return Air Means That The Air Is Returned To The Air-handling Unit, And Exhaust Air Means That The Air Is Vented To The Atmosphere.

- **Facility** : The Built Environment Within Which The Clean Area Installation And Associated Controlled Environments Operate Together With Their Supporting Infrastructure.

- **Good Engineering Practice (GEP)** : Established Engineering Methods And Standards That Are Applied Throughout The Project Life Cycle To Deliver Appropriate, Cost-effective Solutions.

- **Hazardous Substance Or Product** : A Product Or Substance That May Present A Substantial Risk Of Injury To Health Or To The Environment.

5. Procedure/Basis of HVAC Design

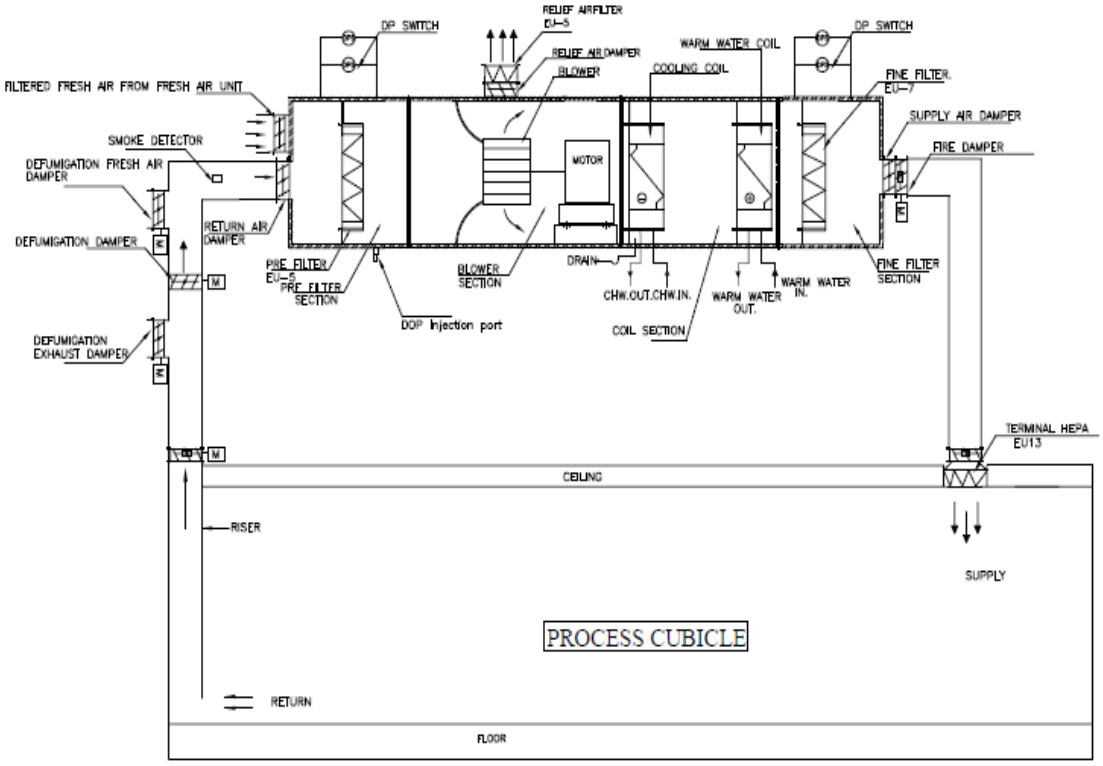
Following Aspects Are Defined In Basis For Design.

The Primary Design Consideration In Hvac System Is For:

1. Product Protection And Avoidance Of Cross Contamination.
2. Personnel Protection And Comfort.
3. Environmental Protection And Compliance With Local Statutory Pollution Norms.

The Processing Areas Will Be Generally Designed, For Maintaining Temperature Of Nmt (Not More Than) 25°c And Relative Humidity (Rh) Nmt 55% Or 60%, Unless Specifically Mentioned By User. The Relative Humidity Requirements Suggested By User Should Be Verified For The Requirements Of The Products Being Produced.

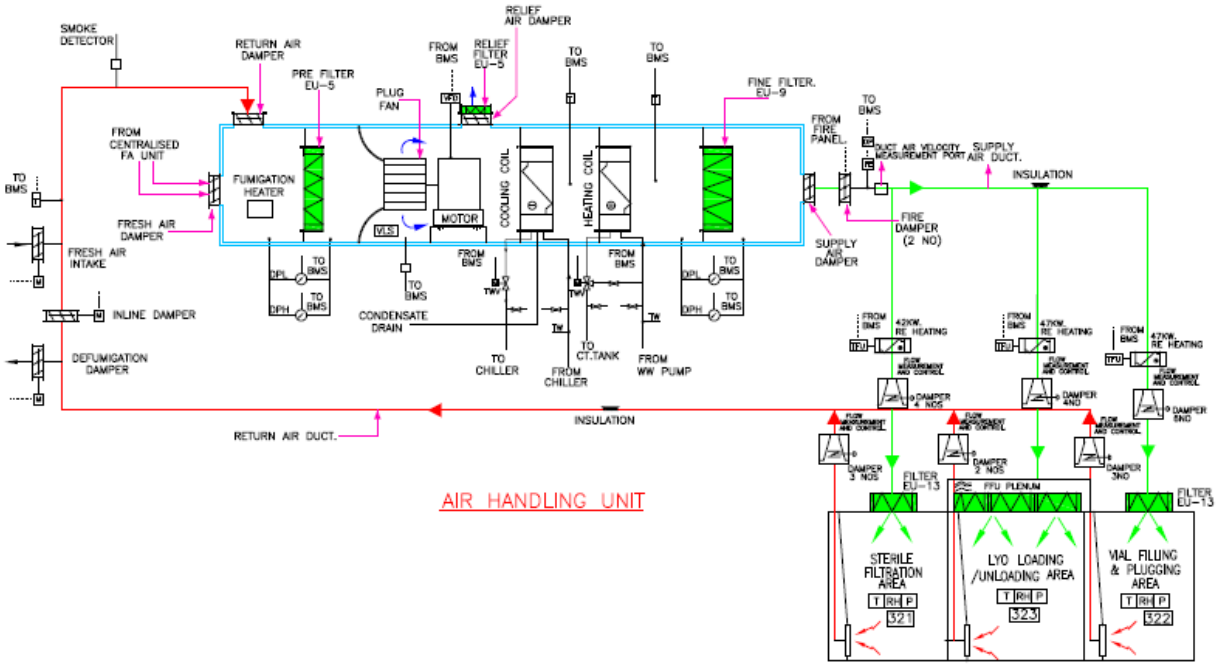
SCHEMATIC DIAGRAM OF AIR HANDLING UNIT WITH EU13 TERMINAL HEPA FILTERS AND ELECTRONIC PRESSURE CONTROL DAMPERS



Remarks : Consider EN 799 and EN 1822 standards in place of Eurovent 4/5 rating :

Eurovent 4/5 Rating	EN 799 & EN 1822
EU4	G4
EU5	M5
EU6	M6
EU7	F7
EU8	F8
EU9	E10
EU13	H14

Schematic Diagram of Air Handling Unit



1. Return air
2. Return air damper
3. Smoke detector
4. AHU mounted return air damper
5. Fresh air damper with EU-4 filter or treated fresh air supply through fresh air AHU
6. Pre-filter section
7. Pre-filter G4 /M5 / M6 / F7 (as applicable)
8. Blower
9. Blower section
10. Magnehelic manometer/differential pressure transmitter (as applicable)
11. Relief air with G4/E10/H14 filter connected to exhaust unit (if applicable)
12. Cooling coil
13. Condensate drain
14. Warm water coil
15. Fine filter section
16. Fine filter M6/F8/E10/H14 (as applicable)
17. AHU mounted supply air damper
18. Fire damper
19. Supply damper
20. Supply air
21. Ceiling
22. Process cubicle
23. Floor
24. Test aerosol injection port

5.1 ALLOCATION OF AIR HANDLING UNIT/AHU ZONING

AHU zoning shall be decided taking into consideration the following points:

1. Functional and operational requirement of production facility.
2. Clean room area classification.
3. Inside room temperature and relative humidity conditions.
4. Containment philosophy for potent compounds.
5. Avoiding cross contamination.
6. Dedicated air handling units for process area with airlock.

5.2 AIRBORNE PARTICLES RELATED TO ENVIRONMENTAL GRADES

Sr. No.	EU GMP Grade Classification	ISO Classification		Maximum Permitted Number of Particles/m3 (=>)	
				0.5 µm (d)	5 µm (d)
1	Grade A	At rest	ISO- 5	3,520	29
		In operation	ISO- 5	3,250	29
2	Grade B	At rest	ISO- 5	3,520	29
		In operation	ISO- 7	3,52,000	2,930
3	Grade C	At rest	ISO- 7	3,52,000	2,930
		In operation	ISO- 8	35,20,000	29,300
4	Grade D	At rest	ISO- 8	35,20,000	29,300
		In operation	Not defined	Not defined	Not defined

	EU GMP Grade Classification				
Sr. No.	EU GMP Grade Classification	Air Sampler cfu/m3	Settle Plates (90 mm) cfu/m3	Contact Plates (55 mm) cfu/m3	Glove Prints (5 fingers) cfu/m3
1	Grade A	<1	<1	<1	<1
2	Grade B	10	5	5	5
3	Grade C	100	50	25	-
4	Grade D	200	100	50	-

5.3 ROOM PRESSURIZATION

Differential pressure and design parameter

1. Rooms with same classification will be designed at minimum 5-10 Pa.
2. Rooms with different classification will be designed at minimum 15 Pa.
3. Leakage of air from higher pressure area to lower pressure area will be considered.

For details, please attach area classification and pressure differential layout.

Room pressure shall be maintained and monitored by installing room pressure sensor and return air duct equipped with motorized damper, with air flow measuring station for Grade B, C and D AHU. In addition, constant air volume (CAV) with bellow arrangement shall be installed over individual return air riser of Grade B AHU.

5.4 Room Air Changes

Air filtration and air change rates should ensure that the defined clean area classification is attained within specified recovery time.

Air change rates ACPH are normally determined by the following considerations:

1. Level of protection required.
2. The quality and filtration of the supply air.
3. Particulates generated by the manufacturing process.
4. Particulates generated by the operators.

Minimum supply air changes based on classification for AHUs shall be as follows:

Sr. No.	EU GMP Grade Classification	Minimum Air Changes Per Hour	Design Minimum Air Changes Per Hour
1	Class B	65	Around 70
2	Class C	40	Around 45
3	Class D	20	Around 25
4	Controlled not classified	10	Around 15

*Actual design air changes can be higher than minimum design air changes as per heat load calculation.

5.4.1 Room Inside Design Consideration

Summary of inside design condition is stated below.

1. Cleanliness Class: Class A (ISO 5)

The unidirectional air flow system is an air recirculation system, located flush with the cleanroom ceiling, which provides a constant ISO5/Grade A (Class 100) environmental condition with unidirectional airflow and linearity of air directly to the working area underneath. The area is provided with a higher pressure compared to surrounding area preventing microbiological and particulate contamination of the product handled within the area.

The unidirectional air flow system assures an even airflow velocity, establishing a vertical unidirectional airflow at 900mm +/- 100mm working height from floor (in case there are exceptions to the working height, these will be taken into account for design and implementation on a case-to-case basis), or at 6-12 inch (~150 -300 mm) below the filter face. The air velocity range at working level is 90±20% fpm / 0.45±20% m/s in the "as built" phase, provided that the air flow is not obstructed by any means and is guided by side hard walls.

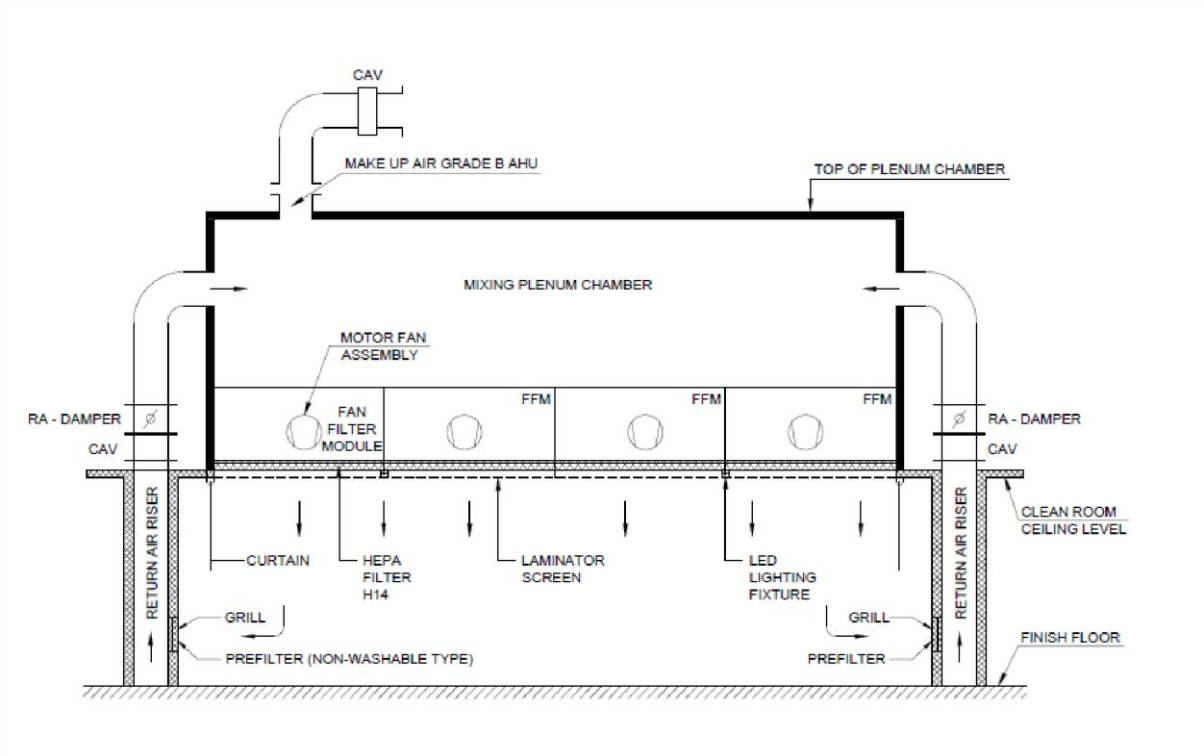
List of Components:

The unidirectional air flow system consists of the following components :

- Plenum horizontal panels and hanger system for FFM suspension.
- Plenum vertical panels and access panel.
- Fan Filter Modules (FFM units).
- Differential pressure sensors.
- HEPA filters.
- Laminator screens.
- Light fixtures.
- Surrounding hard walls curtains/partition (optional).
- Human Machine Interface (HMI).
- Control cabinet (21 CFR compliant system).
- Power cabinets.
- Remote I/O cabinets.
- Power and control cables.

Sr. No.	Technical Parameters	Design Consideration
1	Air velocity	0.45 m/s ± 20%
2	Design temperature	20 ± 2 °C
3	Design relative humidity	35 – 55 %
4	Filtration level in unit	
5	HEPA Filter:	99.995 % Down to 0.3µ (Type H14)
6	At supply terminal	0.3 µ HEPA filters (Type H14) supply air plenum chamber with fan filter module and laminar screen.
7	From room return	Low level return riser with grill with pre-filter (non-washable type).

SYSTEM OVERVIEW



The unit consists of an upstream mixing air plenum installed covering the recirculating units, called Fan Filter Modules (FFMs). The low level return air risers in the cleanroom are connected by ducts to the mixing plenum. Pre-filters should be installed into return air risers; within low level risers (located in the cleanroom wall) with G4 filters (-washable type).

The plenum is of horizontal and vertical panel design, and is constructed from 40mm ±2mm thick sandwich PUF panels, and is suspended from the building bare ceiling. On the outside of the plenum, penetration plates for the pressure sensors tubes and electrical cabling are provided for connection the FFMs inside the plenum.

Each unit will consist of a certain number of interconnected FFMs to cover the appropriate area. Each FFM housing contains of a HEPA filter mounted underneath a fan. The pattern form will cover the critical path of downstream machines and work surfaces. The FFMs are cGMP compliant, well designed, and manufactured to meet all cleanroom requirements for pharmaceutical manufacturing process areas, and especially to pass the leak test according to the ISO 14644-3 standard.

All maintenance activities relevant to HEPA filter and fan replacement will be from the room side. Each FFM is equipped with a differential pressure sensor to monitor and control fan speed according to the HEPA filter loading. An additional differential pressure sensor will be used to measure the differential pressure across each HEPA filter

Below the HEPA filters, laminator screens are mounted to provide a flush finish to the cleanroom ceiling. They are made of perforated stainless steel panels.

2.0 Cleanliness Class : Class B (ISO 7)

Sr. No.	Technical Parameters	Design Consideration
1	Number of minimum air changes	65 ACPH
2	Minimum design air changes	Around 70 ACPH
3	Design temperature	20 ± 2 °C
4	Design relative humidity	35 – 55 %
5	Filtration level in AHU	
a.	Pre-filter	90-95% down to 10µ (Type G4)
b.	Intermediate filter	95% down to 3µ (Type F7)
c.	Intermediate filter	75% down to 0.3µ (Type F9)
d.	HEPA filter	99.995 % down to 0.3µ (Type H14)
e.	Bleed air filter	NA
6	At room supply terminal	0.3 µ HEPA filters (Type H14) supply air terminal HEPA box with bottom SS 304 capsule type perforated sheet.
7	Fresh air	From TFA technical area.

3.0 Cleanliness Class : Class C (ISO 8)

Sr. No.	Technical Parameters	Design Consideration
1	Number of minimum air changes	40 ACPH
2	Minimum design air changes	Around 45 ACPH
3	Design temperature	20 ± 2 °C
4	Design relative humidity	35 – 55 %
5	Filtration level in AHU	
a.	Pre-filter	90-95% down to 10µ (Type G4)
b.	Intermediate filter	95% down to 3µ (Type F7)
c.	Fine filter	85% down to 0.3µ (Type F9)
d.	Bleed air filter	NA
6	At room supply terminal	0.3 µ HEPA filters (Type H14) supply air terminal HEPA box with bottom SS 304 capsule type perforated sheet
7	From room return	Low level return riser with SS 304 capsule type perforated sheet.
8	Fresh air	From TFA technical area.

4.0 Cleanliness Class: Class D (ISO 8 at rest)

Sr. No.	Technical Parameters	Design Consideration
1	Number of minimum air changes	20 ACPH
2	Minimum design air changes	Around 25 ACPH
3	Design temperature	20 ± 2 °C
4	Design relative humidity	35 – 55 %
5	Filtration level in AHU	
a.	Pre-filter	90-95% down to 10µ (Type G4)
b.	Intermediate filter	95% down to 3µ (Type F7)
c.	Fine filter	85% down to 0.3µ (Type F9)
d.	Bleed air filter	NA
6	At room supply terminal	0.3 µ HEPA filters (Type H14) supply air terminal HEPA box with bottom SS 304 capsule type perforated sheet.
7	At corridor supply terminal	Supply air diffuser with bottom SS 304 capsule type perforated sheet.
8	From room return	Return air low level return riser with SS 304 capsule type perforated sheet.
9	From corridor return	Return air diffuser with SS 304 capsule type perforated sheet.
10	Fresh air	From TFA technical area.

5.0 Cleanliness Class : Controlled not Classified (CNC)

Sr. No.	Technical Parameters	Design Consideration
1	Number of minimum air changes	10 ACPH
2	Minimum design air changes	Around 15 ACPH
3	Design temperature	23 ± 2 °C
4	Design relative humidity	NMT 60
5	Filtration level in AHU	
a.	Pre-Filter	90-95% down to 10µ (Type G4)
b.	Fine filter	95% down to 3µ (Type F7)
6	At room supply terminal	Supply air diffuser
7	From room return	Return air diffuser
8	Fresh air	From AHU technical area

6.0 CONTAINMENT FEATURES

1. BIBO type HEPA filter shall be provided at return air duct of for potent drugs formulation.

2. H14 type filter shall be considered for purge air section of classified AHUs which do not have BIBO filter arrangement.

3. Pressure sink is considered for installation between classified and unclassified rooms. This will be installed at the point of conveyor exit from classified room. This will consist of H14 type HEPA filter and a dedicated exhaust fan. There shall be back up with UPS power.

4. Sink and bubble arrangement are considered in personnel exit and entry gowning rooms of classified area handling potent compounds.

6.1 FILTER CLASSIFICATION

Sr. No.	Description	Efficiency
1	Pre-filter in AHU	G-4 as per EN 779
2	Fine filter in AHU	F-7 as per EN 779
3	Fine filter in AHU	F-9 as per EN 779
4	HEPA filters at terminal	H-14 as per EN 1822

6.2 INTERNAL LOADS

6.2.1 LIGHTING LOAD

For cooling and heating, estimated lighting load shall be 2 watts/sq. ft.

6.2.2 EQUIPMENT LOAD

Equipment load calculation shall be based on following parameters: latent heat, sensible heat of equipment

6.2.3 Diversity Factor

Diversity factor shall be considered as per process schedule considering simultaneous operation of lab equipment.

6.2.4 Fresh Air

Minimum Fresh Air (MFA) shall be the maximum of either

1. 2 ACPH or 15 CFM per person + 0.18*area in Sq. Ft

OR

2. Ex-filtration from room/room exhaust air.

6.2.5 Occupancy

Light work activity of worker shall be considered for estimating heat load.

Heat Gains as per ISHRAE Handbook

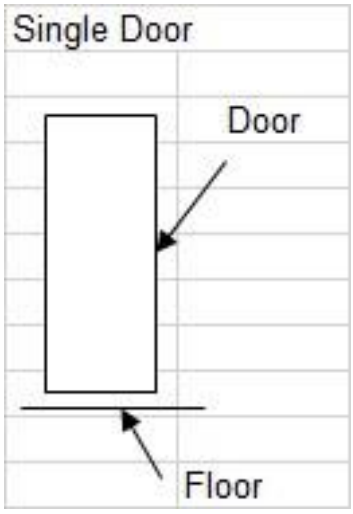
Sr. No.	Light Bench Work	Heat Gains	
		SENSIBLE (BTU per Hr /Person)	LATENT (BTU per Hr /Person)
1	At 22.7 °C (73deg F)	G-4 as per EN 779	

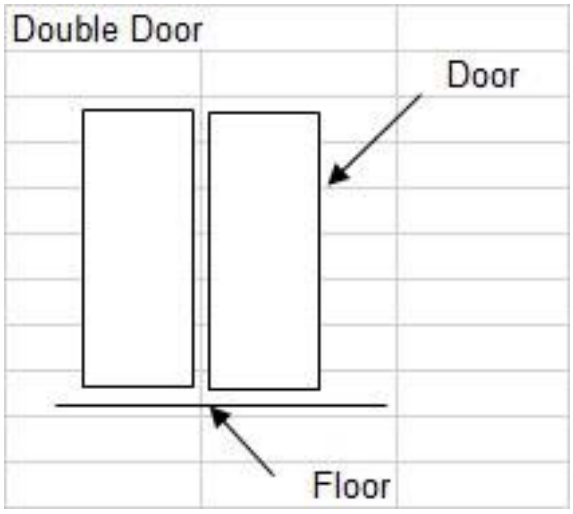
6.3 LEAKAGES THROUGH DOOR GAPS

For calculations of air leakage due to pressure difference between two areas, following door gaps will be considered :

Doors:

Bottom	3-5mm
Sides & top	2-4mm
Centre (double leaf doors)	2-10mm

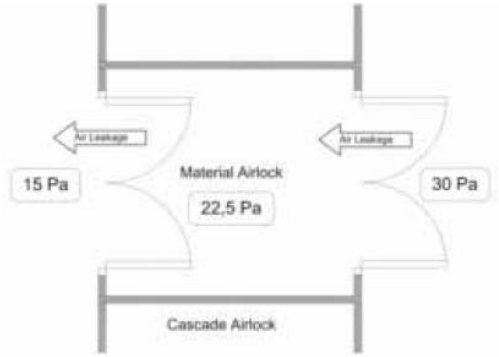




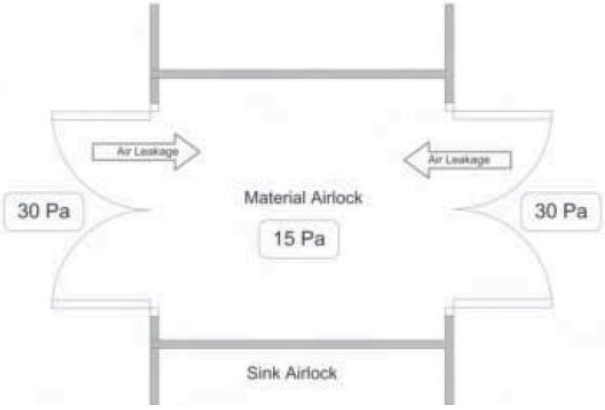
Note : There should be no air leakage through equipment installed in partitions.

DESIGN CONCEPTS ON PRESSURE GRADIENTS LINE

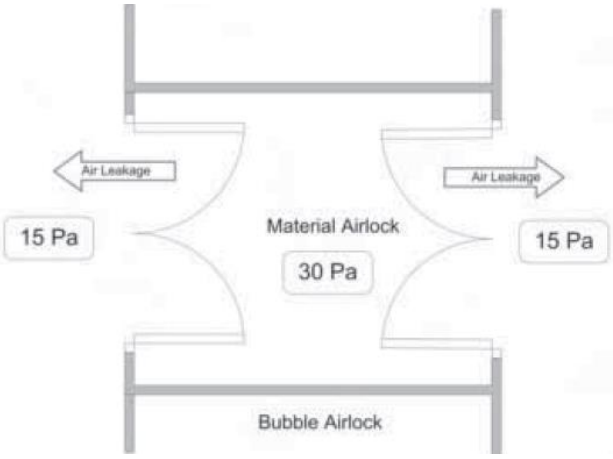
- Cascade Airlock



- Sink Airlock



- Bubble Airlock



AIR FLOW PATTERN

- Low levels pick up, i.e., riser, is proposed in all the areas. All risers will be provided without filters.
- For sampling, dispensing, i.e., where density of powder generation is low, riser will not be provided.
- All other non-process rooms can have ceiling return.
- Location of the supply and return modules/risers will be planned to achieve the following:
    1. To generate sweeping effect in rooms with risers.
    2. Uniform air distribution to avoid stagnation points.
    3. Movement of air from a relatively clean zone to lesser clean zone within the room.
- Filter in return riser is recommended in order to reduce ducting contamination and carry over of powders/choking of AHU pre filters and chilled water coil.

7.0 OTHER CONSIDERATIONS

1. Heat gain from ceiling load shall be considered.
2. External wall should be 230mm thick brick wall, with 15mm plaster on both sides.
3. Operation of the HVAC system shall be designed as per process requirement and will be operated from HVAC control system.
4. All areas shall be operated at time and there all heat gains shall be consider from interconnecting areas(if any).
5. Motorised volume control damper shall be considered for installation in order to maintain pressure gradient across rooms for classified area.
6. Defumigation shall be considered as part of HVAC system; accordingly motorised dampers shall be considered for defumigation requirement for Grade B AHU.
7. All volume control dampers should be motorized
8. All fire dampers provided on supply air duct shall be of motorised type, and return air duct shall be of fusible link type, and shall have provision to be upgraded for motorized operation.
9. Inside room condition shall be maintained before start of the process.
10. Safety features shall be designed for zero access to moving parts, and mechanical guards for all rotating parts.
11. Safe access to all equipment shall be designed for maintenance.

8.0 METHOD OF COOLING/HEATING LOAD ESTIMATION

Room-wise cooling load estimation for summer, monsoon and winter months shall be carried out in order to determine peak cooling and heating load.

AHUs shall be provided with heating coils as compensatory heating. This coil shall be of capacity sufficient to maintain room design condition.

AHU cooling coil shall be sized for cooling TR and actual dehumidified volume flow rate worked out from heat loads.

AHU heating coil shall be sized for heating for actual dehumidified volume flow rate worked out from heat loads.

Reheat and heating calculations shall be based on the consideration that there is zero equipment loads in room during peak conditions.

AHU shall be selected for 10% safety on the calculated minimum volume flow rate value.

Fresh air shall be separately conditioned in treated fresh unit in order to isolate seasonal loads on AHU coil.

9.0 CONTROLLING SCHEME

All control strategies shall be developed to meet the airflow, temperature, and RH conditions required in each area of the facility. For controlling these parameters, BMS system with DDC controller shall be considered.

Room Temperature and Relative Humidity

The room temperature and RH shall be maintained by varying chilled water flow through cooling coil with the PIBCV (Pressure Independent Balancing Control Valve). Which will be modulated based on Return Air Temperature/RH sensor (T+RH sensor), i.e., when actual RAT (return air temperature) increases above set RAT, chilled water valve open or when the actual relative humidity increases above set relative humidity, chilled water valve will modulates (moves towards open position).

When actual RAT goes below the set point, or relative humidity goes below the set point, chilled water valve will modulate (move towards close position).

In addition, a hot water reheat coil with 3-way valve shall be used for heating the air, if room temperature falls below the set point. PIBCV and 3-way control valve shall work in tandem so as to maintain the desired temperature and RH all the time.

Smoke detector shall be provided on return air duct. During smoke detection, AHU fan must be isolated before any fire damper are closed.

Room Pressure

1. Room pressure will be controlled by use of motorized volume control devices.

2. Every classified room will be provided with motorized volume control damper in main return air duct. This device will also have inbuilt airflow measurement station. Air flow input will be provided to motorized damper during balancing.

3. A differential pressure sensor will be installed in room for monitoring actual room pressure. Based on feedback from pressure sensor, motorized damper will modulate the return air.

4. Maximum and minimum air flow values will be set for each room and will be monitored through airflow measuring station.

5. Additionally, every return air riser of Grade B will be provided with CAV (Constant Air Volume).

Room differential pressure shall be controlled through BMS system.

Airflow Control :

EC-motors with integrated electronic control / Or VFD controlled energy efficient motor can easily be varied in speed to match airflow demand. Control system shall be compliant with 21CFR part II.

10.0 BRIEF HVAC SYSTEM DESCRIPTION

10.1 Low Side System

10.1.1 Air Handling Units

Air handling units will be of double skin construction in sections, with structural frame of extruded heavy aluminum profiles. AHU shall have thermal brake profile.

AHU panels should be in double skin sandwich type. The outer skin should be of 0.63 mm (24G) pre-plasticized galvanized or powder coated galvanized sheet steel, and the inner skin should be of 0.8 mm (22G) plain stainless steel (SS304) construction made of 43±2 mm thick mineral wool panels with thermal break profile. Air tight access panel with suitable neoprene gaskets should be provided in the fan section, coil and filter section. Units shall be specially designed to meet arduous and corrosive atmosphere.

All AHU shall be of blow-through arrangement type. The capacity of air handling unit is selected based on the higher volume flow rate (ft3/min) value between dehumidified air quantity, and the air quantity is calculated as per the minimum number of air changes to be maintained.

PIBCV control valve for chilled water manifold shall work in tandem to maintain the desired temperature and RH at all times, and hot water coil of the 3-way type controlled with temperature sensor shall be provided to take care of temperature control.

AHU fan with motor and filter capacity shall be selected at 10% higher capacity than the design air quantity. AHU catering to classified area (ISO 7) shall have defumigation arrangement.

AHU fan with motor and filter capacity shall be selected at 10% higher capacity than the design air quantity. AHU catering to classified area (ISO 7) shall have defumigation arrangement.

10.2 AHU Design Parameters

Sr. No.	Description	Particulars
1	AHU blower selection	Fresh air cfm + return air cfm + 15% safety
2	Chilled water coil entry temperature	5-7 ºC
3	Chilled water coil exit temperature	9-11 ºC
4	Coil hot water entry temperature	35-50 ºC
5	Coil hot water exit temperature	20-30 ºC
6	Face velocity across filter	Not more than 450 FPM
7	Face velocity across coil	Not more than 450 FPM
8	Type of fan AHU	Plug fan
9	Fan selection at best efficiency point	Maximum 55Hz motor frequency & minimum 70% fan static efficiency
10	Maximum water pressure drop across coil	15 ft of water column
11	Velocity across fresh air louvers	450 FPM

10.2.1 Blowers

Blowers for air handling units shall have backward-curved blades and external rotor motors (EC).

Blowers shall be selected based on the air handling unit capacity and the static pressure in the system. All centrifugal fans shall be in accordance with AMCA standard and the balancing quality as per ISO1940 and AMCA standards.

Grade B & C AHUs are provided with dedicated fans for supply air and return air. The purpose of twin blower are given below:

1. Quick defumigation without disturbing room pressure differentials.
2. Better control on room pressure difference as dedicated supply and return fans of desired capacity are provided.

10.2.2 Motors

EC fans are driven by energy-saving motors with electronic control (commutation unit) ensuring optimal operating efficiency. Motor capacity (KW) shall be as per the ratings calculated from the blower selection chart. Motors shall be high efficiency type (IE-3) in order to have energy savings in blower operation. EC motors have longer service life due to lower winding temperatures resulting in lower wear and tear. EC motors with integrated electronic control can be easily varied in speed to match airflow demand.

10.2.3 Cooling Coils

Cooling coils shall have adequate capacity determined from the heat load calculations, and shall be sufficient to remove outdoor air total heat and room total heat. Tubes for the cooling coil shall be of copper, and fins shall be of aluminium. Cooling coils should be certified from AHRI.

10.2.4 Defumigation Section

Defumigation arrangement is provided for Grade B AHU.

Dedicated motorized dampers for 100% fresh air intake are planned on AHUs are also excellent for quick defumigation. Dedicated motorized dampers for 100% exhaust air are provided.

10.2.5 Filters

Filter section shall be provided with ports to measure pressure drop across filter section.

Filters for air handling units shall be selected based on the total air handling unit capacity. Filters shall be classified as per Eurovent standard 4/5 or EN779/1822.

Terminal HEPA filters shall have minimum efficiency of 99.995 % as per EN 1822 Standard.

10.2.6 PIBCV Control Valves

Each AHU shall be provided with a pressure independent control cum balancing valve on chilled water. Automatic balancing valve / Control valve will operate on getting signal from respective return temperature & RH sensors to maintain inside desired conditions. For smooth commissioning ability, balancing valve in manifolds and main branch also included along with proper metering requirements.

10.2.7 Fire Dampers

Motorized fire dampers shall be installed in supply air duct and fusible link fire dampers with limit switch shall be installed in return air duct at AHU outlet. Fire damper shall be CBRI tested as per UL 555 fire damper standard.

10.2.8 Return Air Riser

Return air shall be picked up from low level return through return air risers in clean rooms areas. Return air risers shall be in-built in wall partition panels with the MOC of the panels.

10.2.9 Air Distribution System

Conditioned air from AHUs shall be distributed through insulated GI ducting. GI ducting insulation material should be closed cell class O nitrile rubber with black glass cloth.

HVAC ducting shall be tested as per SMACNA and duct leakage test method.

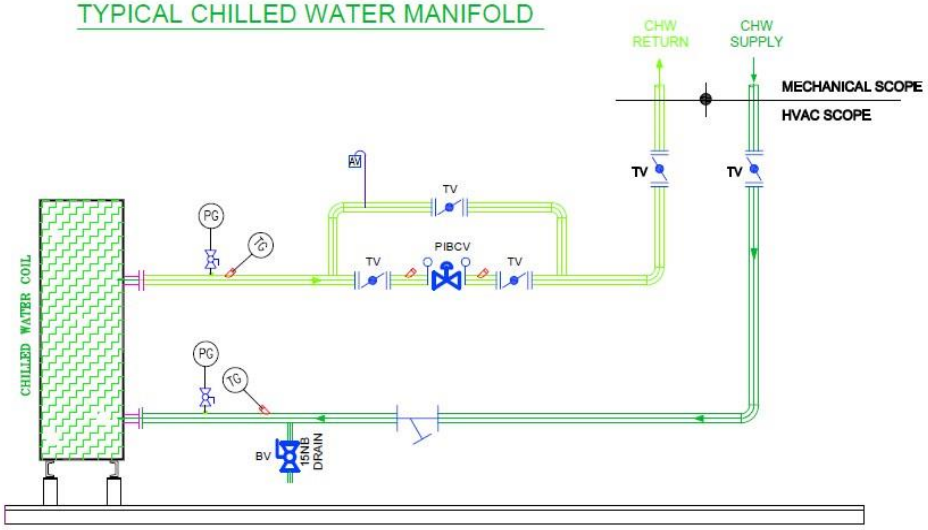
10.2.10 Chilled Water and Hot Water AHU Manifold Piping

Chilled water and Hot water pipes shall be of MS C class conforming to grade IS 1239 construction, complete with fittings, bends, elbows, unions etc. All chilled water pipe shall be insulated with 50mm thick puff block (TF Quality) with 24G Aluminium cladding for the manifold pipe. Valves and hot water pipes shall be insulated with elastomeric nitrile rubber insulation covered with factory backed aluminium foil.

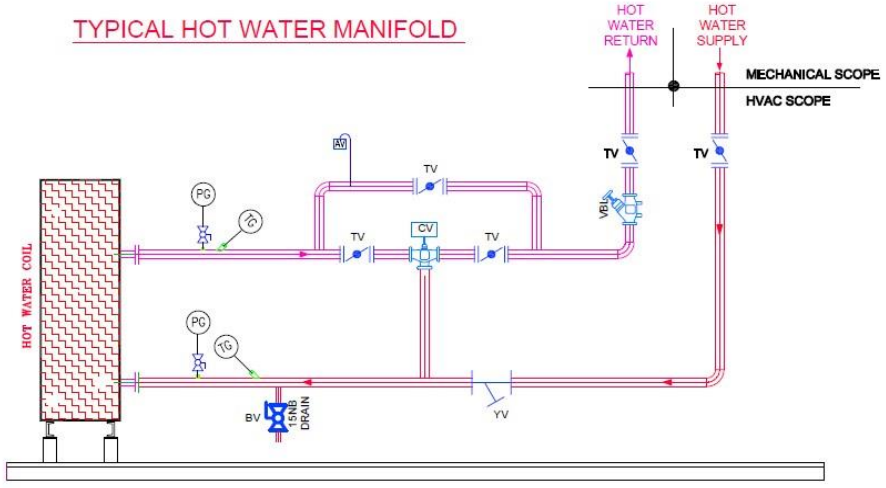
AHU manifolds shall have ball valves (up to 40 mm) or butterfly valves (above 40mm) for isolation. Y strainers shall be provided at the inlet of the cooling and heating coils, and PIBCV valves on the chilled water return side. 3-way motorized control valves on hot water return side shall be provided at the outlet of the coils. Balancing valve shall be provided at return side of hot water line. Pressure and temperature ports shall be provided at inlet and outlet of each cooling and heating coil of AHU in order to measure the pressure and temperature locally.

Note : Minimum size of pipe shall be 25NB.

TYPICAL CHILLED WATER MANIFOLD



TYPICAL HOT WATER MANIFOLD



10.2.11 Dynamic Pass Box

Dynamic pass box will be used for transfer of material between two classified areas, or between unclassified area and classified area. Complete pass box will be in SS construction or MOC of partition panels, having H-14 grade HEPA filter as final filtration. Pass box will be PLC controlled with Magnehelic gauge provided on panel for checking pressure drop across HEPA filter. Doors will have electromechanical locking system. This will ensure that even in case of power failure only one door shall open at any given time. Once material is loaded and doors are closed, cycle will start and blower shall run at designed speed. Once cycle is completed, the opposite door shall unlock. In between the cycle, no one shall be able to open either of doors without aborting the cycle. Through touch panel, blower speed may be changed. After the cycle is over, the blower shall continue to run but at a lower pre-determined speed. Pass box shall have PAO port for checking upstream PAO concentration.

Dynamic pass box should be validated as per following tests:

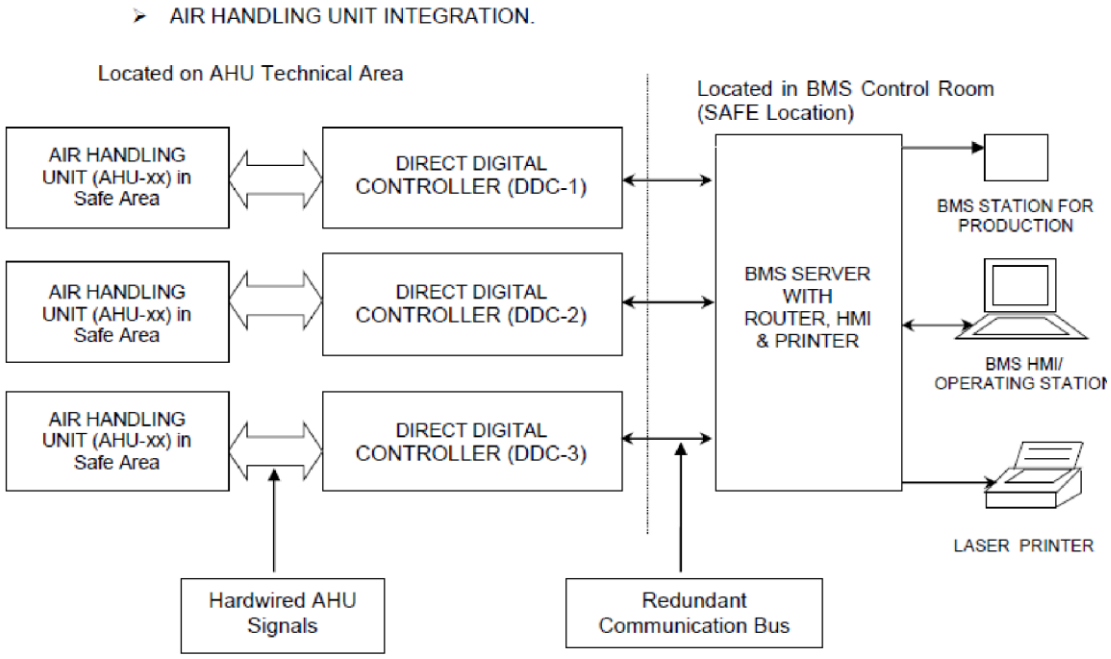
1. Air changes per hour.
2. Filter integrity test
3. Non-viable counts (3 consecutive counts).
4. Viable particle count,- done by QC during PQ.

11.0 BMS SYSTEM FOR HVAC

Building service system shall be capable of controlling and monitoring conditions such as temperature, humidity, airflow, and pressurization of HVAC. The DDC controller of individual AHUs shall communicate with the BMS. The BMS shall have data collection, trending, reporting, and alarm management functions.

The BMS is intended to seamlessly connect devices throughout the building regardless of subsystem type, i.e., variable frequency drives and low voltage lighting systems should easily coexist on the same network. The network shall be capable of communicating in C-bus, Modbus, Ethernet, RS485, some other protocol, and or any combination of these protocols. The control system shall include the interfaces necessary to facilitate operation and configuration. The prime function of THE BMS shall be to control HVAC to meet desired conditions along with energy savings.

BMS CONTROL BLOCK DIAGRAM :



11.1 Design Basis (HVAC BMS)

The HVAC-BMS control system comprises of BMS server, Router, HMI AND laser printer. HVAC system shall have Direct Digital Controllers (DDC) for controlling and monitoring AHUs, i.e., one DDC for one AHU to be controlled (if possible).

BMS for HVAC shall be designed to capture HVAC parameters such as supply air temperature, apparatus dew point (temperature), return air temperature and RH, room temperature and RH, supply air flow, AHU filter bank status using differential pressure switch, AHU fan motor frequency, exhaust air fan status, and AHU fan status signals for data logging and archiving.

AHUs shall start and stop through BMS operating station when AHU is in auto mode.

The data obtained in BMS shall have electronic records, electronic signatures and control for identification codes and passwords. Detailed real time graphical representations of equipment and systems are to be implemented. The graphical approach will constitute a friendly interface for the operator, and allow monitoring of specific operating conditions. Trending of data will be graphical as well as numerical.

DDC will be suitably located at technical area near AHUs electrical panels and will use controller to execute, in a fully stand-alone manner, all control loops using the Proportional-Integral-Derivative (PID) type control. The panels will receive the electronic signals of 4 to 20 mA or 0-10V from the sensing devices, such as temperature, humidity, and other data, and the panels will process this information, and limit electronic output signals for the control of actuators and other mechanical controlling devices. There shall be provision of 20% Spare I/Os..

BMS HMI or Operating Station

Operating station or HMI for BMS shall have latest configuration like the latest Intel Pentium processor, DVD writer, 19" color TFT LCD screen, multimedia keyboard, optical scroll mouse and A4 size color laser printer.

Power Supply

Power supply for DDC panels and BMS control system shall be 230 V AC at 50 Hz. All DDC panels, BMS server, etc. shall be powered through UPS.

11.2 HVAC BMS Control Logic

AHU Control Philosophy

All AHUs shall be installed at technical area with their local control panel and DDC. All DDCs shall be connected to BMS server through router. AHU shall have auto and manual modes of operation. The auto/manual selector switch shall be located on the local control panel near the AHU.

Control and Monitoring

Auto/Manual Mode

If the Auto/Manual selector switch is in 'Manual' mode, the AHU will operate and controlled only through local electrical control panel. BMS HMIoperator station will only monitor the actions. If the Auto/Manual selector switch is in 'Auto' mode, the AHU will be operated only from BMS HMI/operator station.

AHU Start/Stop Command:

Following interlocks should be true to start the AHU in auto mode:

1. Fan access door should be closed
2. Supply air fire damper should open
3. Auto/Manual switch should be in auto

AHU Chilled Water Control Valve:

1. Chilled water valve should proportionally open with respect to increase in return air RH and vice versa (i.e., direct acting).
2. Chilled water valve should open even when RH is within limit if return air temperature is high (i.e., direct acting)
3. Chilled water control valve percentage open feedback shall be available at BMS HMI/operator station.

When chilled water fails:

1. Room temperature will increase.
2. Due to increase in room temperature, hot water valve automatically closes fully.

AHU Hot Water Control Valve:

1. Hot water valve should proportionally close with respect to increase in return air temperature and vice versa (i.e., reverse acting)
2. Hot water valve percentage open feedback shall be available at central BMS
3. Overrides when hot water supply fails:

When hot water fails:

1. Room temperature will reduce.
2. Due to reduction in room temperature, RH will increase further and chilled water valves will open fully.
3. To avoid this situation, chilled water valve shall close automatically when return air temperature drops to 17° C, and open again when temperature increases above 20° C. Manual override for operating the valves should be considered .

Fresh Air and Exhaust Air Damper:

Fresh and exhaust air dampers are manually operated. These dampers shall be manually opened or closed by operator.

Filter status monitoring:

The filter status shall be monitored using differential pressure switch installed across each filter bank in air handling unit.

11.3 Field Instrumentation for HVAC BMS

All sensors and field instruments shall be weatherproof for AHUs located in safe areas.

1. Sensors

a. All sensors shall be equipped with 4 to 20 mA or 0 to 10 VDC transmitters.
b. The accuracy of the sensors shall be as follows:

Temperature : ±0.5°C
Relative humidity : ±2%

c. These will be used to monitor and control the environmental conditions.
d. Temperature and RH sensor mounted in the return air shall be used to control 2-way PIBCV chilled water and hot water control valves. These valves shall have manual override facility.

2. Control Valve

a. 2 way PIBCV and 3way control valve shall be of the globe type, complete with motorized actuator to be installed in the chilled water and hot water manifolds for AHUs.
b. Valves shall have manual override facility for manual operation.
c. These shall be complete with modulating plug, replaceable seals and discs, stainless steel stems, and throttling guides.
d. These shall be used to modulate the capacity of the cooling and heating coils, based on temperature and RH sensor output.

3. Temperature and Humidity Sensors

a. Temperature and humidity sensors will be mounted in the AHU return air duct.

11.4 Direct Digital Controller

DDCs are microprocessor-based controllers with the control logic performed by software. Analog-to-Digital (A/D) converters transform analog values into digital signals that a microprocessor can use. Analog sensors can be resistance, voltage, or current generators. Most systems distribute the software to remote controllers to eliminate the need for continuous communication capability (stand-alone). The computer is primarily used to monitor the status of the energy management system, store back-up copies of the programs and record alarming and trending functions. Complex strategies and energy management functions are readily available at the lowest level in the system architecture. Calibration of sensors is mathematical; consequently, the total man-hours for calibration are greatly reduced. The central diagnostic capabilities are a significant asset. Software and programming are constantly improving, becoming increasingly user-friendly with each update. DDCs provide improved effectiveness, improved operation efficiency, and increased energy efficiency.

11.5 BMS Features

11.5.1 Electronic Record and Traceability

BMS must have the ability to generate accurate and complete copies of records in both human readable and in electronic form, in both onscreen or PDF formats, suitable for inspection, review and copying by authorized personnel. Records shall be protected, and should enable accurate and ready retrieval through the record retention period.

11.5.2 Security Features:

BMS shall have following security features:

-Electronic signing and authorization.
-User specific access according to authority level.
-Signature element , including password, controls.
-Unlimited unique user accounts and passwords.

11.5.3 User Access Control:

BMS must have user access control through unique username and password protection facility. Each user can be set up for specific access rights. Following features shall be adopted as a minimum level for security.

1. System shall not accept password having length less than 6 characters.
2. User account shall be automatically disabled after three (3) consecutive login failures. Only administrator shall have the right to enable the disabled account.
3. User shall be automatically logged out when station remain idle for ten minutes.
4. User password shall expire after 180 days. The software shall deny access to user with an expired password.
5. System shall accept only complex password.
6. User log in, events and system configuration changes shall be registered in the audit trail. Audit trail shall have details like user, action, old and new value, date, and time etc.

11.5.4 Electronic Signature:

Electronic signature shall be in accordance with 21 CFR Part-11. All user action can be configured to require signing, or signing and authorization. The ability to sign or authorize is configured on a user-by-user basis, and incorporates signature element controls. Unique users are ensured by retiring, and not by deleting, accounts.

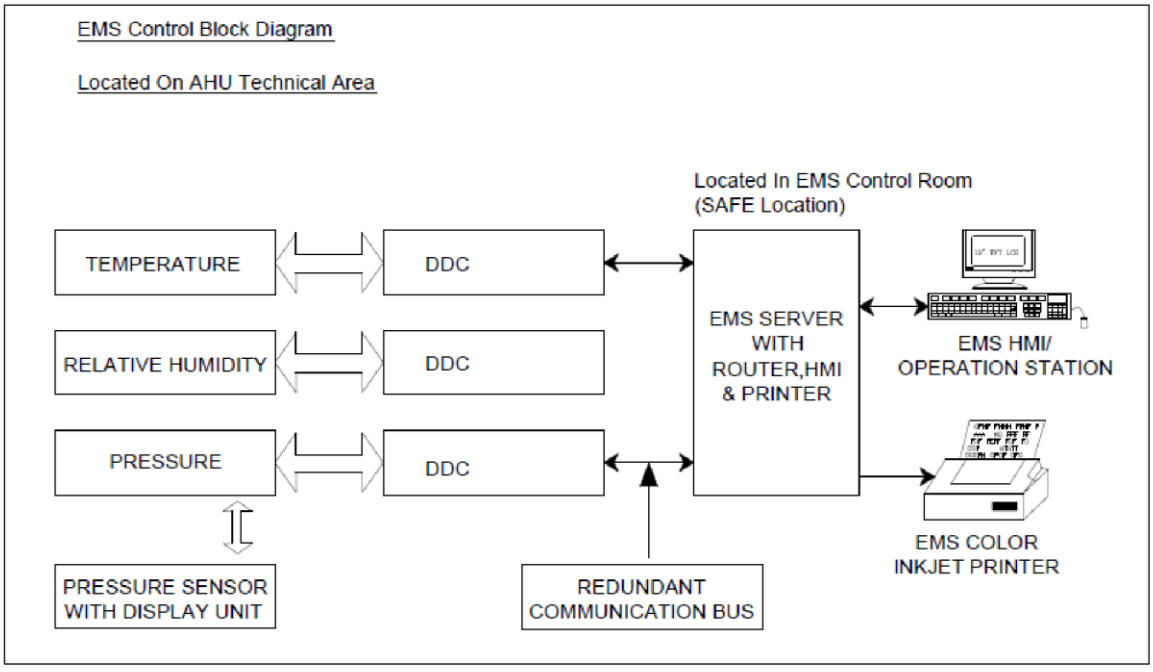
12.0 ENVIRONMENT MONITORING SYSTEM (EMS) FOR HVAC

The environment monitoring system shall carry out the monitoring, control and recording of various parameters as below:

1. Room temperature.
2. Room relative humidity.
3. Room pressure.
4. Door interlocking status.

EMS system shall consist of room display units with inbuilt temperature and RH sensors, pressure sensor with display units, converters, and operating station with software. EMS shall have data collection, trending, reporting and alarm management functions.
The network shall be capable of communicating in Modbus, Ethernet, RS485, another protocol and/or any combination of these protocols. The system shall include the interfaces necessary to facilitate operation and configuration.

Room display units shall be installed in safe area, and EMS computers and servers shall be installed in the control room in a safe area, and shall be fully weatherproof.



12.1 Design Basis (EMS)

The EMS system consists of EMS server, converter, display units, color laser printer, and related equipment. The EMS is capable of alarm management, historical data collection, and archiving. It will also have the ability to record and monitor inform like room temperature, RH, pressure, etc. Hence, it will have :

1. Room temperature, RH, and pressure display units with inbuilt relevant sensors.
2. DDC.
3. Operating station with software.

FDA, EMEA and other regulatory bodies require accurate measurement and storage of HVAC parameters, and if storage medium is electronic, the method must comply with FDA 21 CFR Part 11 requirement.

The system is modular in nature and permits expansion of both capacity and functionality through the addition of display units and DDCs. The failure of network connection should not interrupt the recording and monitoring at other operation devices.

The data obtained in EMS shall have electronic records of 5 minute intervals, electronic signatures and control for identification codes and password control features. Detailed real time graphical representations of equipment and systems shall be implemented. The graphical approach will constitute a friendly interface for the operator, and allow monitoring of specific operating conditions. Trending of data will be graphical as well as numerical.

EMS system shall be located at EMS control room in safe area. The communication between EMS central station and display units shall be on redundant communication bus such as Modbus/Ethernet/RS485, etc.

EMS Operating Station

Operating station/HMI for EMS shall have the latest configuration like latest Intel Pentium processor, DVD Writer, 19" color TFT LCD screen, multimedia keyboard, optical scroll mouse and A4 color laser printer.

Power Supply

Power supply for display units and EMS system shall be 230 V AC at 50 Hz. All display units, EMS server, and other related equipment shall be powered through UPS.

Temperature Mapping:

There is an increasing awareness that storage areas need to be environmentally mapped to protect product quality and customer safety. A comprehensive temperature mapping study will ensure that your storage area is accurately monitored, properly maintained, and in compliance with all the applicable regulations.

Temperature mapping of your warehouse or storage area can be time consuming work, but external agency/vendor offers practical solutions to simplify the validation process in five steps to ensure that it is cost effective for your business while maintaining the highest standards of quality and reliability.

The following risks should be considered as part of the mapping plan :

1. Goods stored close to the loading dock may be affected by drafts.

2. Goods stored near the north facing wall and windows may be affected by solar heat.

3. Lights can be a source of heat. Goods placed on high racking in close proximity to a light may be at risk.

4. Goods movement and other activity in the more trafficable areas of the warehouse are likely to cause drafts.

5. Goods stored on tall racking are likely to have a wide temperature variation between the top and the bottom racks.

AHU DRAIN LINE DESIGN IN CONTAMINATION OF VIEW:

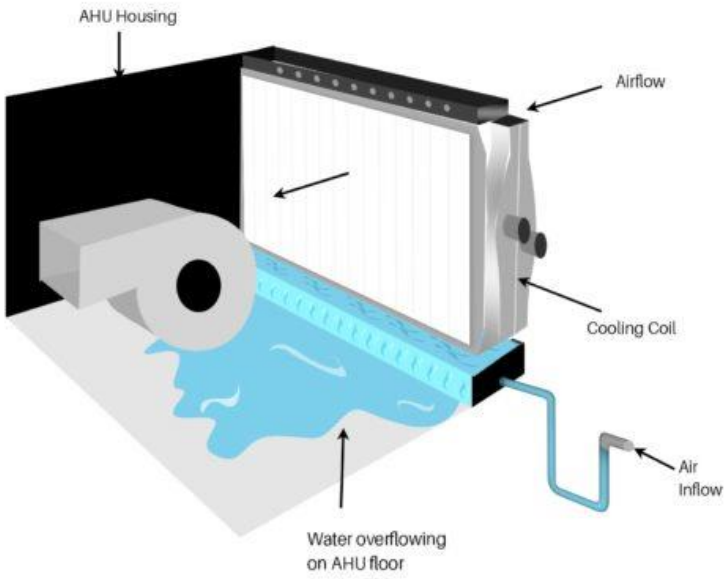


FIGURE 1: Drain Pan Flooding

Once we fixed the trap, the problem went away. It came at the cost of $2,000, which included the cost to raise the AHU by 4 inches. The client was not happy about the change. There have been other cases where the AHU had to be raised, or condensate pumps had to be installed because the details were not thought out during design. The cost of these changes could be in the tens of thousands of dollars.

Ignoring coil condensate design makes engineers look incompetent. It can cause health issues because of mold and algae growth when not noticed early. Sizing the condensate trap is commonly overlooked, and there is no good literature that covers all aspects of design.

What is condensation?

When people think of condensation, it is common to think of water droplets accumulating on a glass of water with ice, or mist accumulating on a car windshield. Humid air condenses easily, which means condensation is much more common near the coast as compared to arid areas.. An air conditioner that moves air at higher velocity produces condensate at a higher rate because condensate volume is proportional to the supply flow rate and the air density. Lower density air will result in a lower condensation rate. In engineering terms, condensation occurs when air hits a surface cooler than its dewpoint temperature. This is what happens at coil surfaces inside an AHU.

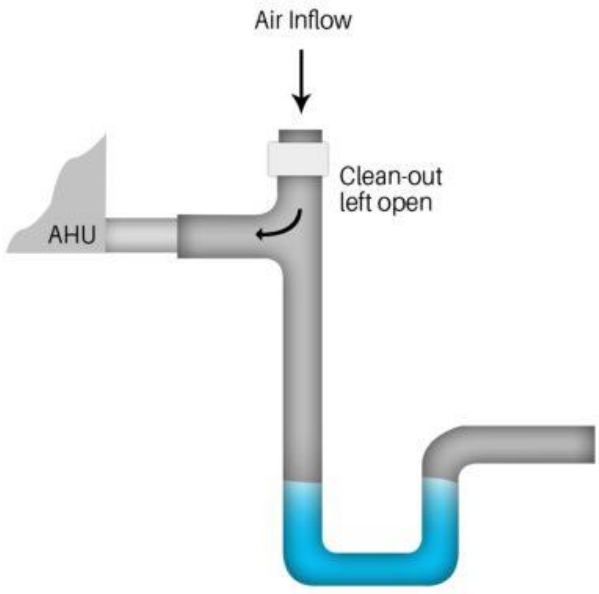


FIGURE 4A: CLEANOUT LEFT OPEN

STANDARD LIMITS FOR TEMPERATURE AND RELATIVE HUMIDITY

Sr. No.	Areas	Particulars	
		Temp. ºC	RH %
1	All areas where environment is maintained under controlled condition with help of air handling unit, e.g., raw material storage, raw material quarantine, primary packing material store, secondary packing material store, etc	15-25	30-60
2	Empty capsule storage area	15-25	40-60
3	Stores sampling area/stores dispensing area	19-25	40-55
4	Raw material stores	15-25	30-65
5	Finished goods	15-25	30-75
6	Shipper store	15-40	30-75

13.0 UTILITY REQUIREMENTS

1.	Electrical power (LT)	415 V +/- 10%, 50 Hz +/- 3%, 3 Phase, 4 wire
2.	Control voltage	24V DC, 50 Hz
3.	Chilled water	5-6 deg. C at AHU inlet
4.	Hot water	37 deg C. at AHU inlet

14.0 SUSTAINABLE HVAC

1. Precise heat load to be carried out as per equipment heat dissipation& input factors, accordingly equipment sizing to be done i.e. AHU capacity & CHW and HW requirement. Proper equipment sizing affect the energy consumption level.

2. Use of high efficiency IE-3 rated motors.

3. Use of EC motor fans in AHUs to achieve power savings

4. Use of pressure independent control cum balancing valve to have smooth loading operation of chillers, and to avoid excess flow in AHU coils due to pressure variation in chilled water supply line.

5. Minimization of fresh air to all systems, limited to pressurization, process make-up and personal needs.

6. AHU with proper thermal bridging and low leakage rate to reduce energy loss and condensation.

7. Optimized designing of duct and pipe routes reduce transmission losses. Low loss pressure headers for both duct and pipes should be considered.

8. Insulation thickness selection is important to minimize thermal losses for all duct work and piping.

9. Optimized number and selection of filters in the system are important. High capacity low pressure drop filters should be used.

10. Low air leakage through ducts should be ensured through duct leak testing as per SMACNA standards.

11. Consideration of the points can provide a cost effective HVAC solution.

15.0 SAFETY FEATURES

1. Electric components shall be designed to comply with LOTO procedure.
2. HVAC system shall be provided with suitable arrangement to acknowledge alarms.
3. Electrical installation shall be in compliance with local code of practice.
4. AHU should trip in case access doors are open.
5. Mechanical guard shall be provided for all rotating parts.
6. Emergency push button should be provided in the electrical panel.
7. Smoke detector shall be installed in return air duct to stop AHU in case of fire.
8. Use of Class O rated insulation both for ducts and pipes should be ensured.
9. No cross contamination of air should be there from areas handling different products or two different cleanliness zones. Pressure in various areas shall be planned accordingly.
10. AHU door panel shall be interlocked with blower (i.e., all rotating components of equipment shall be interlocked).
11. Marine light shall be interlocked, i.e., light shall be ON in each section when access door is open.
12. AHU fan guard shall be considered and should be of perforated type guard which prevents the door closing if person is inside the AHU blower section.
13. Interlocks shall be hard-wired and shall not be controlled by software.
14. Fire scape corridor pressurization unit should be provided.

16.0 DOCUMENTATION

Vendor shall check functional specifications, Piping and Instrumentation Diagram (P&ID), general arrangement drawings, component list, instrument list, control and electrical drawings, equipment datasheets and performance curves, calibration and test certificates, loading data, or any other drawing and document required for installation, commissioning, operation, and qualification of system. The drawings and documents shall be provided as hard copies and, wherever possible, in electronic version.

Vendor shall be responsible for maintaining design conditions.

The supplier shall provide documentation reflecting “as built” condition with final delivery. The supplier shall specifically provide following documents & not limited to:

1. Duct cleaning & pressure testing report as per SMACNA/DW144 standards.
2. AHUs datasheets
3. Fan(s) speed measurement report
4. Filter Data Sheets
5. Filter List
6. HEPA filters factory integrity test certificate
7. Pipe, valves test certificates
8. GI sheets test certificates
9. Grille/diffuser test certificates
10. Insulation material test certificates
11. GA drawing / wiring drawing/ single line diagram of all electrical panels
12. HVAC Airflow & Instrument Schematics
13. Test certificates of all cables and cable tray material
14. Room Balancing Report (CFM adjustments)
15. In-situ Integrity test of HEPA filters Test Record
16. Room Pressure differential Test Record
17. Pressure differential across filters Test Record
18. Room Air Change Rate Test Record
19. Smoke Test & Videography for unidirectional flow
20. Room Relative humidity Test Record
21. Room Temperature Test Record
22. Particulate Sampling test program and sampling points schedule
23. At rest, as built and as operation non-viable particulate count Test Record for classified areas.
24. Recovery Rate Test Record 25. Catalogues for bought out items.
25. Calibration certificates
26. Design Qualifications, Installation Qualifications, Operational Qualifications.

17.0 PERFORMANCE TESTS

Performance of HVAC system shall be demonstrated for both “at rest” and “in-operation“ conditions. Non-viable counts shall be as per ISO standards 14644 Clean Room & Associated Controlled Environment. Viable counts shall be as per EU GMP and US FDA guidelines. The latest editions of these standards shall be followed for testing and acceptance of the system. At the very minimum the following tests shall be performed during system qualification:

1. Air borne particulate testing (non-viable particle count): 3 readings.
2. Air flow pattern (smoke flow study) with videography.
3. HEPA filter integrity test.
4. Pressure/temperature/RH test for 3 days.
5. Pressure balancing/air balancing for 3 consecutive days.
6. Area recovery test.
7. Air velocity.
8. ACPH.
9. Containment leak test for aseptic area.

18.0 REFERENCE STANDARDS

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19.0 ABBREVIATIONS

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Application of BMS in Pharma

CONTENTS

1 Introduction

1.1 PURPOSE

- The purpose of this document is to serve as design guidance document for Building Management System (BMS) proposed for the facilities in the pharmaceutical industry.

1.2 SCOPE

- The scope of this document is limited to providing a design guidance for a BMS installation to be installed and operated for GMP designated hardware and software system providing monitoring, alarming, trending, reporting, and archiving of the data collected from proposed stand-alone field controller units, performing building management and automatic environmental control functions in the pharmaceutical industry.

- The BMS shall be documented, designed, and installed to conform to validation procedures of the pharmaceutical industry, and current industry standard practices, and to cGMP requirements, regulations, and guidelines, where applicable.

- The BMS must also be configured for 21 CFR Part 11 compliance and provide a validation framework that will assist in maintaining the BMS in a validated state for the system's life cycle.

2 Overview

2.1 KEY OBJECTIVES AND BENEFITS

- The key objective is to provide guideline for procuring BMS software in order create a manufacturing environment based on the clean room class requirements. Air handling systems are the main tools for reaching the required parameters in a clean room, and they play a major role in the quality of pharmaceuticals. They must be designed properly and treated as critical systems.

- After successfully qualifying the clean room, it is required to demonstrate its continued compliance. Routine environment monitoring program should be followed as a part of quality assurance along with additional monitoring and triggers like shutdown, replacement of filter elements, maintenance of air handling systems, etc.

- This can be achieved most efficiently by adopting BMS. The major benefits are :

    - Stand-alone precision control of parameters achieved with the help of continuous self-tuning using adaptive control technology.

    - Centralized monitoring and control using all such networked stand-alone controllers.

    - Optimum energy utilization as per need of process and product requirements.

    - Versatile and user friendly graphical interface helps ease of operation for centralized systems.

    - Improve individual AHU components and overall clean room performance by maintaining the following main parameters (influencing level of protection) to the desired performance specifications:

        a. Air handling systems.
        b. Number of particles in the air.
        c. Number of microorganisms in the air or on surfaces.
        d. Number of air changes for each room.
        e. Air velocity.
        f. Airflow pattern.
        g. Filters (type, position).
        h. Air pressure differentials between rooms.
        i. Temperature and humidity.

- The BMS shall provide the environmental controls and monitoring of the products manufacturing facility, which is used to manufacture and package products.

3 Operational Requirements

3.1 CAPACITY

- Supplier shall design the system with sufficient capacity to accommodate each AHU system requirement as defined in I/O list.
- Supplier shall include 20% excess capacity for I/O, memory and data collection, and storage in stand-alone controller.
- The supplier has to provide space and facility to expand one module in each panel for future expansions.
- The supplier has to license 50% excess capacity in central server software for future additions of AHU systems.
- There shall be at least two (2) clients or web client licenses, and 1 server on the BMS network and capability to increase the number of stations if required in future.
- The supplier shall design the BMS network separately for critical and non-critical stand-alone controllers and shall have the facility to add a separate network in future.
- The supplier shall design the LDU network separately and shall have the facility to add a separate network in future.

3.2 PROCESS REQUIREMENTS AND CONTROL

- Each AHU system requirements is as listed below :
    - Room parameter monitoring and user interface requirement in BMS shall be available.
    - Alert and action alarm limits for the room parameter shall be available.
    - Process and instrumentation diagrams shall be available.
    - Room pressurization requirements (if applicable) shall be available.
    - Required I/O list shall be available for system design.

3.3 FUNCTIONS

- The BMS shall be capable of system scheduling and monitoring, alarming, point trending, point adjustments and overrides.

- The BMS shall be capable of generating an audit trail for all user actions. The audit trail shall include user name, date, time, terminal ID, user action, and reason for action.

- The system data shall be sampled and logged at configurable frequencies from 1 second and above.

- The BMS shall be capable of system scheduling such as night setback, morning warm-up, etc.

- The BMS shall be capable of generating an audit trail for all alarm acknowledgements, login, logout, and point adjustments.

- The BMS shall be capable of allowing manual operation of equipment and devices. When AHU blower motor control is kept in manual it should be designed to give an urgent alarm.

- The BMS network shall have a flexible topology designed to ensure data flow under all load conditions. It shall have key requirement resilience and the use of redundant networks (in future, if required) so as to ensure that communications continue in the event of a network failure. The BMS architecture shall be designed to use a high-speed redundant star network topology. The network shall be capable of communicating in BACnet, Ethernet, RS 485, another protocol and or any combination of these protocols.

4 Hardware

Note : All the hardware to be supplied by the OEM/integrator need to have vertical mobility for upcoming version of software for a period of 10 years from date of installation.

4.1 SYSTEM NETWORK CONTROLLER (SNC) (if required)

- These controllers are designed to manage communications between the Programmable Equipment Controllers (PEC), Application Specific Controllers (ASC), and Advanced Unitary Controllers (AUC) which are connected to its communications trunks, manage communications between itself and other System Network Controllers (SNC), and with any Operator Work Stations (OWS) that are part of the BAS, and perform control and operating strategies for the system based on information from any controller connected to the BAS.

4.2 CONTROLLERS AND FIELD DEVICES

- Building automation/management controllers (DDC or Direct Digital Controllers) are used to provide the inputs, outputs, and global functions required to control the mechanical and electrical equipment. Most BAS manufacturers provide a variety of controllers tailored to suit specific needs. Shown below is a list of the most common BAS controllers.

- Communications interface: provides the communication interface between the operator workstation and the lower-tier controller network. On a polling controller network, a communications interface is used to transfer data between the controllers.

- Remote IO: provides the interface between BMS controller and remote IOs thereby reducing the controller requirements.

- Primary controller: provides global functions for the BAS control network that can include real-time clocks, trend data storage, alarms, and other higher-level programming support. Some BAS manufacturers combine all these functions into one primary controller, while other manufacturers have separate controllers that are dedicated to each global function.

- Secondary controller: contains the control logic and programs for the control application. Secondary controllers usually include some on-board input/output (I/O) and may interface to expansion modules for additional I/O. Inputs include temperatures, relative humidity, pressures, and fan and pump status. Outputs include on/off, and valve or damper control. Also included in this group are application-specific controllers that have limited capability and are designed for a specific task. Examples include controllers for variable air volume terminal unit (VAV) boxes, fan coil units, and multistage cooling and heating direct-expansion (DX) air conditioning systems.

- Field controllers should have an independent program to operate, monitor, and control of AHUs, ventilation blowers, dust collectors, point exhaust, and scrubbing machine as per the procedure explained in “sequence of operation for HVAC equipment”.

- The DDC shall be capable of storing all process data/event/alarms, in case of communication loss with the supervisory station.

- The DDC shall be capable of integrating with devices like VFD, dehumidifier controller, room display unit, etc., with various protocols like Modbus TCP/IP (LAN), BACNET/Modbus RTU, etc.

- The controller shall have an internal time clock with the ability to automatically revert from a master time clock on failure.

- Following a power loss and subsequent power restoration, the field controllers should restart and execute application data files stored in RAM.

- The controller shall be fully programmable with full functionality.

- Controller should Support simulation/debug mode.

- In the event that the application data files have been lost from RAM, the controller should be capable of loading these files from flash memory into RAM, provided that the files were saved in flash memory.

- In the event of a power loss, UPS should be provided to field controllers for at least ten minutes so that the controllers can continue operating. This should allow data collection from all the parameters to monitor environmental conditions of the critical areas during power failure.

- In the case of communication failure between the controllers and the front-end hardware, the controller should be in stand-alone mode, i.e., it should continue to execute the program without any intervention.

- The controller should be capable of logging all events and modifications within its own memory.

- Backfilling: BMS controller shall have storage capacity of 2 Gb (or sufficient storage capacity) of user storage, and it can store the data during communication loss between SCADA(BMS) system and DDC controller. BMS controller shall have the functionality of backfilling room/AHU parameter data (such as room temperature, room RH and room DP, filter DP or other defined parameters), so that if the connectivity between DDC and SCADA fails, DDC continues to store data. When connectivity resumes, the data must be automatically backfilled to the BMS system.

- The controller platform shall have standard HVAC application programs that are modifiable to support both the traditional and specialized sequence of operations.

- The controller housing shall be UL plenum rated mounting to either a panel or DIN rail (standard EN50022; 7.5mm x 35mm).

- The controller shall have a mix of digital inputs (DI), digital TRIAC outputs (DO), analog outputs (AO), and universal inputs (UI).

- Analog outputs (AO) shall be capable of being configured as digital outputs (DO).

- Input and output wiring terminal strips shall be removable from the controller without disconnecting wiring.

- Input and output wiring terminals shall be designated with color coded labels.

- Universal inputs shall be capable of being configured as binary inputs, resistive inputs, voltage inputs (0-10 VDC), or current inputs (4-20 mA).

- The controller shall have a visual indication (LED) of the status of the device, as below:
    a. Controller operating normally.
    b. Controller in process of download.
    c. Controller in manual mode under control of software tool.
    d. Controller lost its configuration.
    e. No power to controller, low voltage, or controller damage.
    f. Processor and/or controller not operating.

4.3 SENSORS AND FIELD DEVICES AND SELECTION APPROACH

- The field devices need to be selected based on:
    - Type of application.
    - Mounting.
    - Operating range.
    - Least count.
    - Accuracy of the measured parameter.

- The field devices for the required application can be selected based on the following criteria:

    - Wall mounted room temperature sensors: each room temperature sensor shall provide temperature indication to the digital controller, provide the capability for a software-limited occupant set point adjustment (warmer-cooler slider bar or switch) and limited operation override capability. Room temperature sensors shall be 20,000-ohm thermistor type with a temperature range of -40°C to 60 °C) (-40 to 140 degrees F) The sensor shall be complete with a decorative cover and suitable for mounting over a standard electrical utility box. These devices shall have an accuracy of ± 0.5 degrees Celsius over the entire range.

    - Duct-mounted and outside air temperature sensors: these are 20,000-ohm thermistor temperature sensors with an accuracy of ± 0.5 degrees C of full scale. Outside air sensors shall include an integral sun shield. Duct-mounted sensors shall have an insertion measuring probe of a length appropriate for the duct size, with a temperature range of -38 °C to 71 °C (-40 to 160 degrees F) The sensor shall include a utility box and a gasket to prevent air leakage and vibration noise. For all mixed air and preheat air applications, bendable averaging duct sensors shall be installed with a minimum 2.438m (8 feet) long sensor element.

    - Humidity sensors shall be thin-film capacitive type sensor with on-board non-volatile memory, accuracy to ±5% at 0 to 90% RH, 12 - 30 VDC input voltage, analog output (0 - 10 VDC or 4 - 20mA output). Operating range shall be 0 to 100% RH and 32 to 140 degrees F (0 to 60 degrees C). Sensors shall be selected for wall, duct or outdoor type installation as appropriate. For areas where powder is handled, sensor frame shall be of SS MOC and shall have cleanable filter for sensing element which will prevent entry of powder.

    - Differential air pressure switches: these should be SPDT type, ULapproved, and selected for the appropriate operating range where applied. Switches shall have adjustable setpoints and barbed pressure tips.

- Differential pressure transmitters: differential pressure transmitters shall be electronic with a 4-20 mA output signal compatible to the DDC. Wetted parts shall be stainless steel. Unit shall be designed to operate in the pressure ranges involved.

- Motorized control dampers that will not be integral to the equipment shall be furnished by the control system contractor. Control damper frames shall be constructed of galvanized steel, formed into changes, and welded or riveted. Dampers shall be galvanized, with nylon bearings. Blade edge seals shall be vinyl. Blade edge and tip seals shall be included for all dampers. Blades shall be 16-gauge minimum and 6 inches wide maximum, and frame shall be of welded channel iron. Damper leakage shall not exceed 10 CFM per square foot, at 1.5 inches water gauge static pressure.

- Volume control damper actuators: these actuators for motorized volume control dampers shall of the range: 0-100% open, input: 24VAC/VDC, output:0-10 VDC.

- Control valves: these shall be of 2-way or 3-way pattern and constructed for tight shutoff at the pump shut-off head or steam relief valve pressure. Control valves shall operate satisfactorily against system pressures and differentials. Two-position valves shall be 'line' size. Proportional control valves shall be sized for a maximum pressure drop of 5.0 psi at rated flow (unless otherwise noted or scheduled on the drawings). Valves with sizes up to and including 51 mm (2 inches) shall be of ’screwed‘ configuration and 63.5mm (2-1/2 inches) and larger valves shall be of ’flanged‘ configuration. All control valves, including terminal unit valves, less than 51 mm (2 inches) shall be globe valves. Electrically-actuated control valves shall include spring return type actuators sized for tight shut-off against system pressures (as specified above) and, when specified, shall be furnished with integral switches for indication of valve position (open-closed). Pneumatic actuators for valves, when utilized, shall be sized for tight shut-off against system pressures (as specified above).

- Control valve actuators: actuators for VAV terminal unit heating coils shall be ’drive-open, drive-closed‘ type. All actuators shall have inherent current limiting motor protection. Valve actuators shall be 24V AC/DC, electronic type, modulating or two-position as required for the correct operating sequence. Actuators on valves needing 'fail-safe' operation shall have spring return to normal position. Modulating valves shall be positive positioning in response to the signal. All valve actuators shall be UL listed.

- Sensor location identification: to identify for selected area, a temperature and relative humidity study needs to be performed to determine the most fluctuating, hottest and the coldest locations. The difference between minimum and maximum temperature for each monitoring point during the study shall be reviewed and the point with maximum difference shall be concluded to be the most fluctuating point. After identifying the most fluctuating location, the BMS sensor shall be placed on the nearest feasible surface in the grid for routine monitoring. Sensors shall be positioned so as to be minimally affected by transient events such as door opening.

4.4 DDC PANEL

- Control power transformers: step-down transformers will be provided for all DDC controllers and devices as required. Transformers shall be sized for the load, but shall be sized for 50 watts minimum. Transformers shall be UL listed Class 2 type, for 120 VAC/24 VAC operation.

- All the panels need to be powder coated with separate earthing probes on the panel and need to be IP66 grade or equivalent. The cable entry to the panel need to be bottom mounted

- The panel needs to have fuse boxes for AO/AI and isolation for AC and DC supply.

- Following power loss and subsequent power restoration AHU, the blower motor should restart based on the last state before loss of power without human intervention for critical AHUs. These can be restarted manually based on operator inputs (when operator initiates power recovery sequence) for other AHUs.

- Line voltage protection: all DDC system control panels that are powered by 120 VAC circuits shall be provided with surge protection. This protection is in addition to any internal protection provided by the manufacturer. The protection shall meet UL, ULC 1449, IEEE C62.41B. A grounding conductor (minimum 12 AWG) shall be brought to each control panel.

- The supervisory system shall be capable of synchronizing date and time with network devices like DDC, client station, etc.

- Wiring, earthing and bonding

Earthing and bonding standards given below are to be used for installation of BMS in a facility

- IEEE C62.41 - Surge Voltages in Low Voltage AC Power Circuits.
- IEEE 142 - Recommended Practice for Grounding of Industrial and Commercial Power Systems.

4.5 SERVER AND DATABASE

- Server hardware shall be sufficient to fulfill the required specification of the BMS software as specified by BMS OEM. Virtual servers are preferred over physical servers considering various benefits.

- The OEM shall provide system software based on server/thin-client architecture, designed around the open standards of web technology.

- The server shall communicate using Ethernet and TCP. Server shall be accessed using a web browser over owner intranet and remotely over the Internet.

- Antivirus must be installed and shall be compatible with BMS software and preferably shall be the same that is used throughout the organization. This has to be confirmed with the BMS OEM at the time of software procurement.

- Windows auto updates shall be disabled. The BMS software OEM shall periodically provide list of latest windows updates which are tested and approved for the software.

- The server software shall be developed and tested by the manufacturer of the system stand-alone controllers and network controllers/routers.

- When power is restored and the server PC is turned on again, the SCADA application should restart without human intervention.

- Database: the BAS server software shall utilize a Java Supported Database Connectivity (JDBC) compatible database such as:
    - MS SQL,
    - Oracle,
    - IBM DB2.

- All the data stamped in database need to be timestamped and non-editable.

Note: proprietary databases are NOT acceptable.

5 Application Software: Thin Client Web Browser Gui

The intent of the thin-client architecture is to provide the operator(s) complete access to the BAS system via a web browser. The thin-client web browser Graphical User Interface (GUI) shall be browser and operating system agnostic, i.e., it will support Microsoft, Firefox and Chrome browsers (current released versions), and Windows as well as non-Windows operating systems.

The web browser GUI shall provide a completely interactive user interface, shall offer, and be configured with the following features as a minimum:

1. Trending.
2. Scheduling.
3. Electrical demand limiting.
4. Duty cycling.
5. Downloading memory to field devices.
6. Real time 'live' graphic programs.
7. Tree navigation.
8. Parameter change of properties.
9. Set point adjustments.
10. Alarm and event information.
11. Configuration of operators.
12. Execution of global commands.
13. Add, delete, and modify graphics and displayed data.

Electronic software components: all software shall be the most current version. All software components of the system software shall be provided and installed as part of this project. Software components shall include:

1. Server software, database, and web browser graphical user interface.
2. System configuration utilities for future modifications to the system and controllers.
3. Graphical programming tools.
4. DDC software.
5. Application software.
6. Any required third party software.
7. If licensing credits are required, provide a minimum of 10% additional license tags to as built control system requires.

5.1 COMMUNICATION STANDARDS AND NETWORK STANDARDS

- The network shall be capable of communicating in Arcnet, Ethernet, RS 485, another protocol, and/or any combination of these protocols.

- Building automation controls network (BACnet): BACnet is a network protocol specifically used for multiple devices to communicate across building automation systems by system users and building system manufacturers. BACnet is developed by ASHRAE to communicate all the devices with common standard protocol. BACnet is a preferred network for building automation system, which is an open protocol that can be integrated with any make of SCADA software which supports BACnet, thereby eliminating the need of proprietary dependency.

Modbus: Modbus is a network protocol best used for industrial automation systems specifically for connecting electronic equipment. Although Modbus is best for industrial applications, its simplicity allows it to be a useful tool for building automation as well.

LonWorks: LonWorks is a communication network protocol useful for building automation applications designed on a low bandwidth, for networking devices through power lines, fiber optics, and other media.

IP Network

All devices that connect to the WAN shall be capable of operating at 10/100/1000 megabits per second and above.

Field Bus (if required)

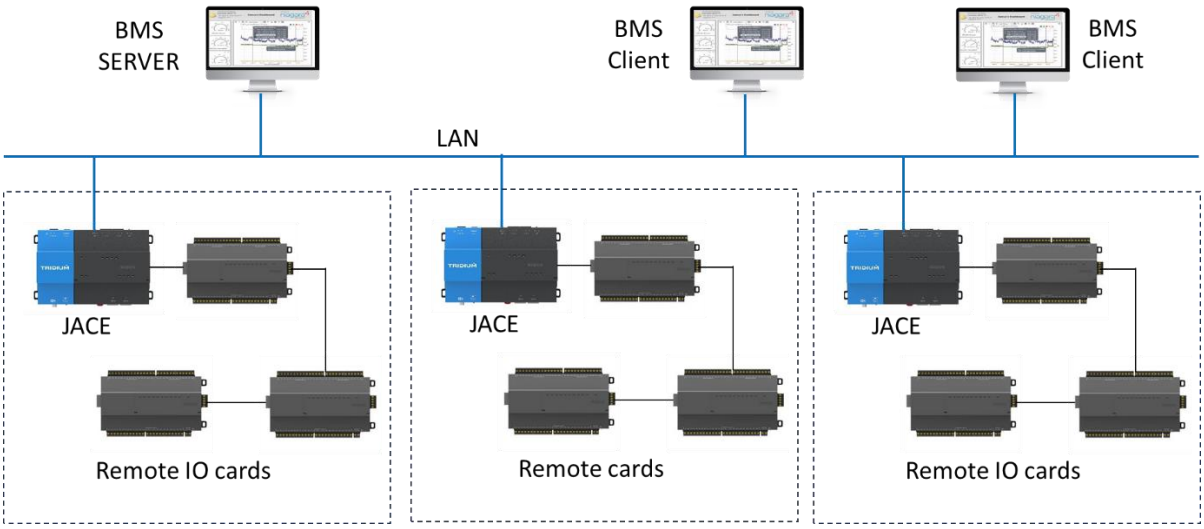
1. The field busses shall be FTT-10A operating at 78 kilobits per second.

The control system shall include the interfaces necessary to facilitate operation and configuration. For example:

- An RS-232 communications port shall be provided.
- A modem communications port shall be provided.
- A high-speed configuration/monitoring connection shall be provided.

The wiring of components shall use a bus or daisy chain concept with no tees, stubs or free topology.
The wiring type and length limitations shall conform to Echelon's Junction Box and Wiring Guideline for Twisted Pair LonWorks Networks.
Each field bus shall have a termination device at both ends of each segment.

Typical BACnet architecture is as shown below :



5.2 POWER FAILURE/RECOVERY

- The BMS shall fail into a safe state upon a power failure. Alarms shall be generated to indicate a power failure occurred.

- In the event of a power loss, 100% power back up UPS should be provided to the server for at least ten minutes so that the operating system and SCADA system can continue operating. This should allow the power failure event to be recovered in the event history, and provide the opportunity for an orderly shutdown of the server and software.

- The controller shall be provided with replaceable battery for support in the event of power failure, and the controller will need to have local memory to save the data in the event of power failure.

5.3 TIME SYNCHRONIZATION

- The system should be capable of time synchronization. All the servers, controllers and database servers, room display units and field devices shall be synchronized to Network Time Protocol (NTP) servers.

- The link for synchronization can also be updated from individual company's own NTP server or from http://time.nplindia.org/. .

5.4 ALARMS AND WARNINGS

- System should provide warnings and alarms for power failure to AHU panel, BMS panel, BMS server, and any other front-end hardware used.

- Alarm time/date stamp: all events shall be generated at the DDC control module level and comprise the time/date stamp using the stand-alone control module time and date.

- Alarm configuration: operators shall be able to define the type of alarm generated per object. A 'network' view of the navigation tree shall expose all objects and their respective alarm configurations. Configuration shall include assignment of alarm, type of acknowledgement and notification for return to normal or fault status.

- The equipment shall have the following critical alarms and warnings :
    1. Communication failures
    2. Hard disk failures
    3. Login to BMS.

5.5 ALARM MANAGEMENT :

- For BMS the complete alarm list and differentiate between critical and non-critical alarms shall be available along with documentation of how 'critical and non-critical' criteria were determined.

- Alarm View: each alarm shall display an alarms category (using a different icon for each alarm category), date/time of occurrence, current status, alarm report and a bold URL link to the associated graphic for the selected system, area or equipment. The URL link shall indicate the system location, address and other pertinent information. An operator shall easily be able to sort events, edit event templates and categories, acknowledge, or force a return to normal in the Events View as specified in this section.

- Alarm Categories: the operator shall be able to create, edit or delete alarm categories such as HVAC, Maintenance, Fire, or Generator. An icon shall be associated with each alarm category, enabling the operator to easily sort through multiple events displayed.

- Alarm Templates: alarm template shall define different types of alarms and their associated properties. As a minimum, properties shall include a reference name, detailed description, severity of alarm, acknowledgement requirements, high/low limit, and out of range information.

- Scheduled reports shall be configured which can automatically generate reports indicating the alarm condition starts, when the alarm is ended, what was the reason for alarm, and the duration of alarm.

- Alarm Summary Counter: the view of Alarm in the graphic pane shall provide a numeric counter, indicating how many alarms are active (in alarm), which require acknowledgement, and total number of alarms in the BAS Server database.

- The BMS shall be capable of receiving hardwired (24VAC/DC to 230VAC contact closure) alarm signals from other systems.

- The alarm system shall include configurable remote notification capabilities. Notification may be set up by group or individual alarms, and should take place via electronic mail or pager.

- The system should provide the interlock and/or alarm for safety of process, product, personnel, and equipment (as applicable).

- The system shall not allow setting of parameters outside the specified range.

- Operator shall able to acknowledge and add comments to alarm. And there should be audio visual indication for alarms and warnings.

- The alarms shall be configured to differentiate between criticality of alarms based on priority or severity.

- The BMS shall include an Alarm Log, and shall be capable of recording when an alarm condition starts, when the alarm is acknowledged, by whom the alarm is acknowledged, and when the alarm condition is removed.

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- The BMS shall have the capability to record when an alarm condition starts, when, who acknowledges it, why (message by user), and when the alarm condition clears.

- There shall be audio visual alarm at alert limit for parameter (as applicable). There shall be hysteresis for the same to avoid frequent alarms on set value. This alarm will not log into alarm report; this is only for engineering alert and warning.

- There shall be audio visual alarm on low and high limit of parameter for room temperature, RH and DP (as applicable). There shall be some delay, preferably 180 seconds, (settable through SCADA) for Room DP; the central hooter shall mute on acknowledge of alarm and shall snooze at every 3 minutes if parameter is not healthy. There shall be two dedicated separate hooter output, one is for room parameter (production area), and other for AHU control and room parameter (service floor).

- Beacon shall glow green when room condition is healthy, and there shall be no audio alarm.

- Beacon shall glow Amber), and buzzer on beacon lamp as well as common hooter will sound, when there is alert limit for (Relative humidity, Temperature, Differential pressure is out of limit after three minute),VFD of AHU of particular room is fail / Trip, VFD Trip alarm will also be displayed on BMS system, buzzer on beacon lamp as well as common hooter in area shall be mute by acknowledging respective alarm from BMS and same shall be snoozed after every three minute, if parameter is not healthy.

- Beacon will glow RED in color and with no buzzer when AHU is off. Beacon will glow RED in color with buzzer ON as well as common hooter will sound, when:

- When AHU is trip, buzzer on beacon lamp cannot be mute till AHU is ON

5.6 OPERATIONAL REVIEW OF DAILY REPORTS AND TRENDS

- The trends, reports and alarms of individual area shall be evaluated on daily basis, and subsequently product impact assessment shall be done for any excursion, based on the area usage and process in area.

- The alarm report shall be viewed on daily basis along with the events.

5.7 APPROACH FOR SETTING LIMITS AND SET POINTS

- The lower and upper limits of a given parameter shall be settable as per user product and process requirements.

- System shall be capable of generating alarms for low and high limits. Alarm limits shall be settable by authorized user level.

- The BMS shall have electronic signature capability to record any changes such as set point change, manual override for actuators, etc. Both single as well as double signatures shall be included depending upon the change. The electronic signature will be highlighted in the events report along with the reasons.

- Changes to alarm limits shall be included in the audit trail.

5.8 DATA SECURITY AND AUDIT TRAIL

- Controls provided with data collection systems intended for use in the manufacture of pharmaceutical products shall be required to meet 21 CFR Part 11 compliance. and the supplier should stipulate the methods by which the relevant criteria are met.

- The system shall enforce unique combination assignment of user identification and password.

- The system shall not give the ability to an administrator to look up other users passwords.

- The system must be capable of automatically forcing users to change passwords on a scheduled basis once the administrator configures the duration before change time limit. The system should prevent reuse of the password.

- All historical files including alarm history, set point changes, trends, etc. must have access under password protection.

- The system must have the capability to generate electronic copies of all data files as well as the ability to create printed copies of these files.

- The system must have the ability to automatically timestamp audit trail entries, and this ability must be secure from human intervention. The audit trail will include tracking of additions and deletions to the system files.

- The system must have a method for assigning user access rights commensurate with their need for access.

- The system shall have a method for intrusion detection.

- System shall monitor failed login attempts. If an incorrect password is entered for a known username, then the system shall allow three attempts for logging in. After the third failed attempt, the system shall lock out that user account and notify the administrator.

- The system shall automatically log off users if no activity is detected at the logged in terminal for a preset (adjustable) inactivity time period..

- The system must be validated to ensure accuracy, reliability, and the ability to detect altered records. Consequently, the design and development testing processes must be fully documented.

5.9 AUDIT TRAIL

- The workstation software shall automatically log and timestamp every operation that a user performs at a workstation, from logging on and off a workstation to changing a point value, modifying a program, enabling/disabling an object, viewing a graphic display, running a report, modifying a schedule, etc.

- It shall be possible to view a history of alarms, user actions, and commands for any system object individually, or at least the last 5000 records of all events for the entire system from a workstation.

- It shall be possible to save custom filtered views of event information that are viewable and configurable in a workstation.

- Audit trails must be secure and not alterable in any manner that would make the alteration of a record undetectable.

- The system shall provide an audit trail for all set point, alarm, trend changes and code changes. It shall also include audit trail of user-defined programs and associated changes. This audit trail shall include user identification with full name linked to the user identification/password gaining access, old value replaced, new value implemented, and date and time.

- The audit trail must be protected to the highest level of access allowed by the system. Audit file backup, archiving and restoration must be included in system instructions.

- The audit trail shall be secured so that no users can change or delete its entries.

- The audit trail must be printable.

- The system shall ensure that the audit trail cannot be disabled.

5.10 ELECTRONIC RECORD AND ELECTRONIC SIGNATURE

- Electronic record shall be available only in non-editable format, reproducible on paper in a readable form.

- The system shall generate audit trail of user actions (create, modify and delete) that includes date and time stamp of the user action, user identification, action taken including old and new values and reason for change.

- Audit trail shall contain who, when, what (old and new values for parameter changes) and why (wherever applicable).

- The system should ask for the password to logged user for any critical parameter/setting change, through popup window (as applicable).

5.11 USER MANAGEMENT AND ACCESS LEVELS

- Access to all Input/output values and system status bits /indication shall be provided through a data-communication link.

- System should have facility for (User ID/Password, Card Reader, Biometric (Fingerprint, eye scan, voice recognition, etc.) to provides security for data and operator access.

- The BMS shall have the capability to configure the number of levels of access and the privileges that each access level has.

- Minimum required levels shall be:
    - View Only
    - Operator
    - Engineer
    - Administrator

- The BMS shall have the capability to configure web access; privileges should be similar to operator level.

- Roles shall reflect the actual roles of different types of operators. Each role shall comprise a set of easily understood English language privileges. Roles shall be defined in terms of View, Edit and Function Privileges.
    - A. View privileges shall comprise navigation, network, configuration trees, operators, roles and privileges, alarm/event template and reporting action.
    - oEdit privileges shall comprise setpoint, tuning and logic, manual override, and point assignment parameters.
    - Function privileges shall comprise alarm/event acknowledgement, control module memory download, upload, schedules, schedule groups, manual commands, and print and alarm/event maintenance.
- User accounts shall be uniquely identified with at least two identification components (for example, user ID and password, user ID and security token and passcode).
- Passwords should be minimum six (6) characters in length and it should be settable with authorized/admin login. Passwords shall meet 'complex password' requirements.
- System shall enforce changing of password upon password expiry after 180 days, and it should be settable with authorized/admin login.
- System shall enforce idle session time-out after 600 seconds (10 minutes). It should be settable with authorized/admin login.
- The password shall be in an encrypted form, both while use and when stored in the system (e.g. **********). No one should be able to view the password.
- System shall enforce user to change his/her password after initial assignment or password reset by administrator.
- The system shall permit only System Administrators to update system clocks used for time-stamping security change audit trails or electronic record audit trails.
- The system shall lock the account after predefined number of unsuccessful login attempts. It should be settable with authorized/admin login.
- The system should log the unauthorized access attempts.

- System administrator shall be able to unlock users that are locked.

- The system shall generate an audit trail of security changes including changes to users' assigned privileges, account creation, lock and unlock activities, password reset activities, etc. At the minimum, the journal shall record the details of security changes (before and after values), date, time, and user (or system process) that performed the change.

- The user must be able to change their own password.

- System administrator shall be able to create a new user.

- System administrator shall be able to delete, deactivate and/or disable a user.

- The system shall permit only System Administrators to update time zone used for time-stamping security change audit trails or electronic record audit trails.

5.12 HARDCOPY/ELECTRONIC DATA COLLECTION REQUIREMENTS

- The hardcopy shall be meaningful, human readable in printed form, from electronically stored data, if required by user. Electronic data shall be collected and stored in tapes, microfilms, compact disc, DVD, digital and other suitable media, designed to assure that backup data are exact and complete, and that it is secure from alteration, inadvertent erasure, or loss.

- The BMS shall have the capability to configure required parameter for data collection, from minimum frequency of 1 second up to any reasonable duration, as set by the competent authority.

5.13 COMPLIANCE WITH 21CFR PART 11

- A detailed white paper on meeting each compliance requirements of 21CFR Part 11 shall be given by supplier.

- System administration users shall have named accounts.

- All compliance requirements shall be verified at site during qualification.

- The electronic signature are required to be filled in case of changes made in the system both single and double type signatures / re-authentication to be included depending upon the type of change.

5.14 DATA RETENTION TIME ON THE SYSTEM

- The system should periodically copy the events from the event files, and place such data in online extended event files for queries and reporting. When the latter becomes full, it should be copied into archive directory, and alarms should be generated to alert the operator to save the archive file to backup storage.

- The contents of the backup storage shall be verified automatically when the backup is complete. The status of the backup should be logged in the event summary and the operator should be given an alert message.

5.15 DATA STORAGE AND RETENTION

- The system shall able to store large amount of historical process and system event data, sometimes running into years. The system shall ensure that values cannot be altered once entered into data storage.

- The system should provide the facility to store the process data on the server or another fileserver on the network. This stored data shall be available at all times to the authorized operator for various reports and trends. The stored data should consist of process, system, and operator events including alarms.

- The disc space should be sized for a minimum of 1 million events online. This data should be backed up on tape for future requirement. Facility shall be prepared to run backup tapes for reports and events

5.16 INTERFACE

User interface for HVAC engineer/operator and production area supervisor / operator .

- The control platform system shall include interfaces with facility management staff and GMP area staff that ensure easy, safe, and reliable operation.

- An operator-interface station shall be provided and mounted near the HVAC equipment area (service floor). This station shall provide the necessary switches, indicators, and devices to operate the HVAC equipment.

- Similar user interface (local display units and digital display units) shall be provided in GMP areas for GMP area staff to monitor the environment conditions as per the requirements.

- Suitable concealed in-wall or pendant mounted local display units for monitoring room parameter, AHU status and alarm display shall be provided in area

- For indicating status of AHU and critical alarms so as to alert the concerned operating personnel, a set of multi-colored indicating lamps of appropriate intensity shall be provided in the critical areas. These should be visible to the GMP operator during his normal working posture. Audible hooter is also desirable for AHU TRIP alarm condition.

5.17 LANGUAGE REQUIREMENT

English language should be used for all information and display.
In order to take care of good interface with other equipment, the BMS shall be designed to seamlessly connect devices throughout the building regardless of subsystem type; hence, variable frequency drives, low voltage lighting systems, electrical circuit breakers, and power metering, etc., should easily coexist on the BMS network.

5.18 ENVIRONMENT

Following are the details of the physical environment in which the system will be operated.

- For room sensors: pharmaceutical clean rooms containing fine product dust along with air being circulated; temperature and humidity in the surrounding area as per the product requirements; typical pharmaceutical environment containing sanitization gases (formaldehyde vapors, etc.).

- Room sensors flush mounted to the surface (concealed in walls or modular partitions), tamperproof, stainless steel cleanable enclosures, with good IP protection against fine dust, water, and detergent sprays, etc.

- For field devices and sensors, service area consisting of all HVAC equipment, utility piping, etc. Area is forced ventilated for ambient temperature and humidity.

- Field devices that are tamperproof, weather proof, and cleanable enclosures having IP protection against dust.

- DDC panels mounted and free standing on floors or walls, or on fabricated supports. Immediate environment is forced ventilated for ambient temperature, and humidity covering all the HVAC and other equipment for pharmaceutical facility. Minor vibration, presence of dust particles, and water dripping are possible.

- For server PC and others, ventilated room in service area are isolated from other equipments. Temperature and humidity are controlled within desired limits using standalone industrial AC unit. In case of virtual server, it shall be located in Data Center which has controlled conditions and necessary protections.

5.19 INSTALLATION REQUIREMENT

Installation Practices for Wiring

- All controllers are to be mounted vertically and per the manufacturer's installation documentation.
- The 230V AC power wiring to each Ethernet or remote site controller shall be a dedicated run, with a separate breaker. Each run will include separate hot, neutral and ground wires. The ground wire will terminate at the breaker panel ground. This circuit will not feed any other circuit or device.
- A true earth ground must be available in the building. A corroded or galvanized pipe, or structural steel must not be used.
- Wires are to be attached to the building proper at regular intervals such that wiring does not droop. Wires are not to be affixed to or supported by pipes, conduit, etc.
- Conduit in finished areas will be concealed in ceiling cavity spaces, plenums, furred spaces and wall construction. As an exception, metallic surface raceway may be used in finished areas on masonry walls. All surface raceway in finished areas must be color matched to the existing finish within the limitations of standard manufactured colors.
- Conduit, in non-finished areas where possible, will be concealed in ceiling cavity spaces, plenums, furred spaces, and wall construction. Exposed conduit will run parallel to or at right angles to the building structure.
- Wires are to be kept a minimum of 76.2 mm (three (3) inches) from hot water, steam, or condensate piping.
- Where sensor wires leave the conduit system, they are to be protected by a plastic insert.
- Wire will not be allowed to run across telephone equipment areas.

Installation Practices for Field Devices

- Well-mounted sensors will include thermal conducting compound within the well to insure good heat transfer to the sensor.
- Actuators will be firmly mounted to give positive movement and linkage will be adjusted to give smooth continuous movement throughout 100 percent of the stroke.

- Relay outputs will include transient suppression across all coils. Suppression devices shall limit transients to 150% of the rated coil voltage.

- Water line mounted sensors shall be removable without shutting down the system in which they are installed.

- For duct static pressure sensors, the high pressure port shall be connected to a metal static pressure probe inserted into the duct pointing upstream. The low pressure port shall be left open to the plenum area at the point that the high pressure port is tapped into the ductwork.

- For building static pressure sensors, the high pressure port shall be inserted into the space via a metal tube. The low-pressure port shall be piped to the outside of the building.

Enclosures

- For all I/O requiring field interface devices, these devices will be mounted in a field interface panel (FIP), where practicable. The contractor shall provide an enclosure which protects the device(s) from dust, moisture, conceals integral wiring, and moving parts.

- FIPs shall contain power supplies for sensors, interface relays and contactors, and safety circuits.

- The FIP enclosure shall be of steel construction with baked enamel finish, NEMA 1 rated with a hinged door and keyed lock. The enclosure will be sized for twenty percent spare mounting space. All locks will be keyed identically.

- All wiring to and from the FIP will be to screw type terminals. Analog or communications wiring may use the FIP as a raceway without terminating. The use of wire nuts within the FIP is prohibited.

- All outside mounted enclosures shall meet the NEMA-4 rating F. The wiring within all enclosures shall be run in plastic track. Wiring within controllers shall be wrapped and secured.

Identification

- All control wires shall be identified with labeling tape or sleeves using words, letters, or numbers that can be exactly cross-referenced with as-built drawings.

- All field enclosures, other than controllers, shall be identified with a Bakelite nameplate. The lettering shall be in white against a black or blue background.

- Junction box covers will be marked to indicate that they are a part of the BAS system.

- All I/O field devices (except space sensors) that are not mounted within FIPs shall be identified with name plates.

- All I/O field devices inside FIPs shall be labeled.

6 Documentation

- Installation, operation, and maintenance instruction documentation for the system shall be developed to a level that is comprehensible to a person who has attended a high school and industrial technician course.

- The supplier shall use the formats described in the GAMP Supplier Guide, Current Version, to produce the documentation. The supplier shall provide the documentation for preliminary review. The supplier shall provide documentation reflecting “as-built” condition with final delivery.

- The suppliers shall provide the following documents upon completion of installation of :
    - As-built control drawings for all equipment.
    - As-built network communications diagram.
    - General description and specifications for all components.
    - Completed performance verification sheets.
    - Completed controller checkout/calibration sheets.

7 Incidence Management

All post go-live malfunctions shall be logged in the incidence log. The details of issues shall be documented. These malfunctions or issues shall be categorized as:

- Software issues - issues observed in software.
- Training issues - issues observed due to inadequate training.
- Procedural issues - issues observed due to deficient procedure.Other issues observed due to reasons like LAN, server, human error, etc.

Trends should be prepared and reviewed as per frequency mentioned in system description, and trending activity should be performed at least once a year or as per frequency defined, whichever is earlier or deemed necessary.

8 Periodic Review

It is recommended that periodic review of the validation be done every three years, or earlier, as required based on the trend of issue log. The issues or the problems identified from the last periodic review or the installation till date shall be reviewed. Any recurrent, potential problems and/or issues shall be identified in the periodic review.

The corrective actions taken and/or to be taken to rectify or minimize the problems shall be documented in the periodic review report. Recommendation for revalidation of the system shall be drawn based on periodic review of the software. It shall aim at ensuring that the system is continuing to perform as intended. The extent of validation activities and test to be carried out shall be based on outcome/s of periodic review, criticality of the system, and risk involved.

Guidance Document for Design, Installation and Testing of Purified Water System

1 Purpose

To provide general procedure and guidelines for designing of water system for pharmaceutical use, i.e., purified water, water for injection and pure steam.

2 Scope

The scope of this document is applicable for designing of new purified water system, water for injection plant, its storage and distribution, and PSG system.

3 Responsibility

- All employees/designated persons and personnel involved in GMP functions, e.g., manufacturing, quality, engineering, safety, etc., are responsible for following guideline documents.
- Site QA head or his designee, and Engineering head shall be responsible for review and following approval procedure as per guideline documents, and take further action(s) as required.

4 Introduction

Water purification is the process of removing undesirable chemicals, biological contaminants, suspended solids and, gases from water. The goal is to produce water fit for specific purposes. Most water is purified and disinfected for human consumption (drinking water), but water purification may also be carried out for a variety of other purposes, including medical, pharmaceutical, chemical, and industrial applications. The method used include processes such as aeration, flocculation, tube settler, mixed bed filtration, chlorination, chlorine dioxide disinfection, membrane filtration, electro-deionization, etc.

5 Regulated Water Qualities

- Non-potable water
- Potable water (drinking)
- Purified water (PW)
- Water for Injection (WFI)

6 Water for Pharmaceutical Use

A crucial starting material for any pharmaceutical product manufacturing.

- **Purified water (PW):**

  Oral liquid dosage forms.

  Solid dosage forms.

  Bulk API.

  Laboratory activities.

  Feed water to WFI and PS generation.

  Cleaning of the above and initial rinses for the below.

- **Water for Injection (WFI):**

  For injectable.

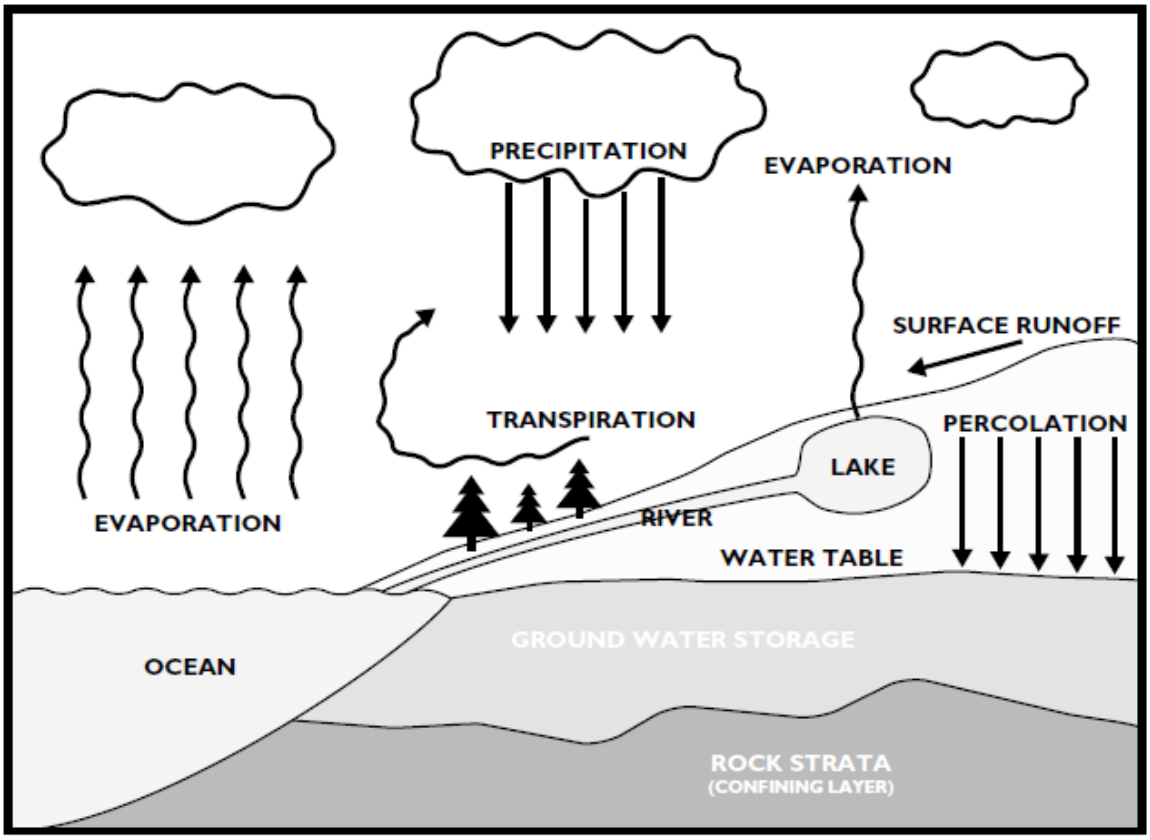
  Sterile bulk API.

  Final cleaning rinses for the above two applications.

- **Water quality and analytical methods:**
  - European Pharmacopeia EP
  - US Pharmacopeia USP
  - Japanese Pharmacopeia JP
  - EMA (European Medicines Agency) - Guidance on Quality of Water for Pharmaceutical Use.
  - FDA (US food and Drug Administration) - Guide to Inspection of High Purity Water Systems - 21 CFR 210/211, 21 CFR Part 11, 21 CFR 177.
  - PIC/S (Pharmaceutical Inspection Convention) - Guide to Good Manufacturing Practice for Medicinal Products.
  - ISPE (International Society for Pharmaceutical Engineering) - Baseline Pharmaceutical Engineering Guide Volume-4, Water and Steam Systems.
  - Potable or Drinking Water (IS 10500:2012), or the specification of WHO.

8 Water - The Problem of Purity

In its pure state, water is one of the most aggressive solvents known, usually called the “universal solvent”. Water, to a certain degree, will dissolve virtually everything to which it is exposed. Pure water has a very high energy state and, like everything else in nature, seems to achieve energy equilibrium with its surroundings. It will dissolve the quantity of material available until the solution reaches saturation, the point at which no higher level of solids can be dissolved. Contaminants found in water include atmospheric gases, minerals, organic materials (some naturally occurring, others man-made), plus any materials used to transport or store water. The hydrologic cycle (Figure 1) illustrates the process of contamination and natural purification.



Natural Contamination and Purification :

Water evaporates from surface supplies and transpires from vegetation directly into the atmosphere. The evaporated water then condenses in the cooler air on nuclei such as dust particles, and eventually returns to the earth’s surface as rain, snow, sleet, or other precipitation. It dissolves gases such as carbon dioxide, oxygen, and natural and industrial emissions such as nitric and sulfuric oxides, as well as carbon monoxide. Typical rain water has a pH of 5 to 6. The result of contact with higher levels of these dissolved gases is usually a mildly acidic condition – what is today called “acid” rain – that may have a pH as low as 4.0. As the precipitation nears the ground, it picks up many additional contaminants – e.g., airborne particulates, spores, bacteria, and emissions from countless other sources.

Most precipitation falls into the ocean, and some evaporates before reaching the earth's surface. The precipitation that reaches land replenishes groundwater aquifers and surface water supplies.
The water that percolates down through the porous upper crust of the earth is substantially "filtered" by that process. Most of the particulate matter is removed, much of the organic contamination is consumed by bacterial activity in the soil, and a relatively clean, mildly acidic solution results. This acidic condition allows the water to dissolve many minerals, especially limestone, which contributes calcium. Other geologic formations contribute minerals, such as magnesium, iron, sulphates, and chlorides. The addition of these minerals usually raises groundwater pH to a range of 7 to 8.5.

This mineral-bearing water is stored in natural underground formations called aquifers. These are the source of the well water used by homes, industries, and municipalities. Surface waters such as rivers, lakes and reservoirs typically contain less mineral contamination because that water did not pass through the earth's soil. Surface waters will, however, hold higher levels of organics and undissolved particles because the water has contacted vegetation and caused runoff to pick up surface debris.

Bacterial Contamination :

One difficulty of water purity is bacterial contamination and control of bacterial growth.
Water is essential for all life. It is a necessary medium for bacterial growth because it carries nutrients. It is an essential component of living cells. Its thermal stability provides a controlled environment.
Water will support bacterial growth with even the minutest nutrient sources available.

9 Identifying Impurities

The impact of the various impurities generated during the hydrologic cycle and/or bacterial colonization depends upon the water user's particular requirements. In order to assess the need for treatment and the appropriate technology, the specific contaminants must be identified and measured.

10 General Qualitative Identification

Qualitative identification is usually used to describe the visible or aesthetic characteristics of water. Among others, these include :

- Turbidity (clarity)
- Taste
- Color
- Odor

Turbidity

Turbidity consists of suspended material in water, causing a cloudy appearance. This cloudy appearance is caused by the scattering and absorption of light by these particles. The suspended matter may be inorganic or organic. Generally, the small size of the particles prevents rapid settling of the material and the water must be treated to reduce its turbidity.
Correlation of turbidity with the concentration of particles present is difficult since the light-scattering properties vary among materials, and are not necessarily proportional to their concentration. Turbidity can be measured by different optical systems. Such measurements simply show the relative resistance to light transmittance, not an absolute level of contamination.

A candle turbidimeter is a very basic visual method used to measure highly turbid water. Its results are expressed in Jackson Turbidity Units (JTU). A nephelometer is more useful in low turbidity water, with results expressed in Nephelometric Turbidity Units (NTU) or Formazin Turbidity Units (FTU). JTU and NTU are not equivalent.

Suspended matter can also be expressed quantitatively in parts per million (ppm) by weight or milligrams per liter (mg/L). This is accomplished by gravimetric analysis, typically filtering the sample through a 0.45-micron membrane disc, then drying and weighing the residue.

The Silt Density Index (SDI) provides a relative value of suspended matter. The measured values reflect the rate at which a 0.45-micron filter will plug with particulate material in the source water. The SDI test is commonly used to correlate the level of suspended solids in feedwater that tends to foul reverse osmosis systems.

Taste

The taste sense is moderately accurate and able to detect concentrations from a few tenths to several hundred ppm. However, taste often cannot identify particular contaminants. A bad taste may be an indication of harmful contamination in drinking water, but certainly cannot be relied on to detect all harmful contaminants.

Color

Color is contributed primarily by organic material, although some metal ions may also tint water. While not typically a health concern, color does indicate a certain level of impurities, and can be an aesthetic concern. 'True color' refers to the color of a sample with its turbidity removed. Turbidity contributes to 'apparent' color. Color can be measured by visual comparison of samples with calibrated glass ampules or known concentrations of colored solutions. Color can also be measured using a spectrophotometer.

Odor

The human nose is the most sensitive odor-detecting device available. It can detect odors in low concentrations down to parts per billion (ppb). Smell is useful because it provides an early indication of contamination which could be hazardous, or at least reduce the aesthetic quality of the water.

Further Analysis

Further analysis should focus on identification and quantification of specific contaminants responsible for the water quality. Such contaminants can be divided into two groups:

1. dissolved contaminants.
2. particulate matter.

Dissolved contaminants are mostly ionic atoms or a group of atoms carrying an electric charge. They are usually associated with water quality and health concerns.

Particulate matter – typically silt, sand, virus, bacteria, or color-causing particles – is not dissolved in water. Particulate matter is usually responsible for aesthetic characteristics such as color, or parameters such as turbidity, which affects water processes.

pH

The relative acidic or basic level of a solution is measured by the pH. The pH is a measure of hydrogen ion concentration in water, specifically the negative logarithm (log) of the hydrogen ion concentration.
The measurement of pH is on a scale of 0 to 14 (Figure 2), with a pH of 7.0 being neutral (i.e., neither acidic nor basic), and bearing equal numbers of hydroxyl (OH-) and hydrogen (H+) ions. A pH of less than 7.0 is acidic; a pH of more than 7.0 is basic.

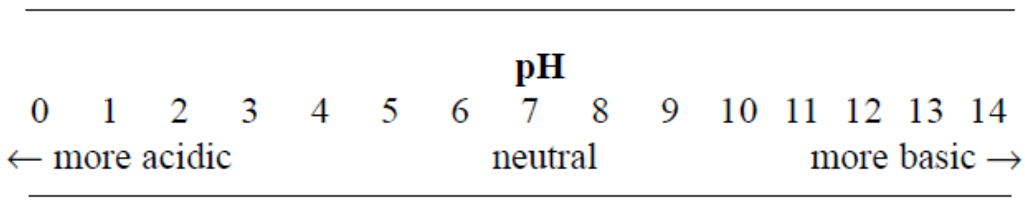


Figure 2 – pH Value

Since pH is expressed in log form, a pH of 6.0 is 10 times more acidic than a pH of 7.0, and a pH of 5.0 is 100 times more acidic than a pH of 7.0. The pH has an effect on many phases of water treatment such as coagulation, chlorination, and water softening. It also affects the scalingpotential of water sources. The pH level can be determined by various means such as color indicators, pH paper or pH meters. A pH meter is the most common and accurate means used to measure pH.

Total Solids

Total Solids (TS) is the sum of Total Dissolved Solids (TDS) and Total Suspended Solids (TSS). In water analysis, these quantities are determined gravimetrically by drying a sample and weighing the residue. In the field, TDS is commonly measured by a conductivity meter.

TDS		TSS	
Organic	Inorganic	Organic	Inorganic
humic acid	reactive silica (dissolved)	algae	silt
tannin	salt ions	fungi	rust
pyrogens		bacteria	floc
			clays

Conductivity/Resistivity

Ions conduct electricity. Because pure water contains few ions, it has a high resistance to electrical current. The measurement of water's electrical conductivity, or resistivity, can provide an assessment of total ionic concentration. Conductivity is described in microSiemens(μS)/cm and is measured by a conductivity meter and cell. Resistivity is described in megohm-cm, is the inverse of conductivity and is measured by a resistivity meter and cell.

Microbiological Contamination

Microbiological contamination can be classified as viable and nonviable. Viable organisms are those that have the ability to reproduce and proliferate. Nonviable organisms cannot reproduce or multiply.

❖ **Bacterial Contamination**

Bacterial contamination is quantified as Colony Forming Units (CFU), a measure of the total viable bacterial population. CFUs are typically determined by incubating a sample on a nutritional medium and counting the number of bacterial colonies that grow. Each colony is assumed to have grown from a single bacterial cell. This is called a Standard Plate Count (SPC) and is the most common method. Other less common methods of enumerating microbial contamination include the Most Probable Number (MPN), which is a statistical probability of the bacterial population in a small sample, and the direct dount, which is an actual count of cells observed through a microscope.

❖ **Pyrogenic Contamination**

Pyrogens are substances that can induce a fever in a warm-blooded animal. The most common pyrogenic substance is the bacterial endotoxin. These endotoxins are lipopolysaccharide compounds from the cell walls of gram-negative bacteria. They can be pyrogenic whether they are part of intact viable cells or simply fragments from ruptured cells. They are more stable than bacterial cells and are not destroyed by all conditions (such as autoclaving) that kill bacteria. Their molecular weight (MW) is generally accepted to be approximately 10,000. One molecular weight (MW) is approximately equal to one Dalton. However, in aqueous environments they tend to agglomerate to larger sizes. Pyrogens are quantified as Endotoxin Units per milliliter (EU/mL). The traditional method for pyrogen detection used live rabbits as the test organism. Today the most common method is the Limulus Amoebocyte Lysate (LAL) test. Endotoxins react with a purified extract of the blood of the horseshoe crab Limulus Polyphemus, and this reaction can be used to determine the endotoxin concentration.

There are several versions of the LAL test ranging from the semi-quantitative 'gel-clot method' to the fully-automated 'kinetic turbidmetric method' which is sensitive to 0.001 EU/mL. There is an endotoxin limit in the pharmaceutical industry for USP Water for Injection (WFI) of 0.25 EU/mL. The LAL test is relatively quick and inexpensive. The LAL test is used if there is a concern about endotoxins in the finished water, such as in pharmaceutical uses. However, due to the swift results and the relatively low cost of the LAL test, other industries with critical water quality needs are beginning to use it as a quick indicator of possible bacterial contamination or Total Organic Carbon (TOC).

❖ **Total Organic Carbon (TOC)**

TOC is a direct measure of the organic, oxidizable, carbon-based material in water. TOC is a vital measurement used in sophisticated water treatment systems, such as electronics grade, where any amount of contamination can adversely affect product quality and yield.

❖ **Biochemical Oxygen Demand (BOD)**

BOD is a measure of organic material contamination in water, specified in mg/L. BOD is the amount of dissolved oxygen required for the biochemical decomposition of organic compounds and the oxidation of certain inorganic materials (e.g., iron, sulfites).

❖ **Chemical Oxygen Demand (COD)**

COD is another measure of organic material contamination in water, specified in mg/L. COD is the amount of dissolved oxygen required to cause chemical oxidation of the organic material in water.
Both BOD and COD are key indicators of the environmental health of a surface water supply. They are commonly used in waste water treatment but rarely in general water treatment.

4 Specific Impurities

Many individual impurities can be quantified through water analysis techniques. Below is a discussion of most ionic individual contaminants.

Common Ions

A number of terms are used to express the level of mineral contamination in a water supply.

Units of Concentration

Unit	Abbreviation	Describes
milligrams per liter	mg/L	(weight per volume)
parts per million	ppm	(weight in weight)
parts per billion	ppb	(weight in weight)
parts per trillion	ppt	(weight in weight)
grains per gallon	gpg	(weight per volume)
milli-equivalents per liter	m eq/L	(weight per volume)

mg/L /17.1 = gpg
ppm /17.1 = gpg
gpg x 17.1 = ppm or mg/L
mg/L (expressed as $CaCO_3$) x 50 = m eq/L
ppm x 1000 = ppb
ppb x 1000 = ppt

❖ **Water Hardness**

The presence of calcium (Ca2+) and magnesium (Mg2+) ions in a water supply is commonly known as 'hardness.' It is usually expressed as grains per gallon (gpg). Hardness minerals exist to some degree in virtually every water supply.

The following table classifies the degree of hardness:

Hardness Level		Classification
mg/L	gpg	
0-17	<1	soft water
17-60	1-3.5	slightly hard water
60-120	3.5-7.0	moderately hard water
120-180	7.0-10.5	hard water
>180	>10.5	very hard water

The main problem associated with hardness is scale formation. Even levels as low as 5 to 8 mg/L (0.3 to 0.5 gpg) are too extreme for many uses. The source of hardness is calcium and magnesium bearing minerals dissolved in groundwater. 'Carbonate' and 'noncarbonate' hardness are terms used to describe the source of calcium and magnesium. 'Carbonate' hardness usually results from dolomitic limestone (calcium and magnesium carbonate), while 'noncarbonate' hardness generally comes from chloride and sulfate salts.

❖ **Iron**

Iron, which makes up 5% of the earth's crust, is a common water contaminant. It can be difficult to remove because it may change valence states, that is, change from the water-soluble ferrous state (Fe2+) to the insoluble ferric state (Fe3+). When oxygen or an oxidizing agent is introduced, ferrous iron becomes ferric which are insoluble and so precipitates, leading to a rusty (red-brown) appearance in water. This change can occur when deep well water is pumped into a distribution system where it adsorbs oxygen. Ferric iron can create havoc with valves, piping, water treatment equipment, and water-using devices. Certain bacteria can further complicate iron problems. Organisms such as Crenothrix, Sphaerotilus and Gallionella use iron as an energy source. These iron-reducing bacteria eventually form a rusty, gelatinous sludge that can plug a water pipe. When diagnosing an iron problem, it is very important to determine whether such bacteria are present.

❖ **Manganese**

Although manganese behaves like iron, much lower concentrations can cause problems in the water system. However, manganese does not occur as frequently as iron. Manganese forms a dark, almost black, precipitate.

❖ **Sulphate**

Sulphate (SO4^2-) is very common. When present at lower levels, sulphate salts create problems only for critical manufacturing processes. At higher levels, they are associated with a bitter taste and laxative effect. Many divalent metal-sulphate salts are virtually insoluble and precipitate at low concentrations.

❖ **Chloride**

Chloride (Cl-) salts are common water contaminants. The critical level of chloride depends on the intended use of the water. At high levels, chloride causes a salty or brackish taste and can interfere with certain water treatment methods. Chlorides also corrode the metals of water supply systems, including some stainless steels.

❖ **Alkalinity**

Alkalinity is a generic term used to describe carbonates (CO3^ 2-), bicarbonates (HCO3-) and hydroxides (OH-). When present with hardness or certain heavy metals, alkalinity contributes to scaling. The presence of alkalinity may also raise the pH.

❖ **Nitrate and Nitrite**

Although nitrate (NO3-) and nitrite (NO2-) salts may occur naturally, their presence in a water supply usually indicates man-made pollution. The most common sources of nitrate/nitrite contamination are animal wastes, primary or secondary sewage, industrial chemicals, and fertilizers. Even low nitrate levels are toxic to humans, especially infants, and contribute to the loss of young livestock on farms with nitrate-contaminated water supplies.

❖ **Chlorine**

Chlorine, because of its bactericidal qualities, is important in the treatment of most municipal water supplies. It is usually monitored as free chlorine (Cl2) in concentrations of 0.1 to 2.0 ppm. In solution, chlorine gas dissolves and reacts with water to form the hypochlorite anion (ClO-) and hypochlorous acid (HClO). The relative concentration of each ion is dependent upon pH. At a neutral pH of 7, essentially all chlorine exists as the hypochlorite anion which is the stronger oxidizing form. Below a pH of 7, hypochlorous acid is dominant, and has better disinfectant properties than the anion counterpart. Although chlorine's microbial action is generally required, chlorine and the compounds it forms may cause a disagreeable taste and odor. Chlorine also forms small amounts of Tri halogenated methane compounds (THMs), which are a recognized health hazard concern as carcinogenic materials. The organic materials with which the chlorine reacts are known as THM precursors.

❖ **Chloramines**

In some cases, chlorine is also present as chloramine (i.e., monochloramine, NH2Cl) as a result of free chlorine reacting with ammonia compounds. The ammonia is added to a water supply to stabilize the free chlorine. Chloramines are not as effective a microbial deterrent as chlorine, but provide longer-lasting residuals.

❖ **Chlorine Dioxide**

This material is often produced on-site primarily by large municipalities via the reaction between chlorine or sodium hypochlorite and sodium chlorite. A more costly source of chlorine dioxide is available as a stabilized sodium chlorite solution. Chlorine dioxide has been used for taste and odor control and as an efficient biocide. Chlorine dioxide can maintain a residual for extended periods of time in a distribution system, and does not form trihalomethanes (THMs) or chloramines if the stabilized sodium chlorite form is used. The possible toxicity of the chlorate and chlorite ions (reaction byproducts) may be a concern for potable water applications.

❖ **Silica**

Every water supply contains at least some silica (SiO_2). Silica occurs naturally at levels ranging from a few ppm to more than 200 ppm. It is one of the most prevalent elements in the world. Among the problems created by silica are scaling or glassing in boilers, stills, and cooling water systems, or deposits on turbine blades. Silica scale is difficult to remove. Silica chemistry is complex. An unusual characteristic of silica is its solubility. Unlike many scaling salts, silica is more soluble at higher pH ranges. Silica is usually encountered in two forms: ionic and colloidal (reactive and nonreactive based on the typical analytical techniques). Silica can be present in natural waters in a combination of three forms: reactive (ionic), nonreactive (colloidal), and particulate.

❖ **Ionic silica (reactive)**

Ionic or reactive silica exists in an SiO_2 complex. It is not a strongly-charged ion and therefore is not easily removed by ion exchange. However, when concentrated to levels above 100 ppm, ionic silica may polymerize to form a colloid.

❖ **Colloidal silica (nonreactive)**

At concentrations over 100 ppm, silica may form colloids of 20,000 molecular weight and larger, still too small to be effectively removed by a particle filter. Colloidal silica is easily removed with ultrafiltration, or can be reduced by chemical treatment (lime softening).

Colloidal silica can lower the efficiency of filtration systems (such as reverse osmosis). Any silica can affect yields in semiconductor manufacturing and is a major concern in high-pressure boiler systems.

❖ **Aluminum**

Aluminum (Al^{3+}) may be present as a result of the addition of aluminum sulfate [$Al_2(SO_4)_3$] known as alum, a commonly used flocculant. Aluminum can cause scaling in cooling and boiler systems, is a problem for dialysis patients, and may have some effects on general human health. Aluminum is least soluble at the neutral pH common to many natural water sources.

❖ **Sodium**

The sodium ion (Na+) is introduced naturally due to the dissolution of salts such as sodium chloride (NaCl), sodium carbonate (Na2CO3), sodium nitrate (NaNO3) and sodium sulfate (Na2SO4).
It is also added during water softening or discharge from industrial brine processes. By itself, sodium ion is rarely a problem, but when its salts are the source of chlorides (Cl-) or hydroxides (OH-), it can cause corrosion of boilers, and at high concentrations (such as seawater) it will corrode stainless steels.

❖ **Potassium**

Potassium is an essential element most often found with chloride (KCl) and has similar effects but is less common than sodium chloride. It is used in some industrial processes. The presence of KCl is, typically, a problem when only ultrapure water quality is required.

❖ **Phosphate**

Most phosphates (PO4 ^3-) commonly enter surface water supplies through runoff of fertilizers and detergents in which phosphates are common ingredients. Phosphates also enter the hydrologic cycle through the breakdown of organic debris. Phosphates are used in many antiscalant formulations. At the levels found in most water supplies, phosphates do not cause a problem unless ultrapure water is required. Phosphates may foster algae blooms in surface waters or open storage tanks

Dissolved Gases

❖ **Carbon Dioxide**

Dissolved carbon dioxide (CO2) associates with water molecules to form carbonic acid (H2CO3), reducing the pH, and contributing to corrosion in water lines, especially steam and condensate lines.
Carbonic acid, in turn, dissociates to bicarbonate (HCO3-) or carbonate (CO32-), depending on pH. Most of the CO2 found in water comes not from the atmosphere but from carbonate that the water has dissolved from rock formations.

❖ **Oxygen**

Dissolved oxygen (O2) can corrode water lines, boilers, and heat exchangers, but is only soluble to about 14 ppm at atmospheric pressure.

❖ **Hydrogen Sulfide**

Contributing the infamous rotten egg odor, hydrogen sulfide (H2S) can contribute to corrosion. It is found primarily in well water supplies or other anaerobic sources. H2S can be readily oxidized by chlorine or ozone to eliminate sulfur.

❖ **Radon**

Radon is a water-soluble gas produced by the decay of radium and its isotopes. It is the heaviest gas known and occurs naturally in groundwater from contact with granite formations, phosphate and uranium deposits. Prolonged exposure may cause human health problems including cancer.

Heavy Metals

Heavy metals such as lead, arsenic, cadmium, selenium, and chromium – when present above certain levels – can have harmful effects on human health. In addition, minute concentrations may interfere with the manufacture and effectiveness of pharmaceutical products, as well as laboratory and industrial processes of a sensitive nature.

Dissolved Organic Compounds

Dissolved organic materials occur in water both as the product of material decomposition and as pollution from synthetic compounds such as pesticides.

❖ **Naturally Occurring**

Tannins, humic acid and fulvic acids are common natural contaminants. They cause color in the water and detract from the aesthetics of water but, unless they react with certain halogens, they have no known health consequences in normal concentrations. In the presence of free halogen compounds (principally chlorine or bromine), they form chlorinated hydrocarbons and trihalomethanes (THMs), which are suspected carcinogens. Maximum allowable limits of THMs in municipal systems have been imposed by the United States Environmental Protection Agency (EPA).

❖ **Synthetic Organic Compounds (SOCs)**

A wide variety of synthetic compounds which are potential health hazards are present in water systems due to the use of industrial and agricultural chemicals. These compounds are not readily biodegradable and leach from soil or are carried by runoff into water sources. Many are suspected carcinogens and are regulated by the EPA.

Volatile Organic Compounds (VOC)

Due to relatively low molecular weight, many synthetic organic compounds such as carbon tetrachloride, chloroform and methylene chloride will easily volatilize. Volatility is the tendency of a compound to pass from liquid into the vapor state. Most are introduced into the water supply in their liquid phase. If ingested, they may be absorbed into the bloodstream. Many are suspected carcinogens.

Radioactive Constituents

Water, in itself, is not radioactive but may contain radionuclides. They are introduced either as naturally-occurring isotopes (very rare) or refined nuclear products from industrial or medical processes, radioactive fallout, or nuclear power plants.

5.0 Design Philosophy

Feed Water Analysis

Water system shall be designed based the raw water parameters. Water treatment system shall be designed based on the sample analysis of raw water considering the parameters as mentioned in the list below.

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Feed Water Analysis

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Sr. No.	Parameters and Units
1	Source of Water
2	Appearance
3	Odor
4	Turbidity (NTU)
5	SDI (Silt Density Index)
6	Color (Hazen Units)
a	Apparent Color
b	True Color
7	Conductivity @ 25°C (µS/cm)
8	Total Dissolved Solids (mg/lit)
9	Total Suspended Solids (mg/lit)
10	Total Hardness as CaCO3 (mg/lit
11	Total Alkalinity (Alk M.) (mg/lit)
a	Alkalinity (Carb.)
12	Total Organic Carbon,(ppb)
13	pH
14	Total Kjeldahl Nitrogen (TKN) (mg/lit)
15	Total Ammonia Nitrogen (TAN) (mg/lit)
16	CALCIUM as Ca (mg/lit)

Sr. No.	Parameters and Units
17	MAGNESIUM as Mg (mg/lit)
18	SODIUM as Na (mg/lit)
19	Phenolpthaein Alk. (ALK P.)
20	CHLORIDE as Cl (mg/lit)
21	Sulphate (mg/lit)
22	Fluoride as F
23	Nitrates as NO3 (mg/lit)
24	Nitrites as NO2 (mg/lit)
25	Phosphate (mg/lit)
26	Iron content as Fe (mg/lit)
27	Ammonia as NH3 (mg/lit)
28	Free Chlorine (mg/lit)
29	Copper as Cu (mg/lit)
30	Zinc as Zn (mg/lit)
31	Manganese as Mn (mg/lit)
32	Potassium as K (mg/lit)
33	Cadmium
34	Selenium
35	Lead
36	Chromium
37	Aluminum
38	Nickel

Sr. No.	Parameters and Units
39	Heavy metals, (if any)
a	Arsenic count
b	Mercury as Hg (mg/lit)
40	Reactive Silica as SiO2
41	Colloidal Silica (mg/lit)
42	Microbial Count (cfu/ml)
a	Pathogens
b	Pseudomonas
c	Salmonella
d	E. Coli
e	T. Coliforms
f	S. Aureus
g	Total plate count (cfu/ml)
h	Total Coli Forms (cfu/ml)
43	Endotoxin (Eu/Ml)
44	Yeast cells
45	Oil and grease

Parameters (Treated Water Quality)

The major outlet quality of the purified water shall be as mentioned below.

S. No	Parameter	Unit	Value
1	Conductivity @ 25°C	µs/CM	< 1.3
2	pH		5.0-7.0
3	TOC	ppb	500
4	TVC	Cfu/ml	< 100
5	Physical appearance		Odorless and clean
6	Heavy materials	ppm	< 0.1
7	Nitrate	ppm	< 0.2
8	Micro Organism ❖ Escherichia coli ❖ Salmonella ❖ Staphylococcus aureus ❖ Pseudomonas aeruginosa		Should be absent

Major Equipment List

Typically, pre-treatment plant will have the following steps of treatment processes:

Pretreatment section	Purified water generation system
Raw water storage tank	Micron filter and buffer tank
System feed pump	Micron cartridge filter
Hypo/CLO2 dosing	Ph correction dosing system
Recirculation of raw water with hypo/CLO2 dosing	SMBS dosing system
Hydro pneumatic system	HSRO system
Multi grade filter/disc filter	EDI system
Bag filter	Storage tank with accessories
Softener system	UV system
UF system	Piping materials with fittings
pH correction dosing system	Point of usage valves
SMBS dosing system	TOC meter
Antiscalant dosing system	Conductivity sensor and transmitter
CSRO system	Auto dumping
Storage tank with Hypo/ClO2 dosing	Flow transmitter
Piping	Back pressure valve
Required instrument for the system	Required instrument for the system

Sr. No.	Type of treatment	Water type	Utilization
1	Infeed water	Raw water	Only for gardening
2	MGF/Disc filtered water	Domestic water	Cooling tower, domestic usage including drinking, wet scrubber feed, feed to MGF
3	Softener treated water	Soft water	Boiler feed, chilled and hot water make up, feed to UF
4	UF filtered water	Potable water	For cleaning of equipment, chilled and hot water make up, feed to RO system
5	CSRO filtered water	Potable water/Process water	For cleaning of equipment, chilled and hot water make up, feed to main RO
6	RO+EDI treated water	Purified water	Process solution preparation, cleaning or rinsing of equipment during washing
7	RO reject water	RO reject water	Feed to cooling tower or ETP
8	EDI reject water	EDI reject water	Feed to cooling tower or ETP

Preferred MOC of Pipeline for Each Stage of Water Treatment System

Sr. No.	Type of connection	Preferred pipeline
1	Raw water infeed	SS 304/GI/UPVC
2	Raw water recirculation	UPVC
3	Raw water tank to MGF	UPVC
4	MGF to storage tank	UPVC
5	Tank to HPS system	UPVC
6	HPS system to softener	UPVC
7	HPS to boiler softener	UPVC
8	HPS to cooling tower	UPVC
9	Softener to UF	UPVC
10	UF to HSRO	UPVC
11	HSRO to RO storage tank	UPVC/SS 304/SS316
12	RO storage tank to RO-2 feed water tank	SS 304/SS 316/UPVC
13	RO storage tank to potable water line	SS 304/UPVC
14	RO-2 tank to RO-2 system	SS 304/SS 316L
15	RO generation to EDI	SS 316 L
16	EDI to storage tank	SS 316 L
17	Storage tank to distribution skid	SS 316 L
18	Potable water line	SS 304

Major Water Contaminants and Treatment

Major Classes of contaminants						
E = Excellent (capable of complete or near total removal **G = Good (capable of removing large percentages)** **P = Poor (little or no removal)**	**Dissolved ionized solids**	**Dissolved ionized gases**	**Dissolved organics**	**Particulates**	**Bacteria/Algae**	**Pyrogens/ Endotoxins/ Viruses**
Purification process						
Distillation	E	G/E (1)	E	E	E	E
Deionization (EDI)	E	E	P	P	P	P
Reverse osmosis	G(2)	P	G	E	E	E
Carbon adsorption	P	P (3)	E/G (4)	P	P	P
Micro filtration	P	P	P	E	P	P
Sub-Micron filtration	P	P	P	E	E	P
Ultrafiltration	P	P	G (5)	E	E	E
UV oxidation	P	P	E/G (6)	P	G (7)	P

1. The resistivity of the water is dependent on the absorption of CO2.

2. The concentration is dependent on the original concentration in the feedwater.

3. Activated carbon will remove chlorine by adsorption.

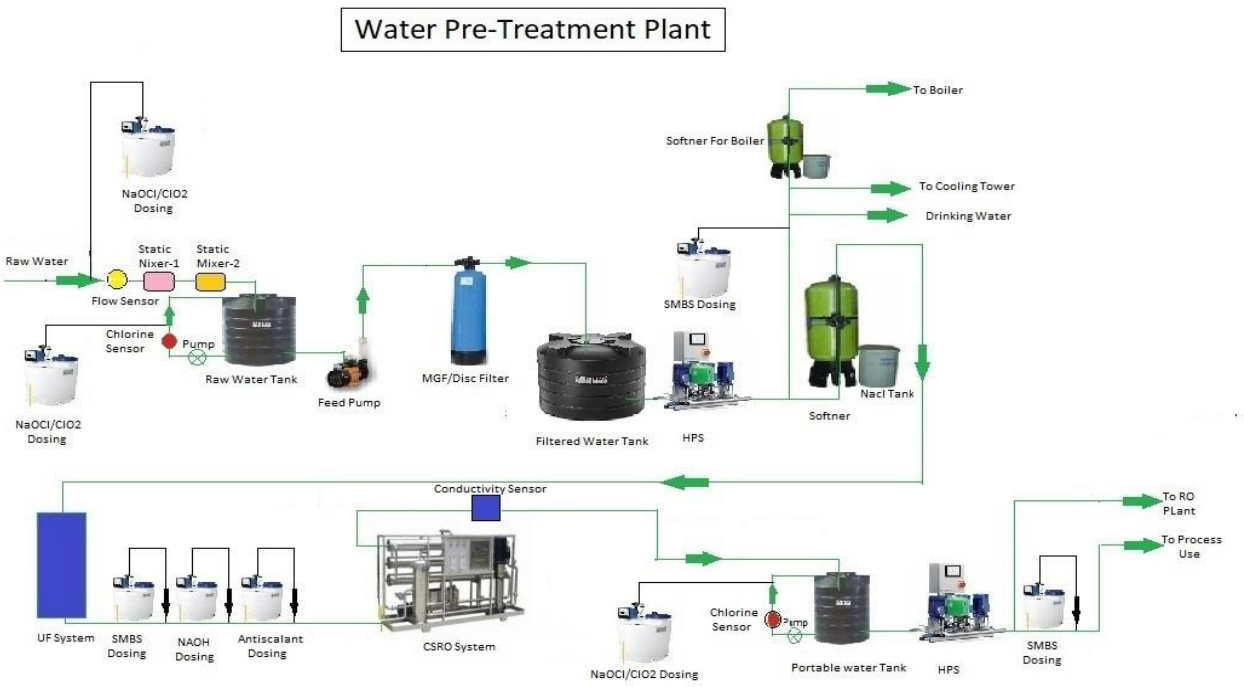
4. When used in combination with other purification processes, special grades of carbon exhibit excellent capabilities for removing organic contaminants.

5. Ultrafilters, being molecular sieves, have demonstrated usefulness in reducing specific feedwater organic contaminants based on the rated molecular weight cut-off of the membrane.

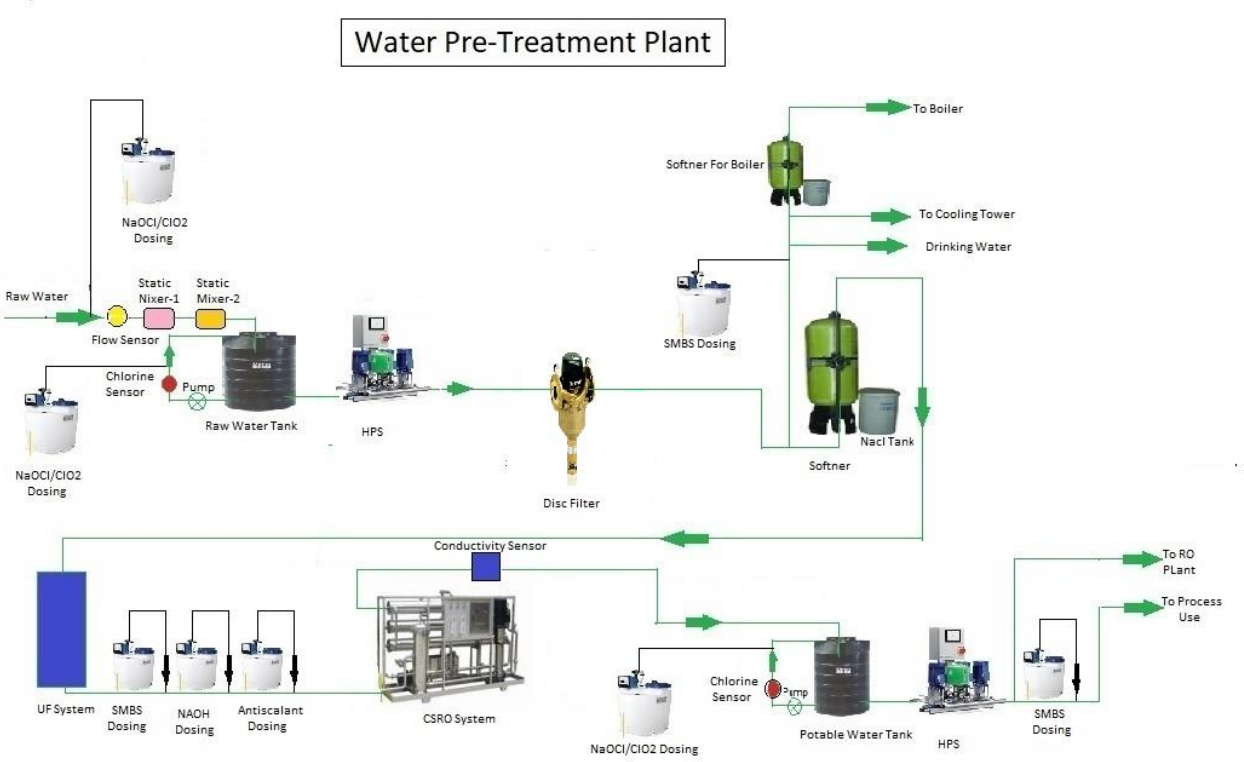
6. 185 nm UV oxidation has been shown to be effective in removing trace organic contaminants when used post-treatment.

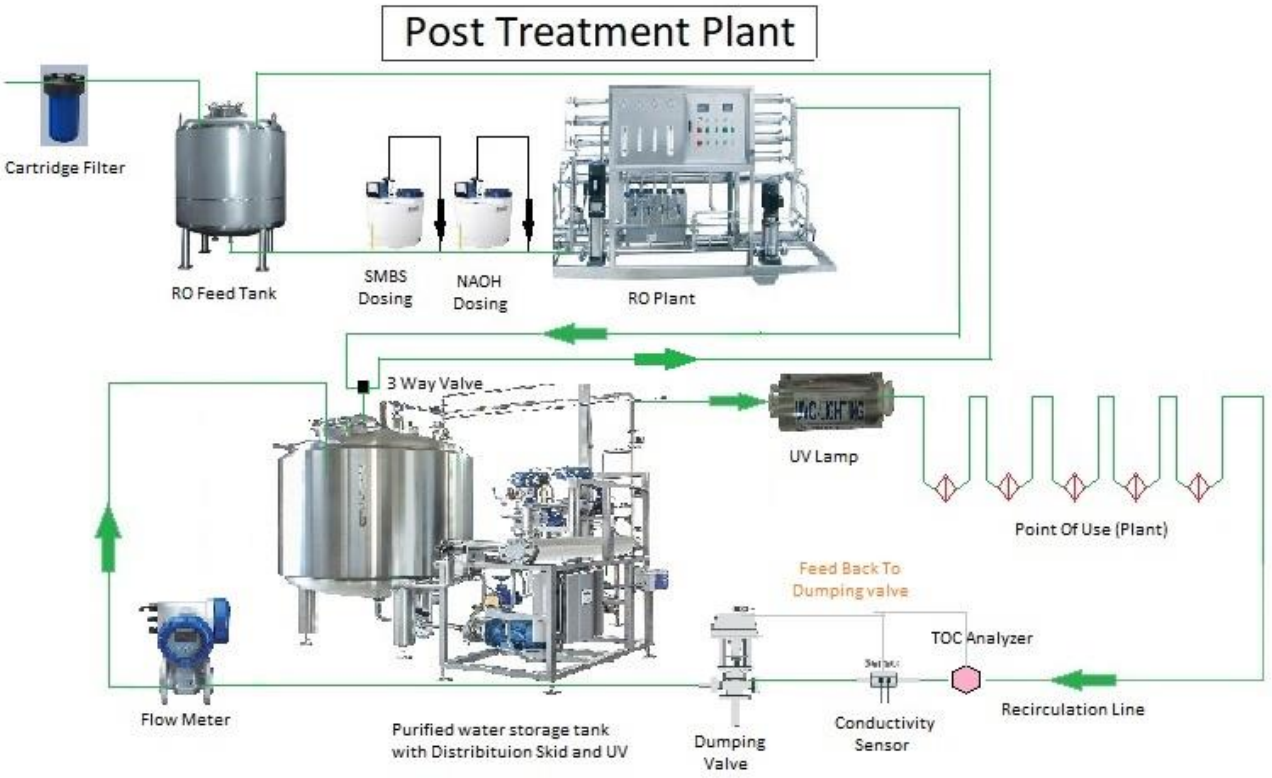
7. 254 nm UV sterilizers, while not physically removing bacteria, have bactericidal or bacteriostatic capabilities limited by intensity, contact time and flow rate.

Water Pre-Treatment with Multigrade Filter



Water Pre-Treatment with Disc Filter




Post Treatment Plant
Cartridge Filter
RO Feed Tank
SMBS Dosing
NAOH Dosing
RO Plant
3 Way Valve
UV Lamp
Point Of Use (Plant)
Feed Back To Dumping valve
TOC Analyzer
Recirculation Line
Flow Meter
Purified water storage tank with Distribituion Skid and UV
Dumping Valve
Conductivity Sensor

Pre-treatment and Purified Water System

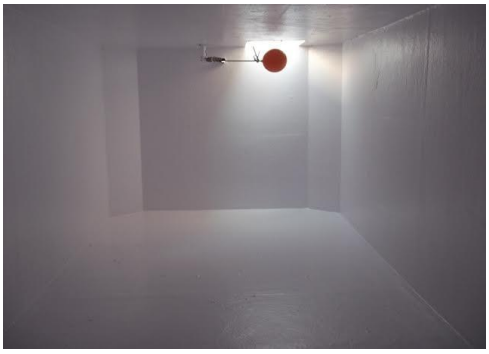
6. Raw Water Storage System

Infeed raw water types:

- Borewell water
- Ground water
- River water
- Well
- Municipality treated water
- Tanker water

Storage Tanks:

a. RCC Tanks



- Suitable capacity RCC tank should be constructed.
- During wall construction, provision of water stopper should be made to avoid leakages due to cold joint of concrete.
- Concrete hunch to be provided at junction of base to wall and wall to wall.

- Tank should be tested after filling with water in naked condition to check the leakages. If leakages are found, it should be grouted with injection chemical grouting to arrest the leakages.
- Water proofing shall be done properly.
- The inside of the should be tiled. Food grade epoxy coating can be applied in place of tiles.
- Tank should have vents.
- Tank should have manholes with SS ladder for accessing the inside of the tank for cleaning.
- Tank should have nozzles like inlet, outlet, drain, overflow, and recirculation.
- Drain should be provided in the lowest partition, or sump should be provided.
- Proper level indication equipment should be placed to check the water level in the tank. Nozzles should be provided accordingly.
- All nozzles, TC joints, flanges should be made of SS316L material.

b. External Storage Tanks

The wall structure consists of Zinc-Aluminum steel, which is fabricated with corrugated profiled wall panels. Zinc-Aluminum steel is non-corrosive.

a. **Liner** : liner should be selected based on the chlorine (PPM) present. Liner should be reinforced PVC, UV stabilized, anti-algae, and food grade.

b. **Nozzles** : nozzles should be selected as per requirement; these should all be either SS304 or Zinc-Aluminum steel.

c. **Scour drain** : -This is required to drain the tank.

d. **Overflow** : This is required for the overflow of water.

e. **Level indicator** : This is required to verify the level of water in the tank.

f. **Manhole** : this is required to get inside the tank.

g. **Internal and external ladder** : These are required to get inside and outside the tank.

h. **Vent** : provision is required at the top of the tank.

Note: If infeed water turbidity is very high, it will be necessary to go for the following treatment.

7. RAW WATER MANAGEMENT

Coagulant Dosing System

This is carried out by the addition of a suitable chemical coagulant which helps in the formation of small flocs by aggregation of suspended solids from the feed water. Coagulant addition encourages colloidal suspended matter for coagulation which forms the basis for flocculation.
The alum dosing system comprises of a tank, dosing pump and a chemical injection assembly.

Poly Dosing System

Poly dosing is carried out by the addition of poly in the feed water which leads to the formation of larger flocs. These large flocs are formed from the small flocs which are generated during the coagulant dosing process. After poly dosing these flocs become more stable and heavier, hence settling of the larger flocs is easier. The poly dosing system comprises of a tank, dosing pump and a chemical injection assembly.

CLARIFLOCCULATOR (FLOCCULATION TANK AND SLUDGE CONE)

Clariflocculator is a combination of flocculation and clarification zone. Initially heavy flocs are formed, during coagulant and poly dosing processes. These is agitated in the flocculation tank and is then settled in a specific period of time at the bottom of the tank leading to formation of sludge. Semisolid sludge and clarified liquid are separated. Clarified water is overflown through weir to downstream equipment for further water treatment. Sludge is deposited in the sludge cone and remaining sludge is transferred for client use.

SLUDGE TRANSFER PUMP

Screw type pumps with desired head and flow rate are placed at the bottom of the clariflocculator unit, to lift sludge and transfer it to the desired client location. One pressure gauge and pressure switch are provided at the discharge of each pump to monitor and regulate pump pressure.

Type of Disinfectant Treatment in Raw Water

1. NaOCl dosing.
2. ClO2 dosing.
3. Ozone.
4. UV disinfectant system.

NaOCl Dosing System

Application :

NaOCl dosing should be used where the water has low microbial growth and pathogens are not present.

Description :

Chlorination is carried out at the raw water inlet to inhibit microbial growth. Incoming water should be dosed with sodium hypochlorite (NaOCl) solution to prevent microbial growth during storage.
The chemical dosing system comprises a HDPE tank, solenoid operated diaphragm, electronic dosing pump, inbuilt low-level switch which will trip the dosing pump at the low level, and a chemical injection assembly. The dosing pump is provided with PVC foot, dosing valves and nylon tubing. By adjusting stroke length of the pump, it can be ensured that dosing pump is dosing the desired quantity of chemical to get the specific concentration as per design. Free chlorine sensor should be used to measure the chlorine PPM. The dosing pump will increase or decrease NaOCl dosing based on the chlorine requirement as per design. Static mixer should be used to mix the dosing chemicals in the proper way in the feed line.

The system should be complete with proportionate dosing pump, dosing tank, and interconnected piping. Dosing tank should have sloping bottom with drain valve. Dosing level shall be 5-6 ppm of free chlorine in the outfeed water.

ClO2 Dosing

Application :

Chlorine dioxide is highly effective in controlling waterborne pathogens while minimizing halogenated disinfection by-products. Chlorine dioxide is a broad spectrum microbiocide as effective as chlorine against viruses, bacteria, and fungi, and more effective than chlorine for the inactivation of the encysted parasites Giardia and Cryptosporidium. Chlorine dioxide is also an effective control strategy for taste, odor, color, iron, and manganese removal.

Description :

Chlorine dioxide is a gas produced by activating sodium chlorite with an oxidizing agent or an acid source. Sodium chlorite is converted to chlorine dioxide through a chlorine dioxide generator and applied as a dilute solution. Chlorine dioxide solutions should be applied to the processing system at a point, and in a manner, that permits adequate mixing and uniform distribution. The feed point should be well below the water level to prevent volatilization of the chlorine dioxide. Sodium chlorite should not be applied directly to potable water. Co-incident feeding of chlorine dioxide with lime or powdered activated carbon should be avoided.

Ozone

Ozone requires less contact time and lower concentrations than chlorine, chlorine dioxide, and chloramines to achieve disinfection, but its instability and reactivity means that it is unable to provide an enduring disinfection residual in distribution. The stability of ozone decreases with increasing pH and temperature. At 15°C and a pH of 7.6 the lifetime of the residual is reported to be in the order of 40 minutes, but at higher temperatures it can be as low as 10 - 20 minutes. This occurs due to a decrease in the efficiency of transfer of ozone into water as temperature increases. Dissolved ozone can react directly or indirectly with the water into which it is dosed. Direct reactions occur with the ozone molecule. Indirect reactions occur with hydroxyl radicals that are formed when molecular ozone decomposes in water. In practice, reactions by both mechanisms are likely to occur in parallel, with the prevailing water quality influencing the extent to which hydroxyl radicals are formed.

The gas is highly corrosive in the presence of moisture; hence, piping and other equipment must be constructed of resistant materials.

Note : Flow switch should be provided in the line to integrate the same with the disinfectant dosage system. In case of no flow in the line, disinfectant chemical dosing stops.

Raw Water Tank Recirculation Pumping :

Raw water recirculation is required continuously to maintain the turbulance in the tank, and to avoid stagnation of the water. It is also used to dose or top up the disinfect chemical in the tank in order to maintain the proper PPM of storaged water in the tank.

Free Chlorin Analyser :

Free chlorine analyser is used to verify the chlorine concentration (PPM) in the tank. Based on the same, quantity of top up of the disinfectant chemical will be decided at tank recirculation line.

UV Disinfection :

Treatment with ultraviolet light is a popular form of disinfection due to its ease of use. Water is exposed at a controlled rate to ultraviolet light waves. The light deactivates DNA leading to bacterial reduction. With proper design and maintenance, UV systems are simple and reliable for a high reduction in bacteria (99+ %), and are compatible with chemically-sensitive membrane and DI systems which are often incompatible with chemicals. UV is used to reduce microbial loading to membrane systems andnto maintain low bacterial counts in high-purity water storage and recirculation systems. If ozone has been added to water, UV is effective in destroying ozone residuals prior to end use. UV will increase the conductivity of water when organics are in the solution due to the breakdown of the organics and formation of weak organic acid.

The disadvantage of UV light is lack of an active residual, and it is effective only if there is direct UV light contact with the microbes. Careful system design and operation is required to ensure bacterial reduction. Inadequate light may only damage bacteria, which can recover. The water must be free of suspended solids that can 'shadow' bacteria from adequate UV contact.

Sr. No.	Type of Disinfectant	Advantages	Limitations
1	Chlorination	Well understood disinfectant capability. Established dosing technology.	Chlorination by-products and taste and odor issues can affect acceptability. Ineffective against Cryptosporidium.
2	Chlorine dioxide	Can be more effective than chlorine at higher pH, and less taste and odor and by-product issues.	Weaker oxidant than ozone or chlorine. Dose limited by consideration of inorganic by-products (chlorate and chlorite).
3	Ozone	Strong oxidant and highly effective disinfectant compared with chlorine. Benefits of destruction of organic micro pollutants (pesticides, taste, and odor compounds).	Bromate by-product and increased assimilable organic carbon (AOC) can impact re-growth in distribution. Complex, energy intensive, and expensive equipment compared with chlorination. Residual insufficiently long lasting for distribution.
4	UV	In general, highly effective for protozoa, bacteria, and most viruses and particularly for Cryptosporidium. No significant byproduct implications.	Less effective for viruses than chlorine. No residual for distribution.

MGF Feed-cum-Backwash Pump (in case of MGF) :

Feed water pump is required to feed the water to MGF/SCF. Additional flow is required for the backwash of MGF. So, a second pump is required to maintain the flow. Based on the scheme, either normal pumping equipment or hydropenumatic system shall be provided.

Hydropneumatic system :

Hydro-pneumatic system is required for pumping the water to respective locations with proper pressure. If pressures go below the set point, the system will automatically start to maintain the respective pressures. System should be properly designed for the respective flow, head and pressure.

Note : MGF/Disc Filtered water shall be pumped to utilities like cooling tower and boiler. It will be de-chlorinated before use.

8. Primary Filtration

- **Multi Grade Filter**
- **Disc Filter**

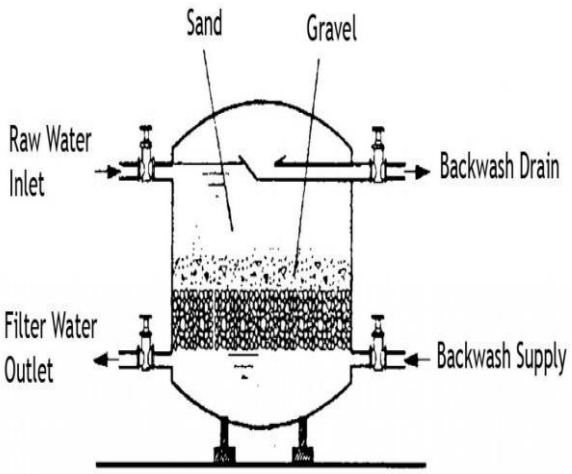
MGF Feed-cum-Backwash Pump (in case of MGF) :

Type : Depth Filtration System

Purpose: Removal of TSS, turbidity from feed water to the system.

Process Description :

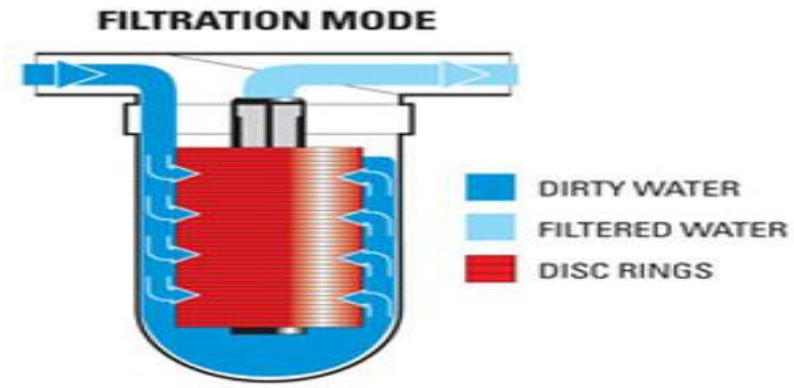
Multi Grade Filter consists of vertical or horizontal pressure sand filters that contain multiple layers of coarse and fine sand (pebbles and gravels) in a fixed proportion. It is a type of deep filter bed with adequate pore dimensions for retaining both large and small suspended solids and un-dissolved impurities like dust particles. As compared to conventional sand water filter, this multigrade filtration system works on higher specific flow rates. It is also a low-cost pre-treatment system for ion exchangers (deionizer and softener) and membrane systems such as reverse osmosis, etc. With high throughputs, high dirt-holding capacity, and capacity to reduce turbidity and TSS (< 5ppm) from water, it protects ion-exchange resins and membranes from physical fouling due to suspended impurities present in the water.



Working Principle :

The working principle of a multigrade filter is quite straight forward. In a multigrade filter or pressure sand filter, water is passed through multiple layers of filter media consisting of graded sand, pebbles, and gravels layers. The contaminants in the water are captured in the media bed and filtered water passes into the discharge manifold at the bottom of the tanks. The next and last step is backwashing, a process of effective removal of captured contaminants from the media bed. After back-washing, the filter is rinsed with raw water and after the required quality of water is achieved the filter is put back into service.

Disc Filter :

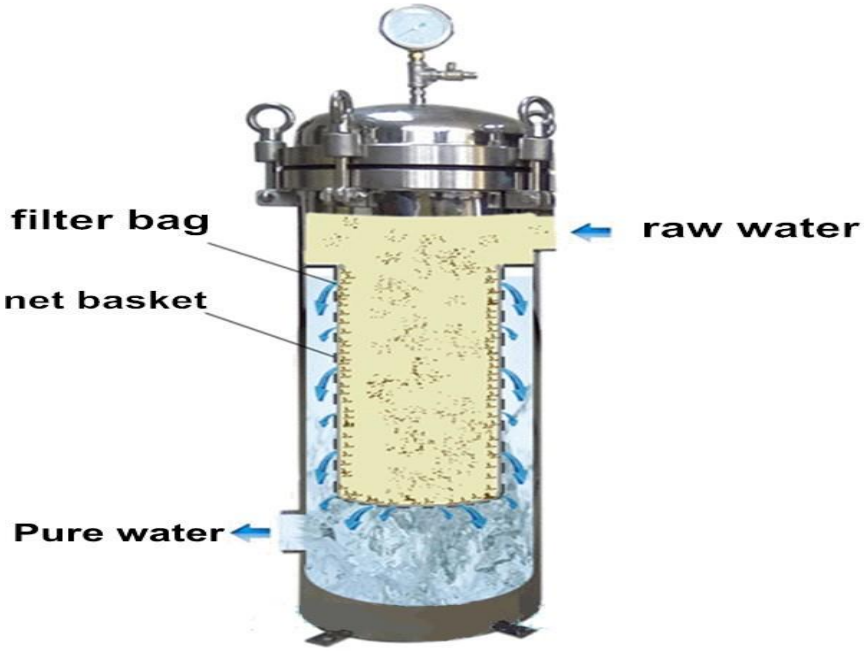


Disc filters are polypropylene discs, grooved on both the sides. It can ensure filtration of total suspended solids up to 100 micron size. When stacked, the groove on top runs opposite to the groove below, creating a filtration element with a statistically significant series of intersecting grooves which trap the solids. The stack is enclosed in a corrosion and pressure resistant housing. During filtration, the discs are tightly compressed together by a combination of the spring's power and the differential pressure, thus providing high filtration efficiency. Filtration occurs while water percolates from the outer diameter to the inner diameter of the element. It creates a unique in-depth filtration.

The innovative depth filter design captures and retains large amounts of solids. It is used for long-term operation in the pre-treatment of water and requires minimal maintenance. It is designed for high flow capacity, has double filter element, and is corrosion free.
The disc filter is self-cleaning automatic type with internal backwash along with a controller. A differential pressure switch is provided across the disc filter to measure the pressure drop across the filter due to clogging of the discs.

Bag Filter :

Bag filter of 40 Micron shall be placed after MGF/SCF to protect the granules in the pipe line.



Softener Unit :

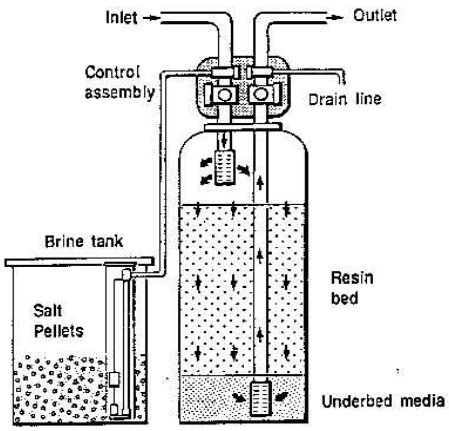
9. SOFTENER SYSTEM

Type : Depth ion exchange system.

Purpose : Removal of total hardness from feed water to the system.

Process Description :

Water softeners remove hardness (dissolved calcium and magnesium) through an ion exchange process. Incoming hard water passes through a tank containing ion exchange resin beads which are super saturated with sodium. As the water passes by the beads, the calcium and magnesium ions replace the sodium ions on the resin and sodium is released into the water. When the resin becomes saturated with calcium and magnesium, a backwash regeneration cycle is instigated. A concentrated salt brine solution (NaCl) is backwashed through the resin, replacing the calcium and magnesium ions on the resin with sodium ions.



Working Principle :

Water is softened by removing the hardness-producing ions, or specifically, the cations of calcium and magnesium. In the ion exchange reaction, sodium is substituted for hardness ions. The anions, bicarbonate, chlorides, sulfates, etc., are not changed in this process.

$$\begin{Bmatrix} Ca \\ Mg \end{Bmatrix} \bullet \begin{Bmatrix} 2HCO_3 \\ 2Cl \\ SO_4 \end{Bmatrix} + Na_2Rz \rightarrow \begin{Bmatrix} Ca \\ Mg \end{Bmatrix} Rz + \begin{Bmatrix} 2NaHCO_3 \\ 2NaCl \\ Na_2SO_4 \end{Bmatrix}$$

The symbol Rz refers to the ion exchange resin which is frequently referred to as zeolite. The original zeolites or materials resembling zeolites, which include greensand or synthetic aluminosilicate cation exchange materials, are very seldom used today because of the more durable and higher capacity styrene-divinyl benzene type ion exchange resins.

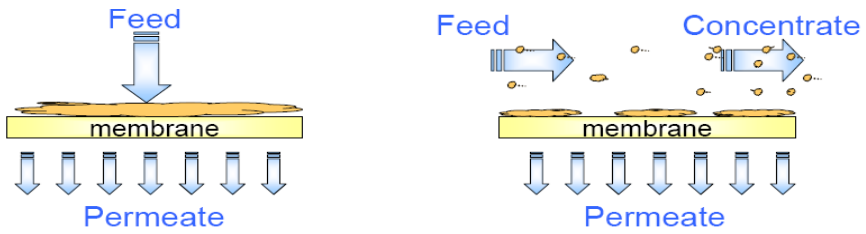
10. ULTRA FILTRATION (UF)

Ultrafiltration (UF) is similar to RO and NF, but is defined as a crossflow process that does not reject ions. UF rejects solutes above 1000 Daltons (molecular weight). Because of the larger pore size in the membrane, UF requires a much lower differential operating pressure, viz. 10 to 100 psig (0.7 to 6.9 bar). UF removes larger organics, colloids, bacteria, and pyrogens, while allowing most ions and small organics such as sucrose to permeate the porous structure.

Type: Cross Flow/Dead-end Filtration System

Purpose: Removal of colloidal, TOC, microbial impurity from feed water to the system.

Process Description:
UF is a pressure-driven membrane separation process that helps to remov particulate matter from aqueous solutions such as water. UF membranes typically have pore sizes in the range of 0.01 to 0.10 µm and efficiently remove bacteria and most viruses, colloids, and silt. The smaller the nominal pore size, the higher the removal efficiency.



Cross Flow & Deadend Flow Configuration

Working Principle

Ultrafiltration is a pressure-driven purification process in which water and low molecular weight substances permeate a membrane while particles, colloids, and macromolecules are retained. The primary removal mechanism is size exclusion, although the electrical charge and surface chemistry of the particles or membrane may affect the purification efficiency. Ultrafiltration pore ratings range from approximately 1,000 to 500,000 Daltons.

As a result, UF membranes are typically arranged in a configuration which maximizes surface area and reduces fouling by using a tangential flow design to reduce solute accumulation at the membrane surface. Tangential flow UF devices may be spiral-wound cartridges containing several square feet of membrane wrapped onto a central core tube or hollow-fiber cartridges containing dozens of thin UF membrane fibers.

SMBS Dosing System

Sodium metabisulfite helps in neutralizing the free chlorine content in water. Free chlorine is harmful to resin of reverse osmosis membrane/EDI as it acts as an oxidizing agent and reduces the life of the resin. The chemical dosing system comprises a HDPE tank, solenoid operated diaphragm, diaphragm dosing pump, inbuilt low level switch which will trip the dosing pump at the low level, and a chemical injection assembly. Dosing pump is provided with PVC foot, dosing valves and nylon tubing. Dosing pump is proportionate type instrument responsive. ORP transmitter will give signal to dosing pump to adjust its stroke length and frequency, in order to change chemical dosage to get the desired output as per the set point of ORP transmitter. Online micron filters of 5-micron nominal rating is placed for SMBS dosing system. The cartridges are of disposable type.

ORP Sensor:

ORP sensor shall be installed at the outlet of SMBS dosing system. ORP sensor will sense the ORP value and transmit the values to PLC. PLC will take necessary actions for any deviations in the ORP values, apart from those readings that are as per set point. If ORP is high, it goes into dumping mode.

Antiscalant Dosing System

RO membrane has a scaling tendency because of the ionic matter, and that affects the performance (flux and pressure requirement) of RO membranes. Hence, feed water to RO system will be dosed with Antiscalant, which helps in arresting the scale forming tendency of water. This is done by sequestering the scale forming components. The chemical dosing system comprises a HDPE tank, solenoid operated diaphragm, electronic dosing pump, inbuilt low-level switch which will trip the dosing pump at the low level, and a chemical injection assembly. Dosing pump is provided with PVC foot, dosing valves and nylon tubing.

By adjusting stroke length of the pump, it can be ensured that dosing pump is dosing the desired quantity of chemical to get the specific concentration as per design.

pH Correction Dosing System

Water from reverse osmosis system shall be dosed with caustic soda (NaOH) to adjust the pH to desired limit, in order to ensure that the CO2 level in water is as per the design requirement to feed to downstream. The chemical dosing system comprises of a HDPE tank, solenoid operated diaphragm, electronic dosing pump, inbuilt low-level switch which will trip the dosing pump at the low level, and a chemical injection assembly.

Dosing pump is provided with PVC foot, dosing valves and nylon tubing.
Dosing pump is proportionate type instrument responsive. pH transmitter will give signal to the dosing pump to adjust its stroke length and frequency to change chemical dosage to get the desired pH as per the set point of pH transmitter. To monitor pH, pH transmitter is installed after NaOH dosing. If pH is out of specified limit, system will go into dumping mode.

11. CSRO System

Ultra-filtrated water with the required flow rate from the ultrafiltration system will be used as a source of feed water for CSRO system. This water with the help of RO Feed Pump is then proposed to dose Antiscalent in the feed prior to the cartridge filter for RO system to prevent saturation of various organic salts especially Silica on RO membrane surface on concentration. Water will be dosed with caustic soda (NaOH) to adjust the pH to desired limit, so as to ensure CO2 level in water is as per the design requirement to feed to RO membrane.

Water will be then pass through 5-micron filter which will remove fine suspended solids, which may clog the RO membrane, if not trapped., Sodium metabisulfite is then dosed in the filtered water in order to neutralize any traces of residual chlorine present in the filtered water and to ensure complete dichlorination.

This chlorine free water is pumped to RO membrane with the help of RO high pressure pump. RO will serve the purpose of reducing TDS. There are three streams in a reverse osmosis system; feed, reject (concentrate), and lastly is permeate (product water).

The system shall be equipped with the components as described below :

CSRO Feed Pumps : (1 Working, 1 Standby)

Water from UF system is distributed for further treatment process. For this, the distribution pump will function at a constant flow during production. Non-return valve is at discharge, so as to avoid back flows.

Butterfly Valves :

Butterfly valves are installed at suction and discharge of RO feed pumps, for isolation of pump during maintenance.

Non-return valves :

Non-return valves are installed at discharge of CSRO feed pumps, to avoid back flow.

Pressure Transmitter :

Pressure transmitter shall be installed at the inlet of process filter, and it will monitor and control the pressure as per set point.

Sampling valve :

It shall be installed at the inlet of cartridge filter, for sampling as per process requirement.

Cartridge filter :

Cartridge filter with 5-micron pore size shall be placed at the suction of CSRO high pressure pump. The cartridges are of polypropylene and housed with UPVC. Sampling valve is installed at outlet for sampling as per process requirement.

Flow Transmitter :

Flow transmitter shall be installed at the discharge of CSRO feed pump, for measuring flow of water inline.

CSRO High Pressure Pumps :

CSRO high pressure pump shall be installed on the frame of the CSRO skid. With this pump, water pressure is boosted to ensure that feed water is able to pass through the spirally wound RO membrane, so that permeate water of the desired quality is obtained. Manual ball valves and pressure transmitter are present at discharge of the pumps.

Variable Frequency Drive :

VFD of CSRO high pressure pump will take necessary action, as required, and the pump flow will be controlled.

RO Membranes :

RO membranes will be installed in the system. RO is finest level of filtration available. RO membranes act as a barrier to all dissolved salts and inorganic as well as organic molecules. Water, on the other hand, passes freely through the membrane creating a purified product stream. RO block comprises of pressure tube with spirally wound chemical sanitizable membrane. Feed water enters the pressure tubes and leave as permeate and concentrate. Sampling valves are installed on all RO membranes for sampling as per requirement.

Concentrate Reject Drain Line of RO Unit:

- **Pressure Gauge:**

  This will be installed at the reject line of RO unit to drain the line, for continuously monitoring pressure in line.

- **Flow Indicator:**

  An inline flow indicator will be installed, for measuring flow of water at RO membrane reject to drain line.

- **Ball Valve:**

  Ball valve will be installed at reject line of RO membrane to drain line, for purposes of isolation.

- **On-Off Ball Valve:**

  On-off ball valve will be installed as a bypass line of RO unit reject to drain.

Permeate Line of RO Unit:

- **Sampling Valve :**

Sampling valve will be installed at permeate/reject line of RO unit, for analysis of water, as per process requirement.

- **Butterfly Valve :**

Butterfly valve will be installed at RO unit permeate to drain line for the purpose of draining.

- **Pressure Gauge :**

Pressure gauge will be installed at the permeate line of RO unit, for continuously monitoring pressure in line.

- **Flow Transmitter :**

Flow transmitter will be installed at permeate line of RO unit, to measure the flow/velocity at RO permeate line.

CONDUCTIVITY SENSOR AND TRANSMITTER

Conductivity sensor and transmitter is installed at RO permeate line, and will monitor and control conductivity. If conductivity exceeds a preset limit value, it will close the product valve and will drain the water out of the system.

Treated Water Tank Recirculation Pumping :

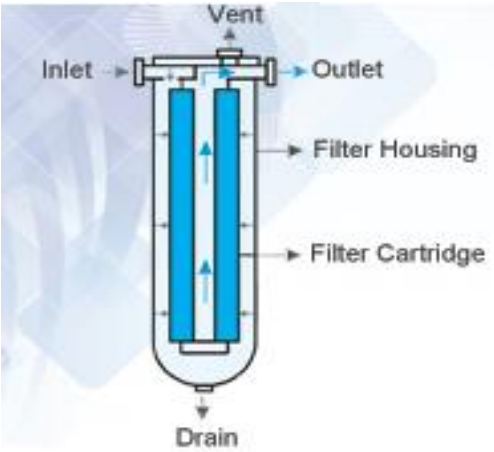
Treated water recirculation is required continuously, in order to maintain the turbulance in the tank, and to avoid water stagnation. Also, it is used to dose the disinfecting chemical in the tank so as to maintain the proper PPM of storaged water in the tank.

Free Chlorine Analyser :

Free chlorine analyser is used to verify the chlorine PPM in the tank. Based on the this value, top up quantity of the disinfectant chemical will be decided at the tank recirculation line.

Cartridge Filter :

Cartridge filter of 5 micron shall be placed before RO system to protect the RO infeed water from solid/dust content in pipeline.



SMBS Dosing System

Sodium metabisulfite helps in neutralizing the free chlorine content in water. Free chlorine is harmful to the resin of reverse osmosis membrane/EDI as it acts as oxidizing agent and reduces the life of the resin. The chemical dosing system comprises a HDPE tank, solenoid operated diaphragm, diaphragm dosing pump, inbuilt low level switch which will trip the dosing pump at the low level, and a chemical injection assembly. Dosing pump is provided with PVC foot, dosing valves, and nylon tubing. Dosing pump is proportionate type instrument responsive. ORP transmitter will give signal to dosing pump to adjust its stroke length and frequency, in order to change chemical dosage to get the desired output as per the set point of ORP transmitter. Online filters of 5 micron nominal rating is placed for SMBS dosing system. The cartridges are of disposable type.

ORP Sensor :

ORP sensor will be installed at the outlet of SMBS dosing system. ORP sensor will sense the ORP value and transmit the values to PLC, which will then take necessary actions for any deviations in the ORP values, apart from those at set point. If ORP is high, it will trigger dumping mode.

pH Correction Dosing System

Water from reverse osmosis system will be dosed with caustic soda (NaOH) to adjust the pH to desired limit, so as to ensure CO2 level in water is as per the design requirement to feed to downstream. The chemical dosing system comprises a HDPE tank, solenoid operated diaphragm, electronic dosing pump, inbuilt low-level switch which will trip the dosing pump at the low level, and a chemical injection assembly. Dosing pump is provided with PVC foot, dosing valves and nylon tubing. Dosing pump is proportionate type instrument responsive. pH transmitter will give signal to dosing pump to adjust its stroke length and frequency to change chemical dosage to get the desired pH as per the set point of pH transmitter. To monitor pH, pH transmitter is installed after NaOH dosing. If pH is out of specified limit, system will go into dumping mode.

12. Purified Water Generation System

Reverse Osmosis System (Hot Water Sanitizable)

High pressure pump will be provided with the system to boost the pressure across the membrane. Reverse osmosis block comprises of SS 304 pressure tubes with spirally wound hot water (85°C) sanitizable membranes. Feed water enters the pressure tube and leaves as permeate and concentrate; the latter leaves the system at the pressure tube, and is circulated back to feed; some part is drained continuously as per design requirement. The system is equipped with its components, instruments, auto and manual valves. RO unit is designed for best recovery.

Type : Cross Flow Filtration System

Purpose : Removal of TDS, TOC Impurity from Feed Water to the System.

Process Description :

RO membranes are used to remove contaminants that are less than 1 nm nominal diameter. Reverse osmosis typically removes 90% to 99% of ionic contamination, most organic contamination, and nearly all particulate contamination from water. RO removes non-ionic contaminants with molecular weights 300 Dalton, and particles, including colloids and microorganisms. Dissolved gases are not removed (e.g., CO2). During reverse osmosis, pretreated water is pumped past the input surface of an RO membrane under pressure (typically 4–15 bar, 60–220 psi) in cross-flow fashion.

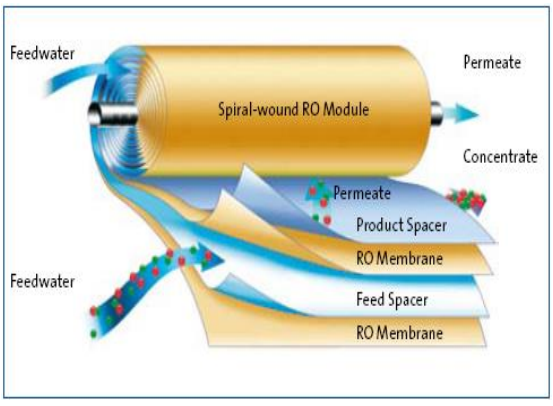
RO membranes are typically thin film composite (polyamide). They are stable over a wide pH range, but can be damaged by oxidizing agents such as chlorine, present in municipal water.

Pretreatment of the feed water with microporous depth filters like UF & RO membrane to remove the particulate matter, softenerand activated carbon for reduction of hardness and carbon contains from water. Pre dosing systems for removal of oxidizing compound, Anti-scalent for lowering the scaling frequency of membrane & pH Correction chemical for lowering or increase the required pH values. Typically, 75%-90% of the feed water passes through the membrane as permeate, and the rest exits the membrane as concentrate that contains most of the salts, organics, and essentially all of the particulates.

Working Principle

The purest form of membrane technology is reverse osmosis. This process removes 95% or more of the salts dissolved in the incoming water. Almost all organic molecules with a molecular mass of more than 100 g/mol are retained by the membrane. Only the water molecules can pass through the membrane, and these form the product output.

A synthetic semi-permeable membrane is used to separate water from dissolved impurities.
When a semi-permeable membrane separates a dilute and concentrated solution of salts, due to osmosis, the water from the dilute solution side passes though the membrane to the concentrated side till osmotic equilibrium is attained. Now, if the pressure is applied and increased gradually on the concentrated side, the flow of water continues to reduce till the applied pressure is equal to the osmotic pressure. Any pressure in excess of the osmotic pressure reverses the direction of flow of water and water from the concentrated side enters the dilute side. This process is called 'Reverse Osmosis.'



LIMITING CONDITIONS ON FEED WATER TO RO UNIT		
Turbidity	NTU	NIL
Free Chlorine	PPM	NIL
Heavy Metals like Iron, Manganese	PPM	NIL
Oil & Grease	PPM	NIL
TOC	PPM	< 3.0 Synthetic organic compounds (SOC) have generally more adverse effects on RO/NF membranes compared with natural organic matters (NOM).
TSS	PPM	NIL
Temperature	°C	< 40
SDI	-	< 4

EDI Unit

RO permeate water is then passed through electro-deionization (EDI) unit. The EDI unit will further polish the TDS (conductivity) and ensure that the purified water conductivity as per the requirement. EDI module will work to produce the desired quality as well as quantity of the product water. EDI unit will work at 95% recovery.

Type : Plate Type System

Purpose: Policing of Water to Produce Purified Water.

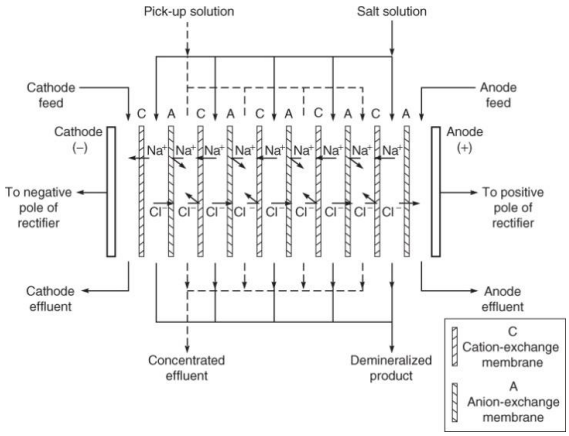
Process Description:

Continuous electro-deionization is a technology combining ion exchange resins and ion-selective membranes with direct current, in order to remove ionized species from water. It was developed to overcome the limitations of ion exchange resin beds, notably the release of ions as the beds get exhausted, and the associated need to change or regenerate the resins.
CEDI beds are typically also smaller and remain in service for much longer periods. CEDI is preferred for many purified water generation applications in pharmaceutical industry, because of its clean nonchemical nature, and the constant flow of high quality water produced. The resins used in CEDI systems can either be separate chambers of anion or cation beads, layers of each type within a single chamber, or an intimate mixture of cation and anion beads.

Working Principle

Reverse osmosis permeate passes through one or more chambers filled with ion exchange resins held between cation or anion selective membranes. Ions that become bound to the ion exchange resins migrate from the dilute chamber to a separate chamber (concentrate) under the influence of an externally applied electric field, which also produces the H+ and OH- necessary to maintain the resins in their regenerated state. Ions in the concentrate chamber are recirculated to a break tank or flushed to waste. The ion exchange beds in Continuous Electro De-Ionization (CEDI) systems are regenerated continuously, so they do not exhaust in the manner of ion exchange beds that are operated in batch mode (with chemical regeneration).

Hot water sanitization has been shown to be more effective than chemical sanitization for controlling microbial growth. Ease of operation, maximum reliability, and low operating costs are signature features of EDI modules. HWS modules are ideal for pharmaceutical, biotechnology, and other applications where chemical-free, instant hot water sanitization is desired. HWS modules produce high purity water without regeneration downtime.



Feed Water Specifications	
Feed Water Conductivity Equivalent, including CO_2 and Silica	< 40 µS/cm
Temperature	41 – 113°F (5 – 45°C)
Inlet Pressure	20 – 100 psi (1.4 – 7 bar)
Maximum Free Chlorine (as CL_2)	< 0.02 ppm
Iron (Fe)	< 0.01 ppm
Manganese (Mn)	< 0.01 ppm
Sulfide (S-)	< 0.01 ppm
pH	4 – 11
Total Hardness (as $CaCO_3$)	< 1.0 ppm
Dissolved Organics (TOC as C)	< 0.5 ppm
Silica (SiO_2)	< 1.0 ppm

Chemical Cleaning System

SS pump with positive suction head and desired flow rate is placed at the CIP feed tank to lift water across the RO. One pressure gauge is provided at the discharge of pump to monitor pressure. Hydrophilic micron filters of 5-micron nominal rating is placed before the antiscalant dosing system. ΔP across micron filter can be monitored to check performance of filter cartridge.

Chemical Cleaning System		
Chemical cleaning pump		
Capacity (m^3/hr)	:	As per requirement
Diff head required (mlc)	:	Vendor to specify
Chemical cleaning tank		As per requirement
Capacity (Ltrs.)	:	As per requirement
Note: Capacity shall be defined as required for cleaning of RO-EDI system.		

13. PURIFIED WATER GENERATION SYSTEM

PW Storage Tank

The size of tank is based on the feed flow rate from the PW system and the peak load of the user points. Purified water from the PW generation system is stored in vertical, limpeted/jacketed/plain insulated storage tanks (depending on customer requirements). The tank is vertical, with top and bottom dished ends made torispherical so as to maintain full drain ability of water in the tank. Tank is internally electropolished to a surface finish of < 0.5 µ Ra and is externally matt finished. Limpet/jacket has provision for steam inlet which will be utilized during hot water sanitization so as to maintain the temperature of purified water as per set point of the temperature transmitter installed in the return line of the distribution system.

Vendor must share the thickness calculations for the tank and dish.

Sr. No.	Description	Specifications
1	Type	Vertical, limpet, SS cladded
2	Operating volume in liters	As per requirement
3	Nozzles	As per requirement, 2 nos. spare nozzles should be considered
4	Shell thickness	6mm/suitable thickness; vendor should provide the calculations for standard positive pressure.
5	Bottom dish thickness	6mm/suitable thickness; vendor should provide the calculations for standard positive pressure.
6	Top dish thickness	6mm/suitable thickness; vendor should provide the calculations for standard positive pressure.
7	MOC of internal shell	SS 316L
8	MOC of internal dish	SS 316L
9	MOC of gasket	VITON
10	MOC of leg	SS 304
11	Limpet thickness	3mm
12	Insulation	Resin bonded mineral wool
13	Insulation thickness	50mm
14	Inside surface finish	Ra<0.4 mirror finish
15	Outside surface finish	Ra<0.8 mirror finish
16	Diameter and height	Based on site condition

Major Components of the Tank :

1. Level transmitter
2. Temperature element and transmitter
3. Back pressure valve
4. Vent filter
5. Pressure safety valve
6. Temperature control valve for steam
7. Compound pressure gauge
8. Rupture disc
9. Spray ball
10. Sight glass
11. Manhole
12. Chilled water/steam manifold

1. LEVEL TRANSMITTER

A level transmitter will be installed in storage tank for monitoring and controlling level of water in purified water storage tank. It has four set points. It operates on the basis of the feedback from PLC signal for low, low low, high, and high high levels. At H level filling will start, at HH level filling will stop, L level pump will start and LL pump will trip.

2. TEMPERATURE ELEMENT AND TRANSMITTER

Temperature element cum transmitter will be side mounted on tank. It will monitor and control the temperature of water in tank during the process of sanitization, and will ensure that the operating temperature is within designed limits.

3. BACK PRESSURE VALVE

Back pressure valve will be installed at the end of re-circulation line in tank, to maintain the return line pressure and water fill in the line.

4. VENT FILTER

The tank may need to be vented to allow filling, and a filter is used at the vent to avoid airborne particulate and microbial contamination inside the tank. To avoid the problem of condensation in the filter, and the resultant potential for colonization and growth, hydrophobic vent filters are used and/or the filters are maintained at a temperature above the tank temperature with electrical heat tracing. Surface temperature element and transmitter will monitor during sanitization. Pressure gauge is installed on vent filter to measure the pressure inline.

MOC of housing shall be SS316L and MOC of membrane for vent filter is single layer PTFE.

5. PRESSURE SAFETY VALVE

Pressure safety valve will automatically release steam from jacket for jacket safety, when the pressure exceeds preset limits..

6. TEMPERATURE CONTROL VALVE FOR STEAM

It will maintain the temperature of water during sanitization, on the basis of feedback from temperature element and transmitter installed on tank.

7. COMPOUND PRESSURE GAUGE

Compound pressure gauge will be installed on top dish of tank and will continuously monitor pressure within the tank. It can display both positive and negative (vacuum) pressures.

8. RUPTURE DISC

Sanitary type rupture disc will be installed on top dish of storage tank. If the pressure increases inside the tank above the set limit, then the rupture disc will burst, releasing the excess pressure created inside the tank, for tank safety.

9. SPRAY BALL

Spray ball will be installed at the recirculation line inside the tank to ensure that tank interior surfaces are flushed continuously. Spray ball will be of rotary type with 360° spray angle pattern. MOC of the ball will be SS316L. This is to avoid the formation of biofilm.

10. SIGHT GLASS AND LIGHT GLASS :

Sight glass and light glass provisions are made on the tank for inspection and monitoring. These will be placed opposite to each other.

11. MANHOLE :

A provision will be made available at the top of the tank for a manhole, in order to facilitate any operator to clean the tank during shut down operation.

12. CHILLED WATER/STEAM MANIFOLD :

- Tank should be made with steam manifold and chilled water manifold.
- Chilled water manifold should be considered when there is a requirement of purified water to be maintained at or below 25 deg C.
- Steam manifold will be used for heating of the purified water during sanitization cycle.
- Chilled water manifold consists of ball/butterfly valves, temperature and pressure gauges, strainer, NRV, auto valve and respective MS/SS piping with nitrile rubber insulation with aluminum/GC cloth over insulation.
- Steam manifold consists of piston/globe valve, strainer, auto valve, pressure gauge and steam trap assembly, with rockwool insulation and aluminum cladding.

PW DISTRIBUTION SYSTEM

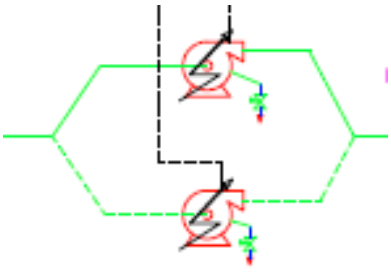
This system consists of sanitary pump for distribution of purified water and also all the instruments to monitor the critical parameters like conductivity, flow at return line, pressure, temperature, etc. All components are mounted on a complete skid which is pre-assembled and tested in our factory before shipping it to the site. It is designed keeping in mind all the requirements of minimum dead legs and 100% drainability.

Major Components on PW Distribution System :

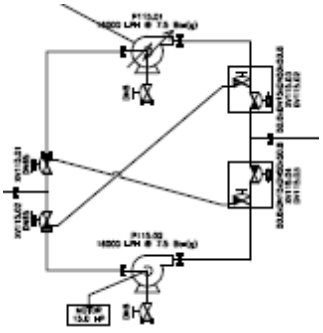
1. Sanitary pumps
2. UV system
3. Pressure gauge
4. TOC meter
5. Conductivity sensor and transmitter
6. Flow transmitter
7. Auto dumping valve
8. Ss 316l pipe line with standard triclover fittings
9. Point of use valves
10. Sampling valves
11. VFD

CIRCULATION PUMPS.

Two centrifugal pumps shall be mounted on distribution skid. The pumps will be continuously operational at desired flow rate and pressure, as per demand and minimum flow in return line. One pump would be working and other will be in standby. Standby pump as always flushed with discharge water of working pump to avoid bioburden. Drain valves is provided to the pump.



Swing Arm Type Design

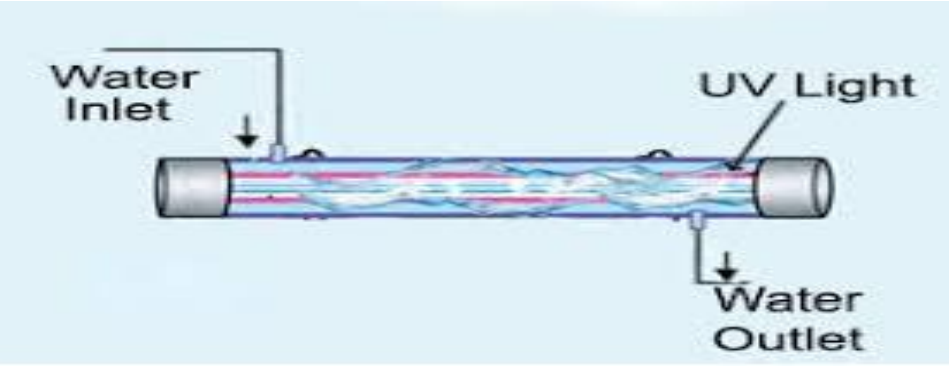


Cross Loop System

- Cross loop design is preferable as it has wetting option, so that when one pump is in operation, the second pump will be wet through X loop. Sanitization of the system can also be done inline. The necessary qualification should be done by quality team for this system.

UV SYSTEM

UV light deactivates DNA leading to bacteria reduction. The effectiveness of the system will depend on the quality of the water in which it is acting, intensity of the light, flow rate of water, contact time, and the type of bacteria present. This has been proved to control microbial growth in the water. This unit will operate at the maximum flow rate of the system, and it will emit UV rays of 253.7 nm which will be monitored on the UV panel. UV rays will be turned off during sanitization.

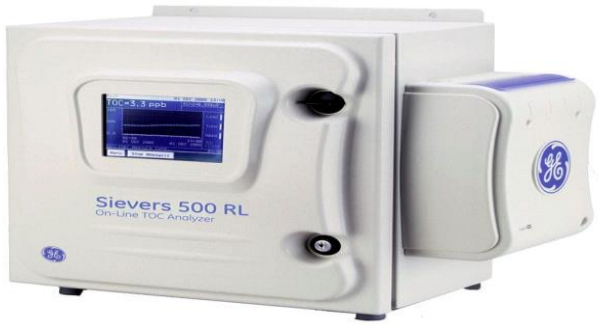


PRESSURE GAUGE

Pressure gauge will be installed on the discharge of centrifugal pumps to measure the pressure of water flowing inline.

ONLINE TOC METER

TOC analyzer indicator cum transmitter will be installed in the return line and this will measure the total organic carbon present in the water. It will transmit the value to the PLC. If TOC exceeds its set limit, the flow diverter valve in the return line will close its inline flow, and will drain the water completely out of the system till the set limit of TOC is achieved.



CONDUCTIVITY SENSOR AND TRANSMITTER

TOC analyzer indicator cum transmitter will be installed in the return line and this will measure the total organic carbon present in the water. It will transmit the value to the PLC. If TOC exceeds its set limit, the flow diverter valve in the return line will close its inline flow, and will drain the water completely out of the system till the set limit of TOC is achieved.

AUTO DUMPING VALVE

The 3-way diverter valve will operate on the basis of feedback from the conductivity transmitter in the return line. If conductivity exceeds its set limit, valve will open to drain and will close return line flow to storage tank, till the normal value is achieved.

FLOW TRANSMITTER

Flow transmitter will be installed on return line, in order to measure flow/velocity in this line.
If the flow/velocity increases or decreases than the set point, PLC will give the signal to VFD to either increase or decrease the speed of the pump to match the set point velocity.
During sanitization mode, the PLC gives signal to VFD to control the flow, as there will be no consumption at the POU, and hence only minimum amount of flow is maintained in the loop.

SS 316L Pipe Line with Standard Triclover Fittings

Pipes :

Stainless steel tubes with bead removed, made from material as per ASTM A 270 TP 316L ERW, 16 SWG; internally electro polished to better than 0.5 Ra, and externally mirror polished to 180 grit.

Elbows :

SS 316L Elbow R = 1.5 D, made from ASTM A 270 TP 316L, 16 SWG tube bead removed, wall thickness to match with respective pipe wall thickness; internally electro polished to better than 0.5 Ra, and externally mirror polished to 180 grit

Tees :

SS 316L Equal Tee, made from ASTM A 270 TP 316L ERW, 16 SWG tube bead removed, wall thickness to match with respective pipe wall thickness. Internal finish shall be electro polished to better than 0.5 Ra, and externally mirror polished to 180grit. All welding shall be automatic TIG orbital welding without external filler wire.

Concentric Reducer :

SS 316L concentric reducer, wall thickness to match with respective pipe wall thickness; internal finish electro polished to better than 0.5 Ra & externally mirror polished to 180 grit.

Eccentric Reducer :

SS 316L eccentric reducer, wall thickness to match with respective pipe wall thickness; internal finish electro polished to better than 0.5 Ra, and externally mirror polished to 180 grit.

TC Ferrule :

SS 316L TC ferrule, made from 316L, wall thickness to match with respective pipe wall thickness; internal finish electro polished to better than 0.5 Ra, and externally mirror polished to 180grit.

TC Blind Ferrule :

SS 316L TC blind, wall thickness to match with respective pipe wall thickness; internal finish electro polished to better than 0.5 Ra, and externally mirror polished to 180grit.

Gaskets :

PTFE enveloped with Viton insert, steam resistant, food grade, class VI plastic.

Tri Clamps :

SS 304 Tri clamps, 2 segments heavy duty with metal wing nut and ‘O’ rings, mirror polished to 180 grit.

Valves :

Sr. No.	Type of Valve	Description	Location
1	Diaphragm valve	2-way manually operated diaphragm valve with body material: SS 316l forged body, end connection: TC as per ASME BPE, diaphragm material: PTFE backed-up EPDM, surface finish: electro-polish Ra≤0.4µm	Above the tank and before vent filter
2	Diaphragm valve	2-way manually operated diaphragm valve with body material: SS 316L forged body, end connection: BW as per ASME BPE, diaphragm material: PTFE backed-up EPDM, surface finish: electro-polish Ra≤0.4µm	Tank drain
3	Pneumatic on/off valve	3-way pneumatically operated block valve for pump suction, body material: SS 316L forged block body, end connection: loop butt weld and branch TC as per ASME BPE, diaphragm material: PTFE backed-up EPDM, surface finish: electro-polish Ra≤0.4µm	Pump suction and discharge
4	Diaphragm valve	2-way manually operated diaphragm valve with body material: SS 316L forged body, end connection: BW as per ASME BPE, diaphragm material: PTFE backed-up EPDM, surface finish: electro-polish Ra≤0.4µm	Pump isolation valve
5	Sampling valves	Manual handwheel operated 3-way zero dead leg type sampling block valve with body material: SS 316L forged block body, end connection: all ends butt weld as per ASME BPE, diaphragm material: PTFE backed-up EPDM, surface finish: electro-polish Ra≤0.4µm	Sampling valve at pump suction, before and after UV
6	Auto dump valve	3-way pneumatic operated block valve for flow diverter, body material: SS 316L forged block body, end connection: all ends butt weld as per ASME BPE, diaphragm material: PTFE backed-up EPDM, surface finish: electro-polish Ra≤0.4µm	Auto dump in return valve
7	TOC sampling valve	pneumatically operated 3-way zero dead leg type block valve for toc with body material: SS 316L forged block body, end connection: loop buttweld and branch TC as per ASME BPE, diaphragm material: PTFE backed-up EPDM, surface finish: electro-polish Ra≤0.4µm	At return line
8	3-way block valve	3-way manually operated t/ l-type user point valve, with body material: SS 316L forged block body, end connection: loop ends butt weld and user point TC as per ASME BPE, diaphragm material: PTFE backed-up EPDM, surface finish: electro-polish Ra≤0.4µm	At point of use
9	4-way block valve with sampling valve	4-way pneumatically operated T-type user point valve with integrated manual sampling valve with body material: SS 316L forged block body, end connection: loop ends and sampling port butt weld and user point TC as per ASME BPE, diaphragm material: PTFE backed-up EPDM, surface finish: electro-polish Ra≤0.4µm	At point of use for direct connection to machine
10	3-way flow diversion valve	Flow divertor pneumatic actuated diaphragm valve 1 no actuator NC and 1 no actuator NO, material: SS 316L forged body, end connection: BW as per ASME BPE, diaphragm material: PTFE backed-up EPDM, surface finish: electro-polish Ra≤0.4µm	Tank inlet

VFD

This will take necessary action and the pump flow is controlled, based on the feedback of flow transmitter installed on the return line.

Sr. No.	Description	Specification
1	Make	
2	Model	V20/any reputed
3	Rating	As per requirement
4	Mounting	Panel mounting

14. Other Recommendations :

1. PW water distribution pipeline should be in loop and at least 1: 100 slope should be maintained.

2. PW generation and distribution system should comply with 21CFR part 11 Compliance and SCADA Integration.

3. All pipelines should be properly coded for identification with heat number. Vendor shall submit the MOC certificate based on destructive method analysis.

4. Above 99% purity Argon should be used for the welding, and a certified vendor should perform the welding. Weld coupons should be provided by vendor for each welding.

5. 20% of daily welding points to be inspected through boroscopy. A certified boroscopy machine and operator should perform the boroscopy.

6. Vendor shall provide day start samples and day end samples on a daily basis with proper coding.

7. Each unit should be properly labelled for identification.

8. Vendor shall provide the isometric drawing with proper identification of weld joints and boroscopy points.

9. Online printing is compulsory for critical parameters.

10. Return velocity should be maintained at 1.2 m/s when there was a peak demand, and VFD should be programmed accordingly.

11. Pump head and flow calculations to be provided by vendor/consultant.

12. Hot water sanitization and/or ozone sanitization for distribution system shall be decided based on the micro trend.

13. In case of ozone sanitization, ozone generator and concentration will be decided based on the last point requirement of 0.2 ppm, travel distance, and shelf life of ozone.

14. To maintain the best ozone concentration in the line, loop should be maintained at less than 25 deg C.

15. Sanitization Cycle

Two types of sanitization options are provided in the system ozone sanitization and hot water sanitization process.

- The sanitization of PW storage and distribution system shall be established on the basis of performance validation. Storage and distribution system shall be sanitized by ozone water at high concentration or by heating the water in tank above 80 deg C and circulating it in loop for a set time.

- It is preferable to sanitize the system once a week or as established during performance validation. The complete system should be designed for periodic sanitization.

- Bio-film formation in distribution loop is an unavoidable phenomenon. As and when the microbial count is found to be exceeding the permissible limits, sanitization of the system shall be performed.

- Whenever the circulation loop is to be sanitized for destruction of bio-film formation or as per validation requirements, the panel should be operated in the sanitization mode. The purified water tank is filled up to 30-40 % of its capacity along with the volume of water in the distribution loop.

- During sanitization, the respective inlet valves feeding to the tanks are closed so as not to allow any additional fresh water till sanitization is over. The water is then ozonized by means of ozone generator which is supplied to the storage tank, or by hot water by means of applying plant steam in the jacket of the storage tank and heating the water to more than 85 deg C.

- After achieving the set concentration of ozone, the ozone generator stops. Timer starts; after 30 minutes, the UV unit starts and brings down the level of ozone to the minimum set point value. The PLC control system should be changed from ‘sanitization’ to ‘normal’ mode. Now, the system is sanitized and ready for usage.

16. SOP

SOP FOR ORBITAL WELDING:

Objective :

In pharma as well as in biopharma industries, where the product comes in direct contact with metal or metal joints, it is required to maintain the process piping and other equipment in clean and sterile condition. So, a standard procedure is developed to facilitate the manufacturer and the user to provide hygienically accepted weld joints in the process piping and systems.

2. Scope :

This shall be applicable for welding of tubes. Every effort has been taken to standardize each step in the orbital welding process, starting from weld edge preparation to final visual inspection of the joint.

11. Procedure:

WELDER QUALIFICATION

Welders will be certified to a qualified welding procedure for the applicable material in accordance with ASME section IX. Welders shall be certified in the use of the specific equipment and material being used in the welding process.

3.1 Check Points

1. Pipe should be cut into pieces as per lengths marked in drawing. The pipe pieces are designated and numbered as SP01, SP02⋯ etc.

2. Make face of pipe right angle to its axis by grinding and polish to smooth surface. The internal and external surfaces near the ends should be cleaned.

3. Both ends of tube should be plugged with the help of welding dams.

4. Both faces of the pipe should be aligned, and tacked at three locations along the joint at an angle 120 deg, using TIG welding machine, without filler wire, with argon gas. The current during welding should be 20-40 amps. The pure Argon gas flow rate for shielding during the tacking process is maintained at 5.0 l/min with the help of gas flow regulator installed on argon gas cylinder.

5. For orbital welding, the tack welded should be installed inside machine clamp head. The alignment of the tungsten head should be check by manually rotating around the joint. The gap between tungsten head and weld joint should be kept at 2.0 to 3.0 mm. The orbital welding machine automatically selects the following weld parameters:

    a. Duration of pre-purge with argon gas.

    b. Duration of post-purge with argon gas.

    c. Strike current for initialization of arc.

    d. Peak current and base current at each level.

    e. Motor RPM.

    One side of the pipe should be plugged, and argon gas purging to joint should be started at 10 liters/min., and to the machine at 5 liters/min. For shielding, flow through joint should be maintained till post–purge time.

6. Orbital welding machine should be started.

7. After completion of welding post-purge time and subsequent cooling, the joint should be remove from the orbital head, and checked visually. The check list is given below.

8. The external surface of weld joint should be cleaned with buffing pad till external surface finish is satisfactory. Both ends of pipe should then be unplugged.

3.2 Check Points

Following things should be checked :

1. Whether weld has fully penetrated around the entire weld parameter with no crevices or entrapment sites. All butt welds shall have full penetration to the ID of the wall thickness.

2. Weld shall be smooth, uniform, and complete. A typical internal weld bead width of 1.5 times the nominal wall thickness should be maintained.

3. Weld shall have a uniform and complete weld bead width. The exterior of the weld bead width shall be straight and uniform around the entire weld circumference; the minimum weld bead width shall not be less than 50% of the maximum weld bead width. The maximum weld bead meander shall be 25% of the weld bead width.

4. There shall be no visible signs of oxidation, or discoloration on weld.

5. Weld should be checked for porosity, pinhole, and cracking.

6. If the joint are of acceptable quality and meets with the above-mentioned criteria, the orbital weld machine printout should be taken.

SOP FOR BOROSCOPY OF ORBITAL WELD JOINTS:

1. Objective:

In pharma as well as in biopharma industries, where the product comes in direct contact with metal or metal weld joint, it is required to maintain the process piping and other equipment in clean and sterile condition. So, a standard procedure is developed to facilitate the manufacturer/user to provide hygienically accepted weld joints in the process piping and systems.

2. Scope:

This shall be applicable for welding of tubes. Every effort has been taken to standardize each step in the boroscopy of the weld joints. Boroscopy should be confirmed for 20% of orbital welded joints on each day devoted to welding of joints.

1 Procedure :

3.1 Images/clips capturing procedure :

1. All the water should be drained from the loop, by opening all user points.
2. The TC clamp of the pipe should be removed
3. It is necessary to ensure that all the water has been removed from the pipe and the pipe is dry.
4. Now, the boroscopic probe should be inserted into the pipe, and images should be taken of clips of weld joints.
5. The images will be displayed on the camera screen. These should be examined thoroughly.
6. The same procedure should be followed for every joint.

3.2 Check Points

The following matters need to be checked :

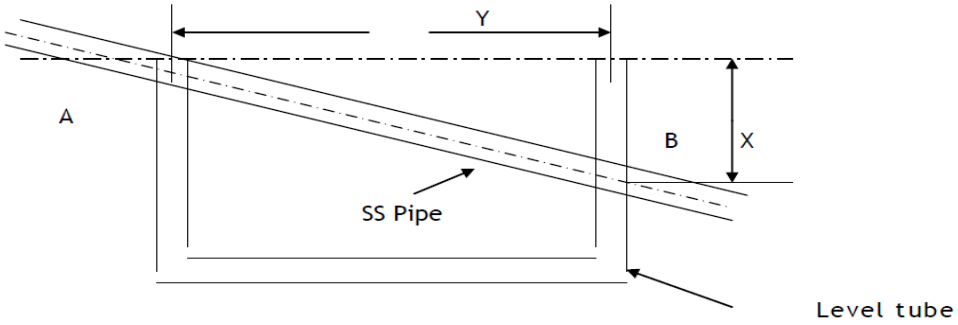
1. Whether the weld has fully penetrated around the entire weld parameter with no crevices or entrapment sites. All butt welds shall have full penetration to the ID of the wall thickness.
2. Weld shall be smooth, uniform, and complete. A typical internal weld bead width of 1.5 times the nominal wall thickness should be maintained.
3. Weld shall have uniform and complete weld bead width. The exterior of the weld bead width shall be straight and uniform around the entire weld circumference; the minimum weld bead width shall not be less than 50% of the maximum weld bead width. The maximum weld bead meander shall be 25% of the weld bead width.
4. There should be no visible signs of oxidation, and/or discoloration on weld.
5. If the joint is found acceptable, and meets with the above-mentioned checks, images can be taken, and the weld numbers can be noted. Images must contain date and time stamps.

SOP FOR SLOPE VERIFICATION

SLOPE DETERMINATION SYSTEM of PW WATER PIPING SYSTEM

Objective :

To ensure that the distribution lines are sloped towards the point of use and slope of the lines is approximately 1mm in 100mm.



Test Procedure :

1. The level tube should be filled with water.

2. Air bubbles should be removed, both the ends balanced, and the water column allowed to stabilize.

3. As shown in the figure above, the length Y of the pipeline from the starting point A to end point B (towards the point of use) should be measured. .

4. One end of the water column should be placed at the starting point A (water level at this point should be corresponding to the center of the pipeline), and the other end of the water column should be placed at the ending point B.

5. If slope of the pipe AB is toward point B, then water level in the tube will rise above the center of the pipeline AB at point B. Now, the tube should be held vertically straight, and the distance X, between the center of the pipeline AB at point B and the water level, should be measured.

6. If slope of the pipeline AB is not observed toward the point of use, i.e., B, the slope of the pipeline should be adjusted, and repeat steps no 1-5 should be repeated.

7. The ratio of X: Y should be calculated and the observation recorded at the respective point on the isometric drawing of the water distribution system.

8. Steps 1 to 7 should be repeated for each segment of the pipeline.

SOP FOR HYDROTEST OF LOOP

PROCEDURE

1. The water in the PW storage tank should be filled up to 40% of the total volume of the storage tank. All the drain valves and point of use in the system should be closed.

2. The system should be set in the manual mode.

3. The pump should be started in the manual mode.

4. The return line diaphragm valve should be close slowly. Then the pump discharge valve should be closed; meanwhile, the pump should be stopped, and it should be observed if that the pressure rises in the distribution loop (line).

5. The entire loop should be pressurized with the help of the distribution pump or the hydro pump (1.5 times the operating pressure).

6. The pressure should be set as per the requirement.

7. The pressure should be checked after one hour; if there is no pressure drop, the loop hydrotest is successful.

8. If there is pressure drop, then the problem should be rectified, and then the hydrotest should be performed again as per the above procedure.

SOP FOR CLEANING, PASSIVATION AND SANITISATION

A) PROCEDURE FOR SELECTING CAUSTIC SODA (NaOH) FOR CLEANING

1. The tank should be filled with water up to 30 % of its capacity, plus the quantity of water that occupies the running pipe length.

2. For a tank of 3000 liters capacity and 200 meters of piping, the storage tank should be filled with (900+80) = 980 liters of water.

3. A 0.5 % solution of NaOH should be taken.

Required NaOH = 980 x 0.5 = 4.9 Kg.

100

Hence, 5 kg (approx.) of NaOH should be taken in 980 liters of water.

- The distribution pump should be started.
- The solution should be recirculated for 60 minutes.
- After 60 minutes, the solution should be drained by opening the loop return dumping valve.
- At low-level, the pump should be switched off. The balance solution should be drained manually from the tank drain, all the point of use valves and all the sampling valves.
- All the valves should be closed.

Note :

1. During the above cycle, all the exit valves, viz. point of uses valves and sampling valves, should be cracked open to allow the solution to drain constantly.

2. All the parts that cannot be cleaned have to be dismantled and dipped into the solution separately for one hour.

FLUSHING :

1. The storage tank should be filled with 980 liters of purified water.

2. The distribution pump should be started.

3. The solution for 15 minutes should be recirculated.

4. Steps 1 to 3 of flushing should be repeated 3 times.

5. The qualities of water from drain parts should be checked by using pH scale.

If neutral, the cleaning and flushing process is over.

B) PROCEDURE FOR SELECTING NITRIC ACID(HNO3) FOR PASSIVATION

1. The tank should be filled with water up to 30 % of its capacity, plus the quantity of water that occupies the running pipe length.

2. For a tank of 3000 liters (assumed) capacity and 200 meters (assumed) of piping, the storage tank should be filled with (900+80) = 980 liters of water.

3. HNO3 5% v/v solution of assumed 70% concentration should be taken.

Required HNO3:

$$\textbf{Step -1: } \frac{980 \times 5}{100} = 49$$

$$\textbf{Step -2: } \frac{49}{70/100 \text{ (Assumed)}} = \frac{49}{0.7} = 70 \text{ liters}$$

Hence, 70 liters (approx.) of HNO3 in 980 liters of water should be taken.

Note : As per ASTM A380, 20 to 50% v/v solution should be recirculated at room temperature for 20 to 60 minutes. Since the pipings and components are electropolished (which itself is a very good passivation procedure), only the joints effected by orbital welding may be considered for passivation by the 5% v/v solution.

- The distribution pump should be started.
- The solution should be recirculated for 60 minutes.
- After 60 minutes, the solution should be drained by opening the loop return dumping valve.
- At low-level the pump should be switched off. The balance solution should be drained manually from the tank drain, all the point of use valves and all the sampling valves.
- All the valves should be closed.

FLUSHING :

1. The storage tank should be filled with 980 liters of purified water.
2. The distribution pump should be started.
3. The solution should be recirculated for 15 minutes.
4. Steps 1 to 3 of flushing should be repeated 3 times.
5. The qualities of water from drain parts should be checked by using pH scale.

If neutral, the cleaning and flushing process is over.

17. List Of Documents Required

Sr. No.	Description	Remarks
1	Water balance sheet	Required
2	Design concept note	Required
3	Material of Construction Certificate (MOC) of contact parts/non-contact parts	Metallurgical/PMI testing certificate for SS316 and SS316L required.
4	TSE/BSE free certificate	To be provided for the product contact parts which are manufactured from animal origin.
5	Latex free certificate (where applicable)	To be provided for the product contact parts which are manufactured from plant origin.
6	Calibration certificates traceable to NIST standard	For measuring instruments.
7	Performance test certificates	Motors
8	Qualification document	DQ, IQ and OQ should be provided.
9	PO copy with annexure	PO copy is required.
10	FAT Report/Performance test certificate	FAT reports are required.
11	Test certificates of bought out items – all components	Required.
12	Back up of software/instrumentation/PLC based system/any other automation related drawings	Required
13	Operation and maintenance manuals	Required
14	P&ID diagrams	Required
15	GA drawing of equipment	Required
16	Equipment position layout	Required
17	Materials gate entry records	Required
18	Certified material test reports	Required

Sr. No.	Description	Remarks
19	Welder qualification records	Required
20	Weld samples of each day startup operation	Required
21	Weld schedule verification	Required
22	Weld maps and identification of each weld by number	Required
23	Coupons or weld machine printout of each joint weld	Required
24	Daily welding log	Required
25	Weld inspection reports and videography with date and time	Required
26	Cleaning and passivation report	Required
27	Line label verification	Required
28	Line device identification and verification checklist	Required
29	Pipe specification document	Required
30	Pipe line index	Required
31	Pipe material certification with heat numbers	Required
32	Pipe surface finish test report	Required
33	Valves and Specialty data sheet	Required
34	Safety valve verification report	Required
35	Water drain ability test reports	Required
36	Line pressure test reports	Required
37	All measuring devices calibration certificate with traceability	Required
38	Welding machine calibration certificate	Required
39	Boroscopic inspection machine calibration certificate	Required
40	Welding gas purity certificate	Required

Sr. No.	Description	Remarks
41	Welder and weld inspector training certificate	Required
42	Manuals of all major components associated with the system	Required
43	Manuals of storage and distribution system including operation, sanitization and PMP procedures	Required
44	Technical datasheet of all components in the system	Required
45	Spare parts list	Required
46	Passivation and hydro test procedures	Required
47	Welding standard operating procedure	Required
48	Valve and dead leg conformation certificates	Required
49	Warranty certificates for major bought out items	Required
50	Video/picture CD of borescope inspection	Required
51	Water balance sheet	Required
	Drawing	Required
52	Approved drawing (GA/dimensional)	Required
53	As built drawing (dimensional)	Required
54	As built drawing - P&ID	Required
55	As built drawing – electrical (SLD)	Required
56	P&ID with all the instruments, user points and sampling points identified and tagged	Required
57	Isometric drawing showing welded joints with weld number and pipe heat number	Required
58	Isometric drawing indicating the slope direction and slope maintained between two points	Required
59	GA drawing of tanks and skid	Required
60	Layout of the pretreatment, PW generation and distribution system in the room	Required

20. STANDARDS

INDIAN STANDARD SPECIFICATIONS FOR DRINKING WATER IS: 10500

Sr. No.	Parameter	Requirement desirable Limit	Remarks
1	Color	5	May be extended up to 50 if toxic substances are suspected
2	Turbidity	10	May be relaxed up to 25 in the absence of alternative
3	pH	6.5 to 8.5	May be relaxed up to 9.2 in the absence
4	Total hardness	300	May be extended up to 600
5	Calcium as Ca	75	May be extended up to 200
6	Magnesium as Mg	30	May be extended up to 100
7	Copper as Cu	0.05	May be relaxed up to 1.5
8	Iron	0.3	May be extended up to 1
9	Manganese	0.1	May be extended up to 0.5
10	Chlorides	250	May be extended up to 1000
11	Sulphates	150	May be extended up to 400
12	Nitrates	45	No relaxation
13	Fluoride	0.6 to 1.2	If the limit is below 0.6, water should be rejected; max. limit is extended to 1.5
14	Phenols	0.001	May be relaxed up to 0.002

Sr. No.	Parameter	Requirement desirable Limit	Remarks
15	Mercury	0.001	No relaxation
16	Cadmium	0.01	No relaxation
17	Selenium	0.01	No relaxation
18	Arsenic	0.05	No relaxation
19	Cyanide	0.05	No relaxation
20	Lead	0.1	No relaxation
21	Zinc 5.0	5.0	May be extended up to 10.0
22	Anionic detergents	0.2	May be relaxed up to 1
23	Chromium as Cr+6 0	0.05	No relaxation
24	Poly nuclear aromatic hydrocarbons	---	---
25	Mineral oil	0.01	May be relaxed up to 0.03
26	Residual free chlorine	0.2	Applicable only when water is chlorinated
27	Pesticides absent	---	---
28	Radioactive	---	---

DRINKING WATER SPECIFICATION: IS: 10500, 1992

(Reaffirmed 1993)

TOLERANCE LIMITS

Sr. no.	Parameter	IS: 10500 Requirement (Desirable limit)	Undesirable effect outside the desirable limit	IS: 10500 Permissible limits in the absence of alternative source
Essential Characteristics				
1	pH	6.5 to 8.5	Beyond this range, the water will affect the mucous membrane and/or water supply system	No relaxation
2	Color (Hazen Units), maximum	5	Above 5, consumer acceptance decreases	25
3	Odor	Unobjectionable	--	--
4	Taste	Agreeable	--	--
5	Turbidity, NTU, Max	5	Above 5, consumer acceptance decreases	10
Following results are expressed in mg/l:				
6	Total hardness as CaCO3	Max 300	Encrustation in water supply structure and adverse effects on domestic use	600
7	Iron as Fe, Max	0.30	Beyond this limit taste/appearance are affected, has adverse effect on domestic uses and water supply structures, and promotes iron bacteria	1.0
8	Chlorides as Cl, Max	250	Beyond this limit taste, corrosion and palatability are affected	1000
9	Residual, free chlorine, Min	0.20		
10	Desirable characteristics			
11	Dissolved solids, Max	500	Beyond this, palatability decreases and may cause gastrointestinal irritation	2000
12	Calcium as Ca, Max	75	Encrustation in water supply structure and adverse effects on domestic use	200
13	Magnesium as Mg, Max	30	--	200
14	Copper as Cu, Max	0.05	Astringent taste, discoloration, and corrosion of pipes, fitting and utensils will be caused beyond this	1.5

Sr. no.	Parameter	IS: 10500 Requirement (Desirable limit)	Undesirable effect outside the desirable limit	IS: 10500 Permissible limits in the absence of alternative source
		Essential Characteristics		
15	Manganese as Mn, Max	0.1	Beyond this limit taste/appearance are affected, has adverse effect on domestic uses and water supply structures	0.3
16	Sulphate as SO4 Max	200	Beyond this, causes gastro-intestinal irritation when magnesium or sodium are present	400
17	Nitrates as NO3	45	Beyond this methanemoglobinemia takes place	100
18	Fluoride, Max	1.0	Fluoride may be kept as low as possible. High fluoride may cause fluorosis	1.5
19	Phenolic compounds as C6H5OH, Max	0.001	Beyond this, it may cause objectionable taste and odor	0.002
20	Mercury as Hg, Max	0.001	Beyond this, the water becomes toxic	No relaxation
21	Cadmium as Cd, Max	0.01	Beyond this, the water becomes toxic	No relaxation
22	Selenium as Se, Max	0.01	Beyond this, the water becomes toxic	No relaxation
23	Arsenic as As, Max	0.01	Beyond this, the water becomes toxic	No relaxation
24	Cyanide as CN, Max	0.05	Beyond this, the water becomes toxic	No relaxation
25	Lead as Pb, Max	0.05	Beyond this, the water becomes toxic	No relaxation
26	Zinc as Zn, Max	5	Beyond this limit it can cause astringent taste and an opalescence in water	15
27	Chromium as Cr6+, Max	0.05	May be carcinogenic above this limit	No relaxation
28	Ploynuclear aromatic hydrocarbons as PAH, Max	--	May be carcinogenic	--
29	Mineral Oil, Max	0.01	Beyond this limit, undesirable taste and odor after chlorination can occur	0.03
30	Pesticides, Max	Absent	Toxic	0.001
31	Radioactive materials a) α emitters Bq/1, Max b) β emitters Pci/1, Max			0.1 1
32	Alkalinity, Max	200	Beyond this limit taste becomes unpleasant	600
33	Aluminum as Al, Max	0.03	Cumulative effect is reported to cause dementia	0.2
34	Boron, Max	1	---	5

18. Procedure for Testing of Purified water conductivity

STAGE 1

Stage 1 is intended for online measurement or may be performed offline in a suitable container.

1. The temperature of the water and the conductivity of the water should be determined with a non–temperature-compensated conductivity reading.

2. Using Table 1, the temperature value should be found that is NMT the measured temperature, i.e., the next lower temperature. The corresponding conductivity value on this table is the limit.

3. If the measured conductivity is NMT the table value determined in step 2, the water meets the requirements of the test for conductivity. If the conductivity is higher than the table value, the team should proceed with Stage 2.

Table 1. Stage 1 Temperature and Conductivity Requirements (for non–temperature-compensated conductivity measurements only)

Temperature in Deg C	Conductivity Requirement (mS/cm)
0	0.6
5	0.8
10	0.9
15	1
20	1.1
25	1.3
30	1.4
35	1.5
40	1.7
45	1.8

Temperature in Deg C	Conductivity Requirement (mS/cm)
0	0.6
5	0.8
10	0.9
15	1
20	1.1
25	1.3
30	1.4
35	1.5
40	1.7
45	1.8
50	1.9
55	2.1
60	2.2
65	2.4
70	2.5
75	2.7
80	2.7
85	2.7
90	2.7
95	2.9
100	3.1

STAGE 2

4. A sufficient amount of water should be transferred to a suitable container, and the test specimen should be stirred. The temperature should be adjusted, if necessary, and, while maintaining it at 25 ± 1°, the test specimen should be vigorously agitated while periodically observing the conductivity. When the change in conductivity (due to uptake of atmospheric carbon dioxide) is less than a net of 0.1 mS/cm per 5 min, the conductivity reading should be noted. [NOTE: conductivity measurements at this stage may be temperature-compensated to 25° or non–temperature-compensated.]

5. If the conductivity is not greater than 2.1 mS/cm, the water meets the requirements of the test for conductivity. If the conductivity is greater than 2.1 mS/cm, proceed with Stage 3

STAGE 3

6. This test should be performed within approximately 5 min of the conductivity determination in step 5, while maintaining the sample temperature at 25 ± 1°. A saturated potassium chloride solution should be added to the same water sample (0.3 mL per 100 mL of the test specimen), and the pH should be determined to the nearest 0.1 pH unit, as directed in pH meter

7. Referring to Table 2, the conductivity limit should be determined at the measured pH value. If the measured conductivity in step 4 is NMT the table value determined in step 6, the water meets the requirements of the test for conductivity. If either the measured conductivity is greater than this value, or the pH is outside the range of 5.0–7.0, the water does not meet the requirements of the test for conductivity.

Table 2. Stage 3 - pH and Conductivity Requirements (for atmosphere- and temperature-equilibrated samples only)

pH	Conductivity Requirement (mS/cm)
5.0	4.7
5.1	4.1
5.2	3.6
5.3	3.3
5.4	3.0
5.5	2.8
5.6	2.6
5.7	2.5
5.8	2.4
5.9	2.4
6.0	2.4
6.1	2.4
6.2	2.5
6.3	2.4
6.4	2.3
6.5	2.2
6.6	2.1
6.7	2.6
6.8	3.1
6.9	3.8
7.0	4.6

WFI and Pure Steam Generation

Water for injection is water of extra high quality without significant contamination. Sometimes it is named as sterile water is primarily used for making solutions for injectable products. A non-sterile version of WFI can be used in manufacturing where injectable products are subjected to terminal sterilization.
The main difference between purified water and WFI is bacterial endotoxin. Refer below table for WFI specification.

Water for Injection	Ph. Eur.	USP
TOC	≤ 0.5 mg/l	NMT 500 ppb
Conductivity	≤ 1.1 µS/cm @ 20°C	≤ 1.3 µS/cm @ 25°C
Nitrates	≤ 0.2 ppm	-
Heavy Metals	≤ 0.1 ppm	-
Aerobic bacteria	< 10 cfu/100 ml	< 10 cfu/100 ml
Endotoxin	< 0.25 IU/ml	< 0.25 EU/ml

Some of the agencies accept purified water as WFI if it passes in bacterial endotoxin test, like USFDA and JP. However, the preferred way to generate WFI is distillation. This is considered as final treatment of water and is used for sterile pharmaceutical products as raw material and for cleaning. For preparation of WFI, feed water shall be of purified water grade, or at least low conductivity/TDS.

1. WFI Generation

WFI can be generated by following processes :

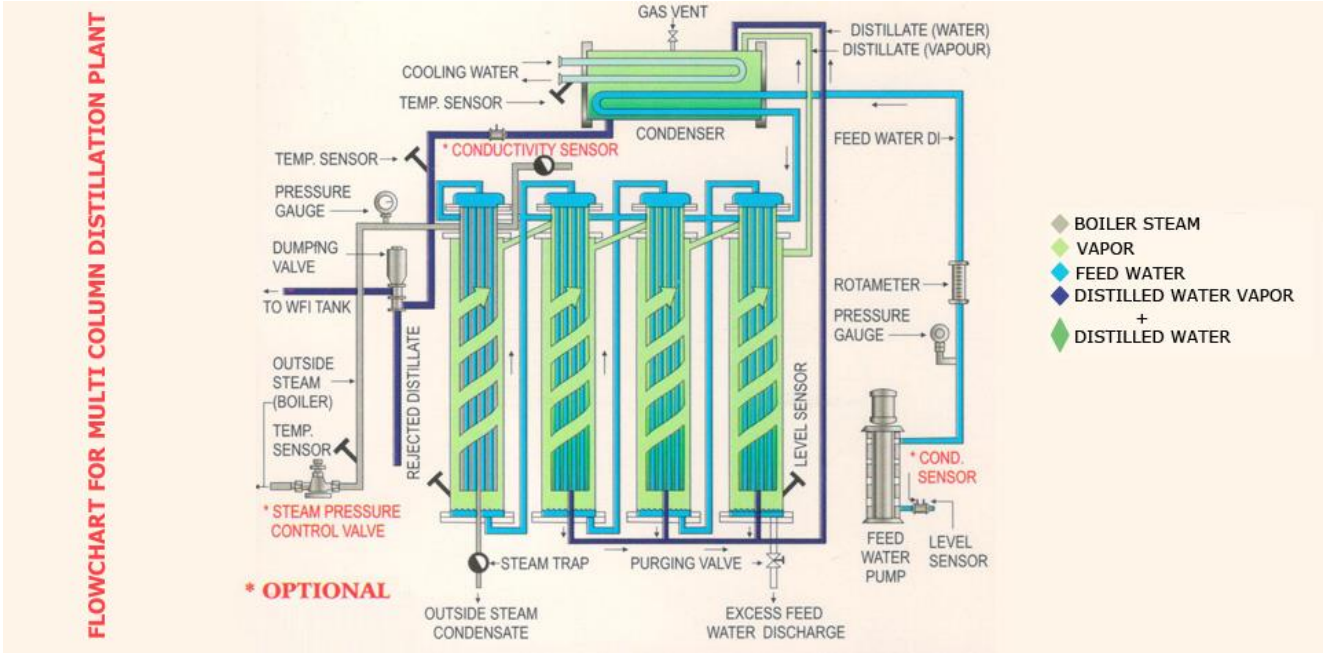
1. Multiple Effect Distillation.
2. Vapor Compression Distillation.
3. Reverse Osmosis + Ultrafiltration (Cold WFI or similar to purified water)

Multiple Effect Distillation Plant

MED system is a well-known method for generation of WFI. Multiple effect stills are multiple column designs which re-uses steam energy through the process, requiring minimal moving parts, but requiring cooling water for final distillation of product.

In the first column, preheated water is converted into pure steam by raw steam (boiler steam) using shell and tube heat exchanger. This pure steam is further used in the second column where it further evaporates water into steam, and so on in the next column.

Finally, the distillate from all columns is passed from condenser to get it cooled to water at 85 deg. C. This water is condensed water or sterile water which is called WFI.



WFI Generation By Multicolumn Distillation Unit

In case of low required capacities (since MED systems consume much energy and cooling water) one can also get WFI from Single Effect Distiller (BRAM-COR Mod. DPSG), that is both a still and a pure steam generator.

This also work on the principle of the natural circulation evaporator. Shell & tube heat exchangers/multi column to avoid cross contamination and higher evaporation efficiency. By converting water into steam & again from steam to distillate water at high temp for Removal/control bacterial endotoxin if any.
Online conductivity & sensors are installed with fully automatic system. If any parameter is on alarm limit or exceed , water is drained through dumping valves.

Major Components of Multiple Effect Distillation Plant

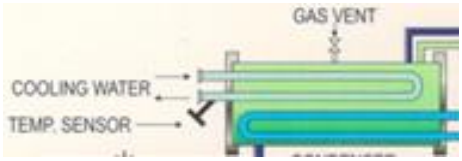
- Feed water pump
- Vent condenser
- Evaporation column
- Condenser vent filter
- Flow diverter valve

Feed water pump

Centrifugal pump shall be mounted on the skid. Pump MOC shall be SS316L and it delivers the feed water to vent condenser for preheating.

Vent Condenser

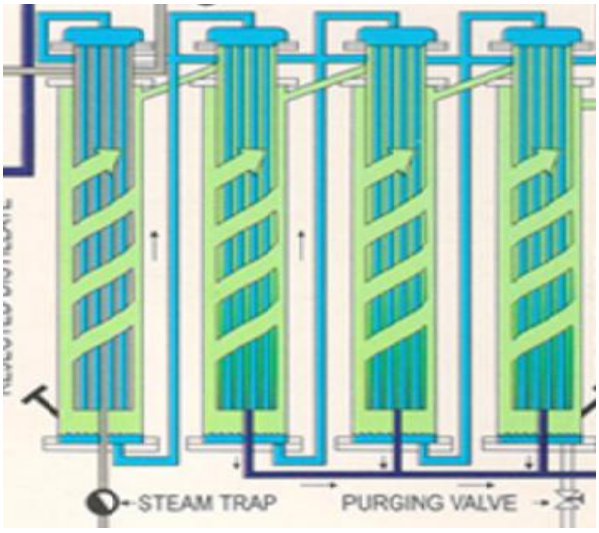
Water vapor is cooled down in vent condenser by feed water. Pre-heated clean steam and gases are fed into the vent condenser, A condenser is designed to transfer heat from a working fluid to a secondary fluid. The condenser relies on the efficient heat transfer that occurs during phase changes, in this case during the condensation of a steam vapor into a liquid. These units are typically made of stainless steel SS 316 L.



Condenser

Evaporation Column

These are the main component. Heating is carried out by plant steam through the coil installed in the main column, This process involves a shell and tube heat exchangers (columns) where heat transfer is done by falling film evaporation. Very high temperatures are reached for every drop of water produced, thus ensuring sterility levels demanded for WFI.



Evaporation Column

Condenser Vent Filter

It is used to remove non-condensable gases from the condenser in the liquid phase. Also, during cool down period of system , air enter through this filter into the column/system as filtered air.

AUTO DUMPING VALVE

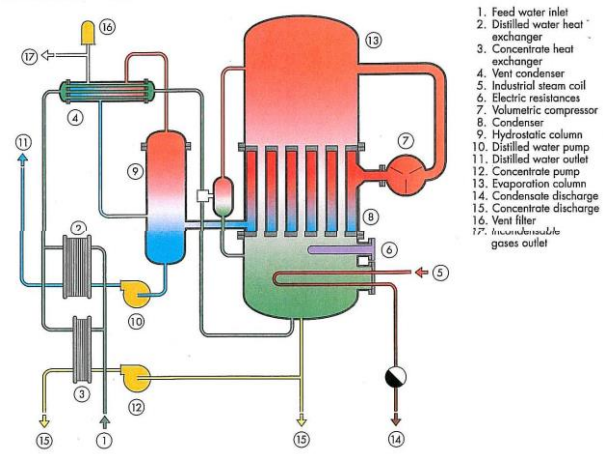
3-way diverter valve will operate on the basis of feedback from conductivity transmitter in return line. If conductivity exceeds its set limit, valve will open to drain, and will close return line flow to storage tank, till the normal value is achieved.

Vapor Compression Distillation

VC system is also known as thermocompression/vapor recompression or thermal/mechanical vapor compression. It is a technology similar to the evaporation systems used for the water desalination (vapor compression is also a common term in the refrigeration industry).

Furthermore, the VC system can be powered by either steam or electric heating, and have a minimal feed water quality requirement due to lower operating temperature.

VCD units are driven by a more mechanical process than MED, involving a compressor and other moving parts to compress steam and increase its pressure/temperature for evaporation.

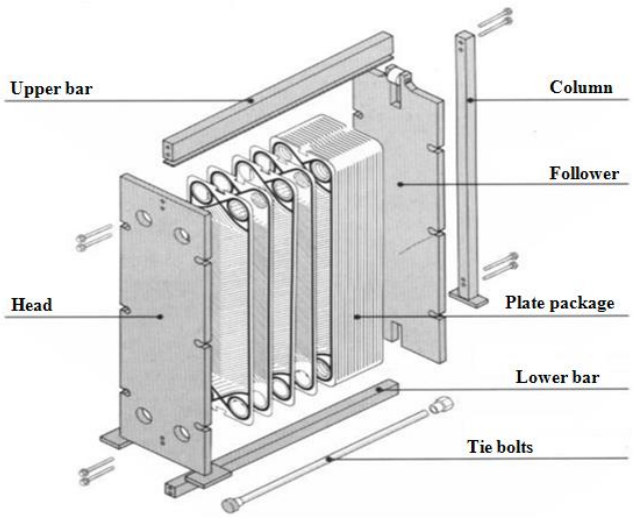


WFI Generation by Vapor Compression Distillation

Major components of vapor compression distillation plant :

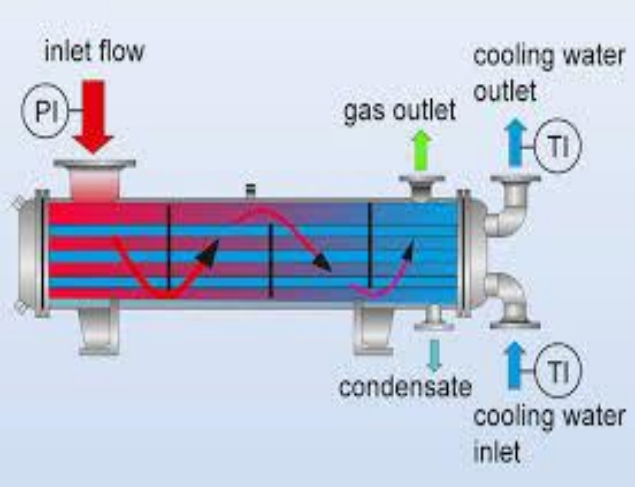
- ❖ Concentrate heat exchanger
- ❖ Distilled water heat exchanger
- ❖ Vent condenser
- ❖ Evaporation column
- ❖ Volumetric compressor
- ❖ Hydrostatic column
- ❖ Distilled water pump
- ❖ Concentrate pump
- ❖ Condenser Vent filter

Concentrate and Distilled Water Heat Exchanger



Heat Exchanger

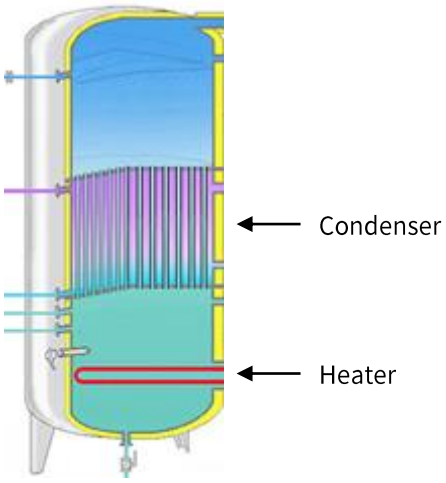
Feed water enters the concentrate water heat exchanger, and is pre-heated through concentrated water. Feed water goes into the distilled water heat exchanger and is further pre-heated through distilled water. As the water pumps through the pipes, it absorbs the heat . A heat exchanger is a device that allows heat from a fluid to pass to a second fluid without the two fluids having to mix together or come into direct contact. These units are typically made of stainless steel SS 316 L.



Vent **Condenser**

Pre-heating clean steam and gases into the vent condenser, A condenser is designed to transfer heat from a working fluid to a secondary fluid. The condenser relies on the efficient heat transfer that occurs during phase changes, in this case during the condensation of a steam vapor into a liquid.
These units are typically made of stainless steel.

Evaporation Column



Evaporation Column

Heating by plant steam in the coil installed in the main column, this process involves a shell and tube heat exchangers (columns) where heat transfer is done by falling film evaporation. Very high temperatures are reached for every drop of water produced, thus ensuring sterility levels demanded for WFI. Separation of the pyrogenic load is achieved through centrifugal forces generated during the upward movement of the steam.

Volumetric Compressor

The feed water, kept at a constant level in the column, evaporates into clean steam which flows up into the dome and from where it is sucked by the centrifugal blower and compressed in the shell of the central condenser where its condensation take place.

Hydrostatic Column

The condensate enters in the WFI hydrostatic vessel where the non-condensable gases are removed from the liquid phase.

Distilled and Concentrate Water Pump

This pump is used for the transfer of WFI from main column and delivered through the distilled water heat exchanger to WFI storage tank.

And Concentrate water pump sucks the concentrate water from the evaporation column and delivered through the Concentrate water heat exchanger.

Condenser Vent Filter

It is used to remove non-condensable gases from the condenser in the liquid phase.

Reverse Osmosis + Ultrafiltration (Cold WFI)

RO system along with ultrafiltration is also used sometimes for generation of WFI. Cold WFI can be produced that meets all the parameters required (USP, EP, JP, Etc.). This is similar to purified water with additional control of bacterial endotoxin.

WFI STORAGE AND DISTRIBUTION SYSTEM

WFI storage and distribution system is also quite similar to purified water generation system. Its controlling and distribution mechanism also remain almost the same except the temperature of water. In WFI generatedater is collected to WFI storage tank and kept circulated with temperature of 80-90 C. Other design parameters, MOC, components, systems, monitoring parameters, etc. are almost the same.

As generated WFI is coming to tank at @ 80-90 C, tanks are usually maintained at similar temperature. Additional heaters/jacketed heating is provided to maintain the temperature.
Sanitization of distribution loop :

As the system operates at a higher temperature of 80-90 C with continuous recirculation velocity of 1 meter/sec, this is considered as self-sanitizing system. If loop is maintained at low temperature, periodic sanitization at 80-90 C is recommended. SIP (Steam In Place) also can be done with tank and loop with condensation removal at user point and return loop.

Following are main components of WFI storage and distribution loop.

- WFI storage tank
- Circulation pump
- Back pressure valve
- Vent filter
- Pressure safety valve
- Rupture disc
- Spray ball
- Sight glass and light glass

- Auto dumping valve
- Level transmitter
- Temperature element and transmitter
- Temperature control valve for steam
- Compound pressure gauge
- Pressure gauge
- Conductivity sensor and transmitter
- Flow transmitter
- SS 316L pipeline with standard TC fittings

WFI Storage Tank

The size of the tank is based on the feed flow rate from the generation system and the peak load of the user points. The tank is vertical with top and bottom dished end made torispherical, so as to maintain full drain ability of water in the tank. Tank is fabricated from SS 316L material and internally electro-polished to a surface finish of < 0.5 µ Ra.

Jacket has provision for steam inlet which will be utilized to maintain the temperature of WFI as per set point of temperature transmitter installed in the return line of the distribution system.

Circulation Pumps

Two centrifugal pumps will be mounted on distribution skid. Pump will be continuously operational at desired flow rate and pressure, as per demand and minimum flow in return line. One pump would be working and other will be in standby. Standby pump as always flushed with discharge water of working pump to avoid bioburden. Drain valves are provided to the pump.

Back Pressure Valve

Back pressure valve will be installed at the end of recirculation line in the tank, to maintain the return line pressure and water fill in the line.

Vent Filter

The tank is vented to allow filling, and a filter is used at the vent to avoid airborne particulate and microbial contamination inside the tank. To avoid the problem of condensation in the filter and the resultant potential for colonization and growth, hydrophobic vent filters are used, and/or the filters are maintained at a temperature above the tank temperature with electrical heat tracing. Surface temperature element and transmitter will monitor during sanitization. Pressure gauge is installed on vent filter to measure the pressure inline.

MOC of housing shall be SS316L and MOC of membrane for vent filter is single layer PTFE.

Pressure Safety Valve

Steam safety valve is provided on the limpet inlet line to the storage tank.

Rupture Disc

Sanitary type rupture disc shall be installed on top dish of storage tank. If the pressure increases inside the tank to above the set limit, then the rupture disc will burst, releasing the excess pressure created inside the tank, for tank safety.

Spray Ball

Water inside the tank must be avoided from getting stagnant and thereby from increasing the bio-load. In order to avoid the same, spray ball is incorporated in the return line of distribution loop, inside the storage tank which will ensure that tank interior surfaces are flushed continuously to avoid the formation of biofilm.

Sight Glass And Light Glass :

Sight glass and light glass provision is made on the tank for inspection and monitoring. t These are placed opposite each other.

Auto Dumping Valve

2-way diverter valve will operate on the basis of feedback from conductivity transmitter in return line. If conductivity exceeds its set limit, valve will open to drain and will close return line flow to storage tank, till the normal value is achieved.

Level Transmitter

A level transmitter will be installed in storage tank for monitoring and controlling level of water in WFI storage tank. It has four set points. It operates on the basis of the feedback from PLC signal for low, low low, high, and high high levels. At H level filling will start, at HH level filling will stop, at L level pump will start, and at LL pump will trip.

Temperature Element And Transmitter

Temperature element cum transmitter will be side mounted on tank. It will monitor and control the temperature of water in tank during the process, and will ensure that the operating temperature is within designed limit.

Temperature Control Valve For Steam

It will maintain the temperature of water during process, on the basis of feedback from temperature element and transmitter installed on tank.

Compound Pressure Gauge

Compound pressure gauge will be installed on top dish of tank and will continuously monitor pressure within the tank. It can display both positive and negative (vacuum) pressures.

Pressure Gauge

Pressure gauge will be installed on the discharge of centrifugal pumps to measure the pressure of water flowing inline.

Conductivity Sensor And Transmitter

Conductivity sensor cum transmitter will be installed on return line to monitor the most critical parameter, i.e., conductivity. If conductivity exceeds its set limit, PLC will give signal to the flow diverter valve in return line, and the valve will close its inline flow and will drain the water completely out of the system till the desired conductivity is achieved. The same unit shall be used to measure the return line temperature.

Flow Transmitter

Flow transmitter will be installed on return line; it will measure the flow/velocity in the return line.

If the flow/velocity increases or decreases than the set point, PLC gives the signal to VFD to either increase or decrease the speed of the pump to match the set point velocity.

As there will be no consumption at the POU, only minimum amount of flow is maintained in the loop.

SS 316L pipeline with standard triclover fittings

Pipes

Stainless steel tubes with beads removed should be used; material shall be as per ASTM A 270 TP 316L ERW, 16 SWG; internal finish shall be electro polished to better than 0.5 Ra, and externally it should be mirror polished to 180 grit.

Elbows

SS 316L Elbow R = 1.5 D, made out of ASTM A 270 TP 316L, 16 SWG tube with bead removed. Wall thickness should match with respective pipe wall thickness. Internal finish shall be electro polished to better than 0.5 Ra and externally mirror polished to 180 grit.

Tees

SS 316L equal tee, made out of ASTM A 270 TP 316L ERW, 16 SWG tube with bead removed. Wall thickness should match with respective pipe wall thickness. Internal finish shall be electro polished to better than 0.5 Ra, and externally mirror polished to 180 grit. All welding shall be automatic TIG orbital welding without external filler wire.

Concentric Reducer

SS 316L concentric reducer, wall thickness should match with respective pipe wall thickness. Internal finish shall be electro polished to better than 0.5 Ra, and externally mirror polished to 180 grit.

Eccentric Reducer

SS 316L eccentric reducer, wall thickness should match with respective pipe wall thickness. Internal finish shall be electro polished to better than 0.5 Ra, and externally mirror polished to 180 grit.

TC Ferrule

SS 316L TC ferrule, made out of 316L, wall thickness should match with respective pipe wall thickness. Internal finish shall be electro polished to better than 0.5 Ra, and externally mirror polished to 180 grit.

TC Blind Ferrule

SS 316L TC blind. Wall thickness should match with respective pipe wall thickness. Internal finish shall be electro polished to better than 0.5 Ra, and externally mirror polished to 180 grit.

Gaskets

PTFE enveloped with Viton insert, steam resistant, food grade, class VI plastic.

Tri clamps

SS 304 Tri clamps, 2 segments heavy duty with metal wing nut and ‘O’ rings, mirror polished to 180 grit.

2. Pure Steam Generation

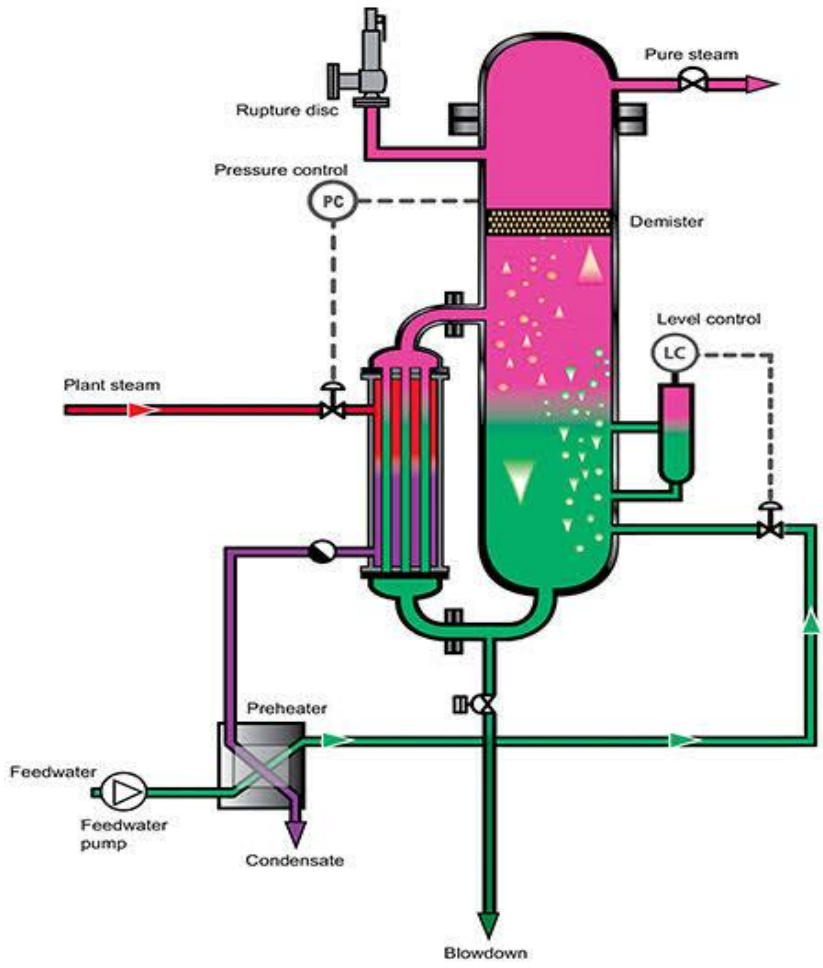
Pure steam is also known as clean steam; it is defined as saturated steam produced from additive-free water, free from non-condensable gases, and dry. Pure steam is used to prevent contamination of vessels, piping distribution systems, and sterile rooms.
Following are the specification of pure steam

Sr. No.	Test	Specification
	MICROBIOLOGICAL STANDARDS	
1	Endotoxins	< 0.25 Eu/ml
2	T.O.C.	< 500 ppb
3	Conductivity	< 1.25 µS/cm
4	Microbial limit	< 10 cfu/100 ml
	PHYSIO CHEMICAL STANDARDS	
1	Ammonia	< 0.2 ppm
2	Calcium	< 0.5 ppm
3	Carbon dioxide	< 4.0 ppm
4	Heavy metals	< 0.1 ppm
5	Total solids	< 0.001 %
6	Chlorides	< 0.5 ppm
7	Sulphates	< 0.5 ppm
8	pH	5 – 7

Pure steam is used for sterilization of products, sterilization of vessels/piping/accessories, sterilization of garments, sterilization in micro labs, etc. For sterilization, temperature of 121 C is maintained for at least 15 minutes.

Pure steam generators are used for generating pure steam. Often the WFI first column also can generate pure steam. The steam generator produces a sterile and pyrogen free clean steam conforming to "Uncondensed W.F.I" standards, suitable for sterilizing medical equipment as machine parts, pipe lines, tanks, etc., at a pressure of 2 to 4 bar corresponding to a temperature of 136 deg C to 152 deg C.

Its design is very similar to the first column of a multi column distillation plant. The feed water is purified water/WFI, first pre-heated to reduce pressure fluctuations in evaporator column, and to remove non-condensable gases. Further, this water enters the column, and is heated and gets converted into steam. This steam is distributed to the user point by SS 316 distribution lines, which are provided with slope and steam trap at 30 Mtr distance, as well as at user point, so as to remove condensate continuously as well in start-up.



Pure steam generator

Major components of pure steam generator

- Feed water pump
- Pre heater
- De-aerator
- Pressure column
    a. Evaporator
    b. Separator
- Vent filter
- Sight glass
- Steam trap
- Control valve
- Safety valve
- Temperature sensor
- Pressure switch
- Conductivity transmitter
- Conductivity sensor
- Pressure gauge/indicator
- Pressure transmitter

Feed Water Pump

Feed water pumping system consists of centrifugal pump made from 316 grade stainless steel. Pump motor is a totally enclosed, fan-cooled design. Centrifugal pumps supply feed water at constant pressure.

Preheater

The feed water is preheated in the condenser to 180°F - 190°F (82° - 88°C), and then further heated in the feed water preheater. The preheaters are 316L grade stainless steel, double-tube sheet shell and tube heat exchangers.

De-aerator

The main function of the de-aerator is to remove non-condensable gases by the shower effect. The de-aerator maintains water level for the column

Pressure Column

Any column which is operates under pressure, or in which pressure more than that of the atmosphere is maintained can be called a pressure column. The external structure consists of TC end connection connect to evaporator, Bonnet at top most side, T.C connection at bottom, Spy glass at mid-section to view water level, stiffed ring at middle to meet aesthetic requirement, An orifice plate on column Duct with T.C fitting, where the pressure indicator is mounted.

Complete column assembly consists of the following.

1. Evaporator

Evaporator

Top Side

Bottom Side

The evaporator is built of SS 316L round tubes mounted in a cylindrical shell with the tube axis parallel that of the shell. The fluid flow inside the tubes and converted into steam production. . The major component of this evaporator is tube i.e tube bundle.

In a heat exchange, the inlet steam heats the water, converting it into water vapor. , . Heating is usually accomplished with steam at low pressure.

2. Separators

Separators are constructed of 316L stainless steel. Vapor separator consists of a steam separation process to ensure endotoxin removal during high and low flow conditions.

Baffle: this supports the tube bundle and directs the flow of fluid for maximum efficiency.

Cyclone: cyclonic separation is designed for efficient removal of particulates from the air, gas or liquid stream. A high speed rotating flow is established within a conical container called a cyclone. Cyclone separator delivers high separation efficiency at low pressure drop through an optimal flow path design.

Vent Filter

Pure steam generator is designed with hydrophobic sterile air vent filter. The vent filter traps the microorganisms and non-condensable gases from the air during suction and discharge of air through pure steam generator.

Sight Glass

Design application: to view the liquid level and evaporation in the column

Piping

The pure steam generator piping system is designed with 316L stainless steel, manually argon welded construction. The fitting is with TC clamp. The piping is designed to reduce condensation and ease of maintenance. MOC, slope, and construction is quite similar to WFI lines.

Gaskets

PTFE enveloped with Viton insert, steam resistant, food grade, class VI plastic.

Steam Trap

The pure steam generator is equipped with a device which eliminates steam condensate from the line. Usually, it is installed at 30 meter length of line, and every user points. Steam trap location shall be at just before the user point connection to ensure removal of condensate from line & ensuring saturated steam in line

Control Valve

The control valve regulates the rate of fluid flow as the position of the valve plug is changed by force from the actuator.

Safety Valve

When the pressure at the column is higher than the set pressure value, the safety valve pops up and releases the excess pressure in the column.

Temperature Sensor

Temperature sensor used to measure the temperature of pure steam, it shall be located at outlet of pure steam generator supplying pure steam to user points.

Pressure Switch

Its prime function is to control the exact pressure and release the excess pressure by opening the exhaust valve. The pure steam generator is equipped with pressure switches to control the following :

1. Compressed air pressure.
2. Pure steam pressure.
3. Feed water outlet pressure.
4. Plant steam pressure.

Conductivity Transmitter

The conductivity sensor is used to measure the conductivity of pure steam as well as in-feed purified water to pure steam generator To sense the Conductivity. The Conductivity sensor is provide For Feed water conductivity & Pure steam conductivity.

Pressure Gauge/Indicator

Pressure gauge measures pressure with respect to atmospheric pressure, which is normally expressed in pounds per square inch gauge (psig). These gauges are placed at :

1. Plant steam inlet
2. Feed water pump outlet
3. Column pressure
4. Compressed air

Pressure Transmitter

Pressure transmitter used to measure the outlet pressure of pure steam and to control the pure steam pressure of main header, it shall be located at outlet of pure steam generator supplying pure steam to user points.

3. Testing of Pure Steam

Steam Quality Testing (SQT) consists of three individual tests designed to test the performance of a steam generation system. These tests demonstrate the quality of steam and therefore its suitability for its intended used to test the Non Condensable Gases (NCGs) Steam Dryness. Superheat. Of pure steam.

Steam is a critical variable in the success and repeatability of the sterilization process. As such, steam quality should be part of the validation of any steam sterilizer.

Steam quality is defined as the measurable physical aspects of steam used for sterilization. These physical aspects include temperature (superheat), dryness (liquid water content), and non-condensable gas content. (Steam quality does not measure the impurity content of the steam.)

Deviations from established ranges of these aspects of steam can result in the following issues :

- Wet loads.
- Damaged loads.
- Unsterile loads.
- Sterilization (biological and chemical) indicator failures.
- Staining and corrosion of instruments and containers.

Almost every sterilizer manufacturer recommends 97% pure steam.

With careful design, following well-established principles, and proper maintenance, the system (steam supply and sterilizer) can be engineered to provide a large margin of security against steam quality noncompliance.

For a production or GMP environment, steam quality testing should be part of annual preventative maintenance and qualification testing.

Steam Quality (SQ) Testing Methods and Acceptance Criteria

When steam quality testing is performed, three parameters are measured:	
Steam dryness	The amount of the steam by weight, i.e., how much is steam and not liquid water.
Non-condensable gases	The amount of the steam by volume that is not steam or water, but is air or other gases, which does not contribute meaningfully to sterility of the load.
Superheat	The temperature of the steam above the temperature of saturated steam for a given moisture content.

Steam Dryness	Non-condensable gases	Superheat
>0.95 w/w*	≤3.5% v/v	≤25K

*For laboratory autoclaves, >0.90 w/w is considered acceptable.

Steam Dryness

Steam dryness is calculated by measuring the temperature change in a known amount of water in relation to the mass of steam that is required to cause that temperature change. Ideally, the temperature rise is exactly proportional to the amount of steam delivered to the water to heat it, resulting in a dryness value of 1.0 (i.e., perfectly dry steam with no liquid water content.) Normally, the dryness value is less than 1.0, as there are thermal losses in any piping system even if it is well insulated. Because the dryness value of the steam at the chamber entry point can be quite a bit lower than the dryness value in the sterilizer, measurements of steam dryness should be made at both locations.

The acceptance criterion for steam dryness (the fraction of steam relative to water – 1.0 = all steam, no water) is at least 0.95, or 95% by weight. A dryness level down to 90% is considered acceptable for laboratory autoclaves; however, steam below this value is considered to be wet steam.

Wet steam does not deliver as much energy to the load as >90% saturated steam, and can cause what is known as “Wet packs”. If the steam is wet, or if the saturation level has decreased since the last validation, the expected sterility assurance level is probably not being achieved. This is especially important for bioburden-based validations, since overkill cycles have more of a safety margin by their very nature.

Non-condensable Gases

Non-condensable gases are generally air, which is a poor sterilant compared to steam. As an example, a typical dry-heat sterilization exposure phase lasts upwards of two hours at a temperature of at least 160°C/320°F. Steam sterilization typically is done with exposure phases of 15 minutes at 121°C/250°F or 3.5 minutes at 134°C. The efficacy difference is notable. For comparison, consider a contact lens manufacturer that must sterilizer contact lens blisters to a 10-6 sterility assurance level. Sterilization can be performed using a steam/air mix cycle that runs at 122°C/252°F for 45 minutes with a steam/air mix of approximately 48% steam (using absolute pressures for the calculation). The same result can be achieved in 15 minutes with saturated steam alone.

In short, non-condensable gases decrease sterilization efficacy. As with wet steam, the sterility assurance level will be less than expected if non-condensable gas content has increased since product sterility validation. The percentage of non-condensable gases in the steam should be less than or equal to 3.5% by volume.

Superheat

The steam is sampled in free expansion into ambient air. The maximum temperature measured at a precise location in the jet is the temperature upon which the superheat analysis is based. When the temperature and moisture content do not match up, two things can happen:

1. If the moisture content is higher than saturation for the temperature, wet loads occur, as discussed previously.

2. When the moisture content is lower than saturation for the temperature, the condition is called superheat. In superheat, the steam is too dry and its energy content is too high. When the steam condenses on the load, the energy released is enough to melt plastic packaging, and actually char paper packaging. Neither is a good outcome.

The amount of superheat present in the steam should be no more than 25 °C (298.15 degrees Kelvin above the temperature in free expansion into atmosphere at the current atmospheric pressure. For all intents and purposes, this corresponds to an upper limit of 125°C in the measurement.

4. Summary and Conclusions

Pre-conditions for good quality of pharmaceutical water production are :

- State of the art design of water generation equipment is needed
- Appropriate pre-treatment technologies are required
- State of the art design of storage and distribution system is needed
- Close monitoring of pure media system and process is required
- Regular maintenance and sanitization is a must
- Skilled operation and maintenance personnel are a must-needed requirement

20. Approval

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Guidance on Compressed Air Systems and Nitrogen

CONTENTS

1. INTRODUCTION

To Define The Procedure For Management Of Compressed Air And Nitrogen Used In The Pharmaceutical Industry.

2. SCOPE

This Guidance Documents Is Applicable To Design Of Compressed Air And Nitrogen Distribution System For Pharmaceutical Formulation Plant/Site.

3. DESIGN OF COMPRESSED AIR SYSTEM

For Process Applications, Compressed Air Systems Should Include:

- On The Supply Side, I.E., Generation, Which Includes Compressors And Air Treatment.
- On The Demand Side, Which Includes Distribution And Storage Systems, Connecting The Gas To The Process Application.

The Supply Side And The Demand Side Of Compressed Air Systems Should Be Integrated, And Should Be Considered As A Complete System In Order To Leverage Overall Efficiency, And Ensure That The Required Air Quality Is Delivered At Specified Flow Rates And Pressures As Required.

This Section Of The Guide Focuses On The Supply Generation Side Of The Compressed Air System. The Supply Side Of The System Should Continuously Provide Clean, Dry Air At The Correct Pressure, Quality, And Flow.

The Design Of The Supply Side Of Compressed Air Systems Should Consider The Following:

- Compressors
- Filtration
- Air Receivers
- Dryers
- System Control

At The User Points, 0.2 Micron Sterile Filters Should Be Installed For Usage Of Air In Grade A And B Area. And For Other Impacted Areas Dominic Hunter Filters With 0.02 Micron Should Be Installed.

Possible Improvements To A System's Operating Efficiency Should Also Be Detailed, To Help Improve Sustainability And To Reduce Operating Costs.

A Single Generation System May Be Used For Both Instruments, Or Facility, Air And Process Air; However, Additional Criteria May Need To Be Met In Order To Achieve Quality Requirements For Process Air. Entire Systems Can Be Designed To Meet The Additional Criteria For Process Air. Alternatively, Further Treatment To Meet These Additional Criteria Can Be Given Only To Air In A Process Branch.

The Design Process Should Include A Risk Assessment To Ensure That The Proposed Design Is Fit For Purpose. The Assessment Should Consider Potential Systems Failures And Ensure That The Controls In Place Are Adequate To Mitigate Risks To Product Quality Or Patient Safety.

4. 4.1 ARRANGEMENT OF SUPPLY SIDE COMPONENTS

AIR DISCHARGED FROM A COMPRESSOR AT PRESSURE WILL USUALLY BE SATURATED AND CONTAIN PARTICULATE (USUALLY WITH A PARTICLE SIZE OF UNDER 10 MM, I.E., AT SIZES BELOW THE TYPICAL SIZE LIMIT OF AN INLET AIR FILTER). IF THE COMPRESSOR IS A LUBRICATED COMPRESSOR, THE DISCHARGE AIR CAN POTENTIALLY ALSO CONTAIN OIL AS A VAPOR OR PARTICULATE. TYPICALLY, OIL CONTENT IN THE DISCHARGE OF A LUBRICATED COMPRESSOR CAN BE AROUND 3 PPM. OIL REMOVAL FILTERS (COALESCING TYPE) SHOULD BE INCLUDED IN THE SEQUENCE IF LUBRICATED COMPRESSORS ARE USED.

WHEN USING A DESICCANT TYPE DRYER, THE TYPICAL ARRANGEMENT OF EQUIPMENT IS:

1. COMPRESSOR
2. GENERAL PURPOSE FILTER (IF PLACED AFTER A LUBRICATED COMPRESSOR, THIS FILTER WILL NEED COALESCING PROPERTIES)
3. OPTIONAL WET RECEIVER FOR CONTROL STORAGE, THAT PROVIDES PURGE AIR WHEN A DESICCANT TOWER REGENERATES, AND PREVENTS AN ARTIFICIAL PRESSURE DROP IN THE COMPRESSOR
4. DESICCANT DRYER
5. PARTICULATE FILTER (DESICCANT BEDS CAN MOVE DURING USE, GENERATING DUST WHICH CAN ESCAPE FROM THE DESCANT TOWER)
6. DRY AIR RECEIVER THAT IS RESPONSIBLE FOR CONTROLLING THE SYSTEM PRESSURE DURING PERIODS WHERE THERE IS A HIGH DEMAND FROM A DISTRIBUTION SYSTEM. THIS RECEIVER PROVIDES 'CAPACITANCE' OR STORED ENERGY TO CONTROL PRESSURE FLUCTUATIONS
7. OPTIONAL SYSTEM PRESSURE CONTROLLER, THAT IS RESPONSIBLE FOR CONTROLLING THE PRESSURE IN A SYSTEM AND CAN OPTIMIZE THE CAPACITANCE IN A DRY AIR RECEIVER. REDUNDANCY OF FILTERS OR DRYER WITH TRANSFER VALVES MAY BE NECESSARY TO ALLOW MAINTENANCE TO BE PERFORMED SAFELY WHILE A SYSTEM IS KEPT OPERATIONAL

Filter Effectiveness Is Dependent On Maintenance And Conditions. Higher Temperatures Reduce Effective Filtration Limits. Manufacturers Usually Rate A Filter's Efficiency At 20 °C (70°F) In Addition, Higher Oil Carryover Will Load A Filter More Rapidly. The Maintenance And Replacement Frequency For Filters Should Be Established In Conjunction With Specialist Suppliers, And Considering The Usage Pattern, System Design, And Ambient Conditions.

Replacement Frequency Of Filters At Generation Point And End User Point Also Depends On Site Specific Requirements, As Well As On Regulatory Inspections, Observations And Recommendations.

The Recommended Replacement Frequency Of Non-sterile Filters Is At Least Once In A Year During Operation Cycle.

For Sterile Filters In Parental Areas, The Replacement Frequency Depends On Usage As Well As Cycles Of Operations. Usually, The Frequency Is 30-45 Cycles Of Operations.

Monitoring Of Air Quality And Periodic Checks Of Filter Condition/Air Supply Quality Should Confirm That Designed Filter Change Frequencies Are Appropriate.

Monitoring Differential Pressure Across A Filter For Pressure Build-up Or Spikes May Not Be Appropriate, As A Collapsed Or Ruptured Element Could Yield A Very Low To No Pressure Differential, And Coalescing Filters May Not Show An Increase In Differential Pressure At The End Of Their Useful Life. Hence, A Procedure For Visual Checking At Regular Intervals Should Be In Place.

Filter Pressure Drops Can Also Vary Depending On The Throughput At The Time The Pressure Drop Is Measured.

4.2 EQUIPMENT SELECTION

Equipment Selection Should Start With A Review Of The User Requirements. Typically, A Specific Volume Flow Rate Or Mass Flow And Pressure Are Required For A Process.

4.3 AIR TREATMENT

Treating Compressed Air To Remove Contaminants Such As Dirt (Viable And Non-viable Particulate), Lubricant, And Water, May Use Equipment Such As:

- Compressor After Coolers
- Filters
- Separators
- Dryers At Centralized Generation System As Well As Pou As Per Requirements
- Air Receivers
- Traps
- Automatic Drains

A Variety Of Standards Can Be Used To Define Air Quality. A Commonly Recognized Standard Is Iso 8573-1:2010 (Reference 7, Appendix 8), Which Identifies Three Classes Of Contaminants:

1. Particulate
2. Water
3. Oil/Oil Vapor

ISO 8573-1:2010 DOES NOT DIFFERENTIATE BETWEEN VIABLE AND NON-VIABLE PARTICULATES. THEREFORE, WHEN USING ISO 8573-1:2010 TO DEFINE PURITY CLASS OF COMPRESSED AIR, FURTHER DEFINITION MAY BE REQUIRED IN THE USER REQUIREMENTS. ISO 8573.2 THROUGH ISO 8573.7 DEFINE TEST METHODS FOR MONITORING THE VARIOUS CONTAMINANTS, BUT THESE HAVE NOT BEEN WIDELY ACCEPTED BY THE PHARMACEUTICAL INDUSTRY. FOR FURTHER INFORMATION ON MONITORING, SEE SECTION 6 OF THIS GUIDE.

THE TABLE BELOW SHOWS AIR QUALITY PARAMETERS/LIMITS AS PER ISO 8573-1:2010

Table-1: ISO 8573-1:2010 Air Quality Class

Quality Class	Max Number of Particles per m3			Water Pressure Dew Point (at Atmospheric Pressure)		Oil and Oil Vapor
	0.1-0.5micron	0.5-1.0 micron	1.0-5.0 micron	° F	° C	mg/m3
0	As specified by the user or equipment manufacturer and more stringent than class 1					
1	≤20000	≤400	≤10	-100	-70	≤0.01
2	≤400000	≤6000	≤100	-40	-40	≤0.1
3	-	≤90000	≤1000	-4	-20	≤1
4	-	-	≤10000	37	3	≤5
5	-	-	≤100000	45	7	>5
6	-	-	-	50	10	>5

FOR NVPC AND VPC TESTS, SPECIFICATIONS CRITERIASHOULD BE SAME AS HVAC QUALIFICATION FOR RESPECTIVE AREAS, GRADE WISE CRITERIA MENTIONED BELOW IN TABLE:

Test Description	Frequency	Limits	Location
Compressed Air/Nitrogen Non-Viable Particulates Count (NVPC) Viable Particulates Count (VPC)	Grade A: every 6 months. Grade B/C/D: every 12 months.	Same criteria as area/system/product where the gas is used.	Immediately downstream of Point-of-Use (POU) filter; representative POU, as specified in PQ or equivalent.

THE MEASUREMENTS RELATE TO STANDARD CONDITIONS OF 20°C (68°F) AND 1 BAR ABSOLUTE PRESSURE (14.5 PSI).

4.2 COMPRESSED AIR FILTERS

COMPRESSED AIR FILTERS DOWNSTREAM OF THE NON-LUBRICATED AIR COMPRESSOR ARE NORMALLY REQUIRED FOR THE REMOVAL OF CONTAMINANTS.

FILTERS SHOULD MEET CRITERIA DEFINED IN THE USER REQUIREMENTS. TYPES OF FILTERS AVAILABLE INCLUDE:

- PARTICULATE FILTERS TO REMOVE SOLID PARTICLES,
- COALESCING FILTERS TO REMOVE HYDROCARBON DROPLETS, MOISTURE DROPLETS, AND PARTICULATES,
- ADSORBENT FILTERS TO REMOVE HYDROCARBON VAPORS AND OTHER AROMATICS (ODORS AND TASTES).

A PARTICULATE FILTER MAY BE RECOMMENDED AFTER A DESICCANT-TYPE DRYER IN ORDER TO REMOVE DESICCANT DUST. A COALESCING-TYPE FILTER MAY BE RECOMMENDED BEFORE A DESICCANT-TYPE DRYER TO PREVENT FOULING OF THE DESICCANT BED IF A LUBRICANT INJECTED COMPRESSOR IS USED UPSTREAM, OR THE LOCAL AIR QUALITY MAY PROVIDE A RISK OF HYDROCARBON IN THE COMPRESSOR DISCHARGE.

Filter Grades Of 0.45 Mm Or 0.2 Mm May Be Employed At Pous. When Reviewing Filters For Their Applicability, Particle Size Removal Ratings (E.G., 0.2 Mm), And The Filter Efficiency Ratings (E.G., 99.97% Efficient) Should Be Reviewed. These Ratings Are Normally Based On Defined Inlet Conditions, Usually 70°F (21°C) At 100 Psig. If The Inlet Conditions Vary From Those Specified, The Filter Manufacturer Should Provide Advice Regarding The Performance Data Based On The Actual System Conditions.

A Typical Sequence Of Filters For A System Is:

1. Particulate Filter: Typically, 1 Mm To 3 Mm For Removing Rust, Pipe Scale, Metal Oxides, And Desiccant Particles.
2. High Temperature Particulate Filter: Temperature Spikes Can Occur When Using A Heated Desiccant Dryer. When The Regenerated Tower Comes Back Online, Heat Generated During Regeneration Is Picked Up By The Compressed Air. Similar Ratings To Standard Particulates Apply, But Can Withstand The Higher Operating Temperatures To 350°F To 450°F (176.7°C To 232.2°C).
3. Coalescing Filters: Coalescing Filters Are Rated For Particle And Liquid Aerosol Droplet Removal. Liquid Droplet Removal Capacity Is Typically 0.001 Ppm By Weight And Aerosol Size Rated At 0.01 Mm.
4. Final Filter: A 0.2 Mm Liquid Rated Cartridge Filter (Down To 0.003 Mm Absolute, Rated For Particles In Gases) May Be Used As A Final Filter To Obtain 'Sterile Grade' Compressed Air. These Filter Cartridges Are Typically Sanitary Style To Minimize The Risk Of Bypass, And Incorporate A Hydrophobic Non-volatile Membrane As The Filter Media.
5. Replacement Frequency Of This Filter Should Be Based On Scheduled Integrity Testing As Well As Recommended Use Of Cycles.

POUS ARE USER POINTS IN AREA WHERE COMPRESSED AIR IS CONSUMING FOR VARIOUS USE SUCH AS PNEUMATIC USE, USE IN PROCESS, ETC. THIS CAN BE BIFURCATED AS CRITICAL/NON-CRITICAL USER POINTS WITH RESPECT TO POINT OF USE. ACCORDINGLY, FILTRATION AND QUALITY SAMPLING/TESTING SHALL BE DETERMINED.

Figure 1
Sterilizing Filter Cartridges and Housing Assemblies for Compressed Air

4.5 AIR RECEIVERS

RECEIVERS CAN BE USED TO PROVIDE SURGE CAPACITY TO MEET PEAK PROCESS NEEDS AND MINIMIZE CHANGES IN SYSTEM PRESSURE DURING PERIODS OF PEAK DEMAND.

COMPRESSED AIR SYSTEMS REQUIRE A RECEIVER. WHEN DEMAND PEAKS ARE SHORT AND LIMITED (USUALLY LESS THAN 60 TO 90 SECONDS), A LARGE AIR RECEIVER MAY ALLOW A SMALLER NON LUBRICATED AIR COMPRESSOR TO BE SPECIFIED. ADDITIONAL BENEFITS INCLUDE THE:

- Improved System Reliability, As The Load Cycles On The Compressor Are Reduced.
- Increased Efficiency, As The Likelihood Of Another Compressor Starting Is Minimized.

A Desiccant Dryer's Purge Can Be The Temporary Push To Peak Demand. Given The Cyclical Nature Of Purge, It Creates A Temporary Artificial Demand On The Compressor For A Brief Period, But Can Be Invisible To The Compressor Controls With A Wet Air Receiver (I.E., An Air Receiver Placed Before A Purge Type Desiccant Dryer).

A Receiver Placed Downstream Of Air Treatment Equipment Can Be Used To Manage Pressure Variation In A Distribution System.

A Rule Of Thumb Used For Sizing A Receiver Is To Use A Unit With A Capacity Of 6 To 10 Times The Compressor Peak Capacity (Free Air Delivery/Second).

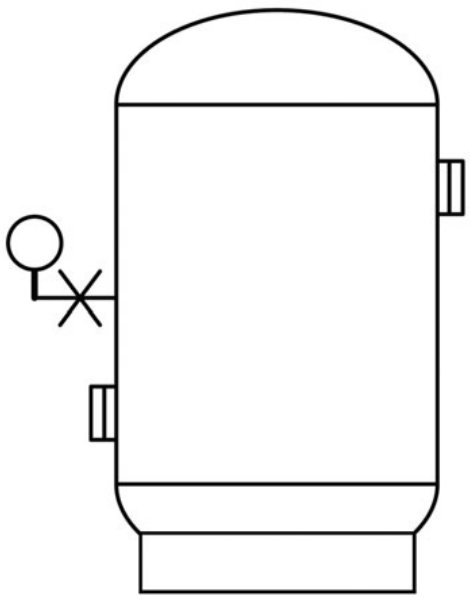


Figure 2
Typical Air Receiver

4.6 TRAPS AND DRAINS

Traps Or Drains Allow The Removal Of Condensate From The Compressed Air System To Protect The Equipment Being Supplied By The System From The Effects Of A Non-compressible Fluid. Automatic Condensate Traps Are Used To Conserve Energy By Preventing The Loss Of Air Through Open Petcocks And Valves.

Methods To Drain Condensate Include:

1. Mechanical Traps,
2. Solenoid Actuated Drain Valves,
3. Zero Air-loss Traps With Reservoirs,
4. Manual.

4.6.1 MECHANICAL TRAPS

These Are Usually Float-type Mechanical Traps With Inverted Buckets As A Secondary Design Feature. Float-type Traps Are Designed To Open Only As Increasing Condensate Raises The Water Level, And Consequently, It Floats. Before The Water Is Fully Evacuated, The Float Reseals The Trap, To Prevent Waste Of Air. These Traps Can Easily Be Blocked By Buildup Of Particulate In The Condensate. The Inspection And Maintenance Of These Traps Should Be Incorporated Into A Maintenance Program. Inverted Bucket Traps May Require Less Maintenance. The Condensate Rate Should Be Sufficient To Maintain The Liquid Level In The Trap To Prevent Loss Of Air.

4.6.2 SOLENOID ACTUATED DRAIN VALVES

SOLENOID ACTUATED DRAIN VALVES ARE ELECTRICALLY OPERATED AND EMPLOY A TIMED SEQUENCE FOR OPENING AND CLOSING.

CONCERNS INCLUDE:

- THE OPEN INTERVAL DURATION MAY BE INADEQUATE TO EVACUATE ALL CONDENSATE.
- THE CLOSED INTERVAL MAY BE TOO LONG, CREATING A BACKUP OF CONDENSATE INTO THE COMPRESSION STAGES.

IN THE ABSENCE OF CONDENSATE AND WHERE EQUIPMENT IS LIGHTLY LOADED, COMPRESSED AIR MAY BE ALLOWED TO ESCAPE.

THE SETTINGS ON THESE UNITS SHOULD BE REVISED DEPENDING ON SEASONAL VARIATION IN OUTSIDE AIR SUPPLIED TO A SYSTEM.

4.6.3 ZERO-AIR-LOSS TRAPS WITH RESERVOIRS

ZERO-AIR-LOSS TRAPS CAN IMPROVE EFFICIENCY OF A COMPRESSED AIR SYSTEM. TYPES OF TRAPS INCLUDE:

1. SOLENOID ACTUATED WITH LEVEL SENSOR.
2. PNEUMATICALLY ACTUATED AIR CYLINDER AVAILABLE WITH ZERO AIR LOSS TRAPS WHICH MINIMISES THE MAINTENANCE AND WITH NO AIR LOSS WITH LARGE ORIFICES. ALSO TYPICALLY PREVENTING THE BUILD OF PARTICULATE IN THE TRAP.

Strainers Are Recommended For All Traps To Prevent The Likelihood Of Sediment Blocking The Passage Of Condensate.

For Systems Designed With A Lubricant Injected Compressor, Condensate Can Be Contaminated With Entrained Lubricant, And Removal Of Lubricant May Be Required Before The Condensate Is Discharged To A Sewer System.

Regional Municipalities Should Be Consulted For Allowable Contamination Levels. An Oil Water Separation System Should Be Included In The Design Of The System, Or The Facility Drains As Required.

4.6.4 MANUAL METHODS

Manual Methods Are Typically Ball Valves Which Require Opening To Discharge Condensate. Manual Valves Are Not Recommended Since They Are Frequently Left Open To Drain Condensate From Moisture Separators, Intercoolers, Refrigerated Dryers, And Filters, Allowing Valuable Compressed Air To Continually Expand To Atmosphere.

5 COMPRESSED GASES/AIR BEST PRACTICES AND MONITORING

- Personnel Involved In Sampling And Testing Shall Be Trained To Perform Respective Duties, Including Training In Aseptic Gowning, Aseptic Area Technique, If Entering Aseptic Manufacturing Areas To Sample.

- Compressed Gases/Air Used For Process Requirements And/Or Pneumatic Operations In Sterile Product Manufacturing Facilities Shall Meet The Same Environmental Criteria As The Classified Areas Within Which They Are Used. These Gas/Air Systems Shall Be Qualified And Periodically Tested To Ensure That Total Non-viable And Viable Particulate Limits Are Not Exceeded. Microbial Monitoring Samples Of Compressed Gases Other Than Compressed Air, Such As Nitrogen, Should Be Incubated Anaerobically.

- Compressed Gases/Air In Direct Contact With Non-sterile Product, Such As Granulators, Shall Be Qualified And Periodically Tested To Ensure That Total Non-viable And Viable Particulate Limits Are Not Exceeded.

- Devices Used For Total Particulate And Viable Sampling Of Compressed Gases/Air Shall Be Specially Designed To Account For Supply Pressure, And Be Calibrated And/Or Standardized And Qualified For Use.

- The Table Below Provides Minimum Requirements For Em Of Compressed Gases/Air

Table-2 : Minimum Monitoring Requirements for Compressed Gases

Test	Testing Frequency	Limits	Location
Sterile Manufacturing Facilities and Classified Areas within Non-Sterile Manufacturing Facilities.			
Compressed gas – viable and non-viable particulates	Grade A: every 6 months. Grade B/C/D: every 12 months. Viable particulates of gas/air that is in contact with product. Every 6 months.	Same criteria as area/system/product where the gas is used.	Immediately downstream of POU filter; representative POU, as specified in PQ or equivalent.
Sterile and Non-Sterile Manufacturing Facilities			
Compressed gas –nitrogen-purity, moisture content, CO, CO_2, O_2 Compressed air - hydrocarbon content (oil traces) and moisture content, O_2, CO_2, NO_x, SO_2.	Every 12 months USP/Ph. Eur. gas Certificate of Analysis/Compliance required for every delivery.	USP/Ph. Eur. Test Specification	Farthest outlet (from the compressor) of each branch/pipe system serving to each building
Note: The requirements mentioned above are the minimum to be followed for routine monitoring. Initially, the monitoring should be more frequent to establish routine monitoring program.			

❖ WHERE MICROBIAL-RETENTIVE FILTERS ARE USED ON COMPRESSED GASES IN GRADE A/B ASEPTIC FILL AREAS (WHERE GASES ARE REQUIRED TO BE STERILE), THESE FILTERS ARE ALSO SUBJECT TO FILTER VALIDATION AND SHALL BE TESTED FOR INTEGRITY BEFORE INSTALLATION AND WHEN BEING REPLACED AFTER USE.

6 COMPRESSED AIR/NITROGEN SAMPLING AND TESTING PROCEDURE

(NOTE: BELOW ARE SOME OF THE METHODS FOR COMPRESSED GASES TESTING; THESE MAY DIFFER SITE BY SITE AS PER REQUIREMENTS).

Option 1

Sampling Procedure for Hydrocarbon (Oil Mist) Content

1. The compressed air point should be selected.
2. The connectors should be attached to the compressed air sampling point.
3. The flow of compressed air should be set as per requirement.
4. A known volume of air is passed through filter cassette holder containing filter paper membrane of known micron size (0.2 µ).
5. About thousand (1,000) liters of compressed air should be passed while maintaining a constant flow.
6. After completion of sampling, the filter paper should be removed and kept under cover for analysis.
7. The airborne particles trapped on the membrane should be further analyzed using using an IR spectrophotometer, as per following details:
   - ❖ IR Scan Region: 3200 to 2700 cm-1
   - ❖ Analysis Method No.: 5026 [NIOSH - National Institute of Occupational Safety and Health].

Compressed Air Sampling Procedure For Moisture Content

1. The compressed air point should be selected.
2. The connectors should be attached to the compressed air sampling point.
3. The flow of compressed air should be set as per requirement.

DEW POINT(°C)	MOISTURE/PPM (Vol/Vol)
- 66	4.59
- 60	10.6
- 55	16.0
- 50	38.8
- 45	71.6
- 40	127.0
- 35	222.0

DEW POINT(°C)	MOISTURE/PPM (Vol/Vol)
- 30	376.0
- 25	629.0
- 20	1020.0
- 15	1640.0
- 10	2570.0
- 5	3980.0
0	6020.0
+ 5	8630.0
+ 10	12120.00

4. A known volume of air is passed through a U-Tube, of predetermined weight containing CaCl2
5. After completion of sampling, the U-Tube is removed and weighed once again on the same balance.
6. The difference is further calculated to give result in ppm, which can be related to dew point (0C) table relating moisture content (ppm) with dew point (OC)

Compressed Air Sampling and Analysis Procedure for Dust Level Analysis for Non-Viable Particle

1. The compressed air point should be selected.
2. The connectors should be attached to the compressed air sampling point.
3. The flow of compressed air should be set as per requirement.
4. The compressed air should be pass while maintaining a constant flow through a tube.
5. The sampling probe of the particle counter should be inserted into the tube.
6. The particle counter should be started to start the sampling. .
7. After completion of sampling, the instrument should be switched off.

8. The reading should be downloaded into a computer.

9. In one example, the airborne particles trapped on the membrane were analyzed to give the particle size range, e.g., the number of particles in the range between 0.3 –0.5 µ, 0.5 – 1.0 µ, 1.0 – 2.0 µ, 2.0 – 5.0 µ, etc.

Microbiological Test for Total Viable Counts

Method f Sampling

During sample collection, compressed air stream is passed through filter cassette holder, containing sterile filter paper, while maintaining a constant flow, adjusted by a rotameter, for 30 minutes. After completion of sampling the filter paper is transferred to a neutral agar plate, and allowed to incubate, and thereafter, analyzed for the number of counts.

Media Used: Nutrient Agar (Ref. Himedia M 001)

Media Preparation and Methodology:

- Nutrient Agar: 5.6 gm of dehydrated media is suspended in 200 ml of water in a conical flask and autoclaved for 15 minutes at 15 pounds pressure (or 1210 C).

- 15 ml of nutrient agar, cooled to 50 0C, is poured in the sterile petri plate; the filter paper which was exposed to compressed air is placed on the agar. The plate is incubated for 72 hours at 22 0C. and for 48 hours at 37 0C.

- After incubation, the number of colonies developed on the filter paper is noted. The numbers of colonies are reported as Total viable bacterial count per filter paper piece.

Compressed Air Sampling and Analysis Procedure for CO, CO2

1. Compressed air is collected in a rubber bladder.

2. The sample is analyzed by Gas chromatograph using methaniZer on Flame Ionization Detector [FID] using the Calibration gas as standard for this purpose.

   Parameters:
   - Oven temperature: 500C
   - Injection temperature: 100 0C
   - Detector temperature: 200 0C
   - Column: - Porapac N

- Methanizer temperature: 300 0C
- Quantity of gas injected: 1 ml.
- Carrier gas flow: 10 ml.
- FID gain: 1000

Sampling and Analysis Procedure for Compressed Air for O2

1. A compressed air is collected in a rubber bladder.
2. The sample is analyzed on gas chromatograph using TCD detector using the calibration gas as standard for this purpose.

Parameters:

- Oven temperature: 400C
- Injection temperature: 100 0C
- TCD detector temperature: 80 0
- Column: Molecular
- Quantity of gas injected: 1 ml.
- Carrier gas flow: 10 ml.
- TCD gain: 10
- TCD filament temperature: 450 0C

Compressed Air Sampling Procedure: Option2

Non-Viable Particle Count Test

1. The test shall be perform using light –scattering discrete-particle counter.which is to be operated as per manual.

2. For measurement of particle count, it is to be ensured that the compressed air line is working in peak condition.

3. The particle count test kit should be placed at the sampling location.

4. The compressed air sampling point should be connected with 100 LPM compressed air diffuser.

5. The compressed air should be flush out for 1 minute.

6. Sampling point details should be added in the particle counter.

7. The outlet of the diffuser should be connected with the particle counter.

8. The particle counter should be run with the sampling amount as per client protocol.

9. The set cycle should be allowed to be completed.

10. The counts of 0.5 µm and 5.0 µm should be recorded in the report.

Tests to be done for Compressed Air Quality Checks

Sr. no.	Test	Test Method
1	Dew point test	With dry ice or with pressure transmitter
2	Water vapor content	GASTEC tubes
3	Traces of oil	GASTEC tubes
4	Carbon dioxide	GASTEC tubes
5	Carbon monoxide	GASTEC tubes

1. Compressed Air Sampling Procedure for Dew Point Test

Dry Ice Method

Dew point test kit has the following components

a. Closed glass chamber,
b. Condenser pipe,
c. Digital thermometer.

1. The dew point testing kit should be carefully placed at sampling point.
2. The compressed air line should be connected with the air connection port of the dew point testing kit.
3. The compressed air line valve should be opened.
4. The acetone in the condenser pipe should be transferred.
5. The thermometer probe should be placed in the condenser pipe; it should be ensured that the probe is properly placed in the acetone solution.
6. Dry ice should be slowly added in the acetone, in order to decrease the temperature inside the condenser tube.
7. The surface of condenser tube inside the glass chamber should be carefully observed for condensation from the compressed air.
8. When such condensation is observed, the temperature should be recorded. This is the dew point.
9. The test should be repeated twice more on the same sampling point.
10. The dew point readings should be noted and the average reading taken.

Pressure Transmitter Method

1. The compressed air dew point transmitter should be placed at the compressed air testing point.
2. Compressed air should be flushed for 1 minute.
3. The compressed air line should be connected with dew point transmitter inlet.
4. The dew point transmitter should be started.
5. The compressed air sampling should be started.
6. The reading will be stabilized after 3-4 minutes (approx.). The stable reading should be noted down.

2. Compressed Air Sampling Procedure for Water Vapor Content

Parameters:

Gastec tube no.	:	6
Measuring range	:	0 to 18 mg/Ltr
Sampling volume	:	100 ml
Sampling rate	:	100 ml/minute
Sampling time	:	1 minute
Color change	:	Green to purple

3. Compressed Air Sampling Procedure for Oil Traces

Parameters:

Gastec tube no.	:	109 AD
Measuring range	:	0.2 to 5.0 mg/m^3
Sampling volume	:	20,000 ml
Sampling rate	:	1 Ltr/minute
Sampling time	:	20 minutes
Color change	:	Pale red to pale blue

4. Compressed Air Sampling Procedure for Carbon Dioxide

Parameters:

Gastec tube no.	:	2LC
Measuring range	:	100 to 2000 ppm
Sampling volume	:	100 ml
Sampling rate	:	100 ml/minute
Sampling time	:	1 minutes
Color change	:	Pale red to yellow

5. Compressed Air Sampling Procedure for Carbon Monoxide

Parameters:

Gastec tube no.	:	1 LC
Measuring range	:	1 to 30 ppm
Sampling volume	:	100 ml
Sampling rate	:	100 ml/minute
Sampling time	:	1 minute
Color change	:	White to pale pink

1	Oil/Hydrocarbon	NMT 0.1mg/m^3
2	Carbon dioxide	NMT 500 ppm
3	Carbon monoxide	NMT 5 ppm
4	Dew point temperature	PDP $\leq$ - 40 ^{0}C at generation point/PDP $\leq$ - 20 ^{0} at user points as per ISO 8573

Compressed Air Sampling Procedure : Option3

Compressed Air Sampling Procedure for Hydrocarbon (Oil Mist) Content

1. Oil indicator should be used for oil content measurement at user points.

2. The above step should be repeated for all user points.

Compressed Air Sampling and Analysis Procedure for Dust Level Analysis Non-Viable Particles

1. The air-borne particle counter (the high pressure diffuser) should be taken to the respective sampling rooms.

2. The user point should be connected to a stainless steel inlet of the high pressure diffuser, in order to diffuse the high pressure of air/gas.

3. The sampling probe of particle counter should be placed at the outlet of the high pressure diffuser, and 1cubic meter of air should be sampled.

4. The printout of the particle counter reading should be recorded.

5. The above steps should be repeated for all user points.

Compressed air sampling and Analysis Procedure for Gas Content

1. The respective gas detector tubes should be used for measuring gas contents.

2. The above step should be repeated for all user points and for all gaseous content measurements as required.

Sampling and Analysis Procedure for Compressed Air for Dew point

1. Use dewpoint meter to determine moisture content.

2. The above step should be repeated for all user points.

Definitions of Terms

DD Filter: range coalescing filters for general purpose protection, removing liquid, water, and oil aerosol to 0.1 mg/m3 (0.1 ppm), and particles down to 1 micron.

PD Filter: range with efficiency coalescing filters removing liquid, water, and oil aerosol to 0.01 mg /m3 (0.01 ppm) and particles down to 0.01 micron.

QD Filter: range activated carbon filter for removal of oil vapor and hydrocarbon odors by adsorption, with a maximum remaining oil content of 0.003 mg/m3.

FC Filter: range coalescing filters for general purpose protection, removing solid particles and small volumes of condensate and oil aerosol to 2 g/m3 , and particles down to 1 micron.

FE Filter: range with efficiency coalescing filters removing fine solid particles, condensate droplets, and oil aerosol to 1 g /m3 and particles down to 0.1 micron.

FF Filter: range with efficiency coalescing filters for general purpose protection, removing of solid particles, the smallest of condensate droplets, and oil aerosol to 0.1 g/m3 and particles down to 0.1 micron.

FG Filter: range activated carbon filter for removal of oil vapor and hydrocarbon odors by adsorption, with a maximum remaining oil content of 0.003 g/m3 .

AO Filter: range coalescing filters for general purpose protection, removing particles down to 1micron including water and oil aerosol content of 0.5 mg/m3 , and particles down to 1 micron.

AA Filter: range coalescing filters for removing particles down to 0.01micron including water and oil aerosol, providing a maximum remaining oil aerosol content of 0.01 mg/m3 ,and particles down to 0.01 micron.

ACS Filter: range activated carbon filter for removal of oil vapor and hydrocarbon odors by adsorption, with a maximum remaining oil content of 0.003 mg/m3 .

AR Filter: range with efficiency Dust dust filtration for the removal of dust particles down to 0.01 micron.

ZCPP2-005C: range with efficiency dust filtration of cartridge filter for the removal of dust particles down to 5 microns.

ZCPP2-1.0C: range with efficiency dust filtration of Domnick Hunter for the removal of dust particles down to 1 micron.

ZHFT/2C: range with efficiency dust filtration of Domnick Hunter for the removal of dust particles down to 0.2 micron.

7. Design of Nitrogen System

DESCRIPTION OF VARIOUS COMPONENTS/EQUIPMENT

A. AIR RECEIVER

Compressed air required at N2 system is at 170 CFM at 7.0 Kg/cm2G. The cold compressed air, after drainage of moisture, is taken to an air receiver to feed to the downstream system. This acts as a temporary storage of air for cyclic consumption in the system. This air receiver is equipped with pressure gauge, pressure transmitter, RTD, safety valve, ADT, and manual drain valve.

The cold compressed air is taken to an impingement baffle type air receiver. The moisture laden air hits the baffle plate, moves downwards thereby draining the moisture by gravity, and then moves up with a relatively low velocity.

An automatic drain trap drains off the moisture in pre-set intervals as controlled by an asynchronous timer. Refer Figure 2 for a typical air receiver.

B. PRE-FILTER

There is a pre-filter in the compressed air line provided with PP candle type filter element. This is required in order to restrict the flow of dust/foreign particle and physical water droplets with the compressed air supply. Filtration level is of 5.0 micron at 99% efficiency. In this filter, a lot of moisture gets condensed; therefore, manual drain valve are provided at the bottom of pre-filter. Flow direction of air should be outside to inside the filter element.

(Pre-filter is PP candle type filter element, of Sansuk make, and 5.0 Micron size).

Note: the filter element should be replaced when the differential pressure (between air inlet and PSA) is high. Maximum pressure drop should be 0.5 Kg/cm2g. The element should be replaced at intervals of 8000 hour of operation, or 1 year, whichever is earlier.

C. INSTRUMENT AIR POT

This acts as a temporary storage for instrument air. Dry instrument air at the pressure of 7.0 Kg/Cm2g is tapped from the bottom of the PSA unit from where the air goes for the operation of various valves. The pressure of the instrument air pot should remain above 6.0 Kg/Cm2g. This ensures optimum operation of PSA unit valves.

D. PSA UNIT

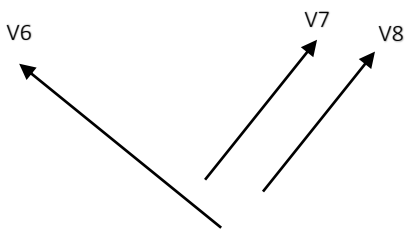
The dry compressed air is now taken to a twin tower PSA unit consisting of carbon molecular sieves. Two vessels are filled with special grade of alumina and CMS to adsorb moisture, oxygen and CO2 present in air. It is important to maintain the tightness of the beds with coconut fiber mats so as to avoid any sort of dusting or fluidization of the carbon molecular sieves.

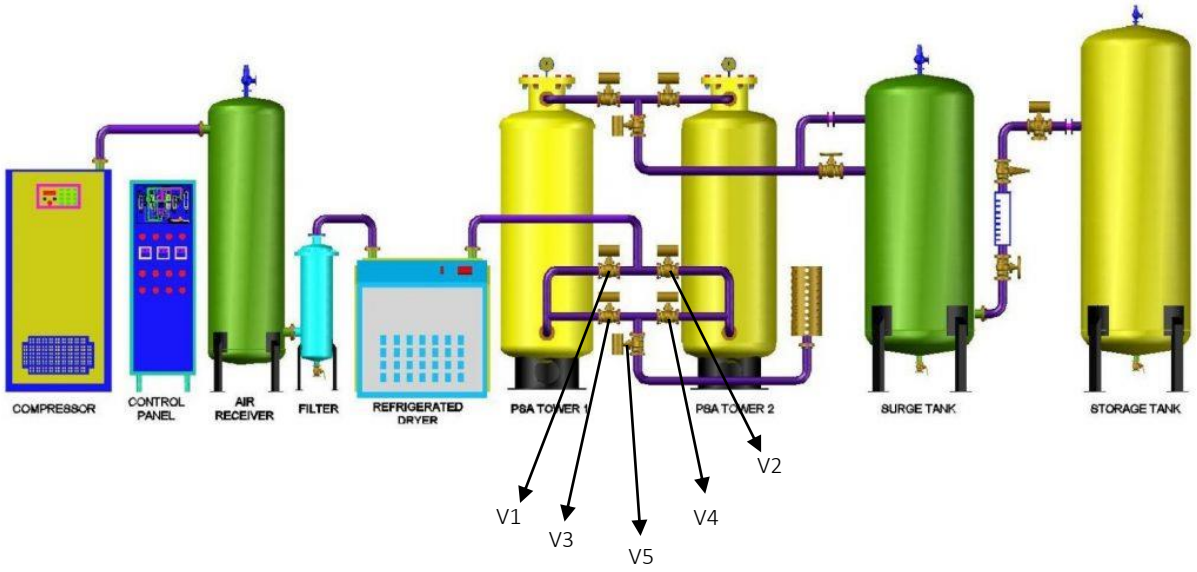
Each tower has air inlet valves (VI and V2) at the bottom, gas outlet valves (V7 and V8) at the top, and exhaust outlet valves (V3 and V4) also at the bottom. Besides these, a valve (V6) is for pressure equalization at the top and a valve (V5) after exhaust valves (V3 and V4) at the bottom. The air inlet line from air receiver has one (1) globe valve (V9) to control the flow of air, so that the pressure in the adsorbing towers goes to 10.0 Kg/Cm2g.

Separation of nitrogen from air is based on selective absorption of oxygen particles in carbon molecular sieves at high pressure. Carbon molecular sieves are adsorbent, with a large number of small pores; the diameter of these small pores are in the same range as those of the molecules of oxygen. Oxygen molecule have smaller diameter than nitrogen molecules; therefore, oxygen molecules enter these pores at pressures higher than 4.0 Kg/Cm2g.

During regeneration, the tower is depressurized to atmosphere to vent off the adsorbed oxygen.

For sequential operation of valves, please refer attached drawing-TIMER-PSA (Sequence Chart for PSA Unit), which is explained as under: At the time when Tower I is in operation valves V-1, V-7 (Inlet and Product valves of Tower –I) V-4 (Exhaust valve of Tower –II) are open. Air enters in Tower I from V-1, oxygen gets adsorbed as the air passes to top of tower and product nitrogen comes out from V-7. This phenomenon continues for 57.5 seconds. At 57.5 seconds, V-5 (common Exhaust valve) and V-6 (Common Product valve) closes. At 58.0 seconds, V-1 will close (Air inlet valve Tower –I) and V-3 (Diaphragm valve of Tower- I) and V-8 (Product valve of Tower II) will open. This is the condition when there is NO AIR INLET, NO PRODUCT OUTLET, . Since V-5 and V-6 are already closed, Nitrogen from Tower I will pass to Tower II (as V-7 and V-8 are open) and Air from Tower I will pass to Tower II (as V-3 and V-4 are open) Thus, Nitrogen passes from top to top, and air (predominantly Nitrogen) passes from bottom to bottom. This is called PRESSURE EQUALISATION. This phenomenon continues for 1.5 seconds. At 58.5 seconds, V-7 (Product valve of Tower I) and V4 (Exhaust valve of Tower II) closes, V-2 opens (Air inlet valve of Tower II). As V-8 (Product valve of Tower II) V-3 (Exhaust valve of Tower I) remains in open condition and V1 (Air inlet valve of Tower I) is in closed condition, Air will enter Tower II and Nitrogen will start coming out from V-8. This is called CHANGEOVER. Finally, at 60 seconds, V-5 and V6 will re-open.





E. NITROGEN SURGE VESSEL

Nitrogen from PSA module will have varying purity depending upon the pressure in the absorber during the one-minute cycle time. This vessel gives product nitrogen at constant pressure with constant average gas purity.

One pressure gauge and one manual drain valve are fitted with the vessel. In the surge tank, one globe valve (V10) is fitted to control the N2 gas production so as to maintain the pressure of around 6.0 Kg/Cm2g, for better performance of PSA. Just after equalization of PSA, the PSA tower pressure is around 3.5 to 4.0 Kg/Cm2g, whereas the surge vessel operates at higher pressure than PSA, i.e., at 5.8 to 6.0kg/cm2g. Hence, production from PSA tower will not be there until the pressure of PSA tower rises above 5.5kg/cm2g. To increase the production time of PSA tower, one non-return valve is fitted with the surge vessel.

F. AFTER FILTER

This is a dust filter in N2 outlet line provided with borosilicate fiber type filter element. This is required to restrict the flow of dust/foreign particles. Filtration level is 1.0 micron at 99% efficiency. In this filter, manual drain valves are provided at the bottom of dust filter. Flow direction of air should be outside to inside the filter element.

(First stage filter is borosilicate type filter element; make: FTI; model No. – 04/10; size: 1.0 Micron).

Note: the filter element should be replaced when the differential pressure between surge vessel andsutlet of N2 gas is high. Maximum pressure drop should be 0.5 Kg/cm2g. The element should be replaced at intervals of 8000 hour of operation or 1 year, whichever is earlier.

G. NITROGEN ROTAMETER

This is an acrylic type nitrogen rotameter fitted at the outlet of the surge vessel. This constantly indicates the amount of nitrogen being fed to the purification system. One (1)gate valve is fitted at the inlet of rotameter to control the flow of raw nitrogen.

H. BACK PRESSURE CONTROLLER.

The back pressure controller is installed after the rotameter to maintain a minimum pressure of 5.5 Kg/cm2g in the surge vessel. When the inlet pressure signal increases to exceed the spring setting, the outlet port of valve will open, and in case this pressure goes down, the controller will close the outlet port. The setting of the back pressure controller can be changed by adjusting the bolt provided at the top.

I. THREE-WAY VENT VALVE

Three way vent valve is a pneumatically operated. With no compressed air signal, its bottom port is open to atmosphere. Thus, when the gas generator is started, the gas, initially of low purity, will go to the atmosphere through this 3-way valve. The valve closes its bottom port when it gets compressed air through the solenoid valve, which gets energized when the vent valve ON option is selected (through ON/OFF selector switch on the vent valve) after checking the quality of product gas for some time.

J. PPM OXYGEN ANALYZER

To monitor oxygen content in the nitrogen gas produced from the PSA, an online PPM oxygen analyzer is installed. This analyzer has a resolution of 1 PPM. The sample is fed to the analyzer from the outlet line of the surge vessel. In case of higher oxygen PPM than the set point, the analyzer will generate a signal to raise a visual alarm, and open the 3-way vent valve to the atmosphere. This will prevent passage of gas with higher oxygen content than desired in to the system, and thus prevent an undesirable outcome.

K. DEW POINT METER

To continuously monitor the performance of the dry air, dew point meter is installed at the outlet of the dryer tower outlet line.

This is a state-of-art and an online dew point meter, equipped with one (1) NO/C/NC changeover contacts, and it would give 4-20 mA signal in the range of 20 to (-) 110OC; the resolution is 0.1OC.

The sample is fed to the dew point meter from the outlet line of the drying tower. A filter-cum-pressure regulator is also installed in the sample line, so that the sensor is protected from dust and over pressure.

L. NITROGEN GAS STORAGE TANK (2KL) SS 304

Nitrogen storage tank is installed at the outlet of PSA nitrogen gas plant for the storage of nitrogen gas and to remove pulsations in the flow of gas. Pressure indicator is provided over the storage tank to check on non-uniform consumption pattern or use of nitrogen gas in case of power failure or breakdown in the plant. The plant is made to trip with the help of a high-pressure transmitter when the pressure of the gas in the tank reaches the upper set limit.

Acceptance Criteria for Nitrogen Gas Quality Test are as below.

Sr. no.	Test	Specification
1	Carbon monoxide	NMT 5 ppm V/V
2	Carbon dioxide	NMT 300 ppm V/V
3	Water vapor	NMT 67 ppm V/V
4	Oxygen	NMT 50 ppm V/V
5	Assay	NLT 99.5 % by V/V of nitrogen
6	Particulate count	Limits in particles/M^3
	Particle Size≥0.5µ	For Grade A: NMT 3520 For Grade B: NMT 3520 For Grade C: NMT 352000 For Grade D: NMT 3520000 For other area: for information only
	Particle size ≥5.0µ	For Grade A: NMT 0 For Grade B: NMT 29 For Grade C: NMT 2900 For Grade D: NMT 29000 For other area: for information only
7	Microbial count	For Aseptic Area: ≥ 1 CFU/ m^3 (action limit) For Clean Area ≥ 5 CFU/ m^3 (action limit) For Other Area: for information area

Best Practice as per Regulatory Guidelines/Requirements

Key Concepts

This Guide aims to promote a scientific risk-based approach to provide an effective basis for the planning, design, and execution of gas system projects. Five key concepts are applied throughout this Guide.

1. Product and Process Understanding

An understanding of the supported process is fundamental in determining system requirements. Product and process understanding is the basis for making science- and risk-based decisions, in order to ensure that the system is fit for its intended use. Efforts to ensure fitness for intended use should focus on those aspects that are critical to patient safety and product quality. These critical aspects should be identified, specified, and verified. Systems within the scope of this Guide support the manufacture and preservation of materials used in many applications including, but not limited to, clinical trials, commercial production of API, and final products. For some manufacturing systems, process requirements depend on a thorough understanding of product characteristics, identification of Critical Quality Attributes (CQAs) and related Critical Process Parameters (CPPs), which enable process requirements to be accurately defined. Specification of requirements should be focused on critical aspects. The extent and detail of requirement specification should be commensurate with associated risk, complexity, and novelty of the system.

2. Life Cycle Approach within a Quality Management System

Adopting a system life cycle approach entails defining activities in a systematic way from system conception to retirement. This enables the optimization of the management control process. The life cycle should form a fundamental part of the organization's Quality Management System (QMS), which should be maintained up to date as new ways of working are developed. As experience is gained in system use, the QMS should enable continuous process and system improvements based on periodic review and evaluation, operational and performance data, and root-cause analysis of failures. Identified improvements and corrective actions should follow change management. A suitable life cycle, properly applied, enables the continuous assurance of quality and fitness for intended use, and achieving and maintaining compliance with regulatory requirements.

3. Scalable Life Cycle Activities

Life cycle activities should be scaled according to:

- System impact on patient safety, product quality, and data integrity (risk assessment).
- System complexity and novelty (architecture and categorization of system components).
- Outcome of supplier assessment (supplier capability).
- Compliance and inspection risk.

Potential business risk also may influence the scaling of life cycle activities. The strategy should be clearly defined in a plan, and follow established and approved policies and procedures.

4. Science-Based Quality Risk Management

Quality Risk Management is a systematic process for the assessment, control, communication, and review of risks. Application of quality risk management enables efforts to be focused on critical aspects of a system in a controlled and justified manner. Quality risk management should be based on clear process understanding and potential impact on patient safety, and product quality. Qualitative or quantitative techniques may be used to identify and manage risks. Controls are developed to reduce risk to an acceptable level. Implemented controls are monitored during operation to ensure ongoing effectiveness.

5. Utilizing Supplier Involvement

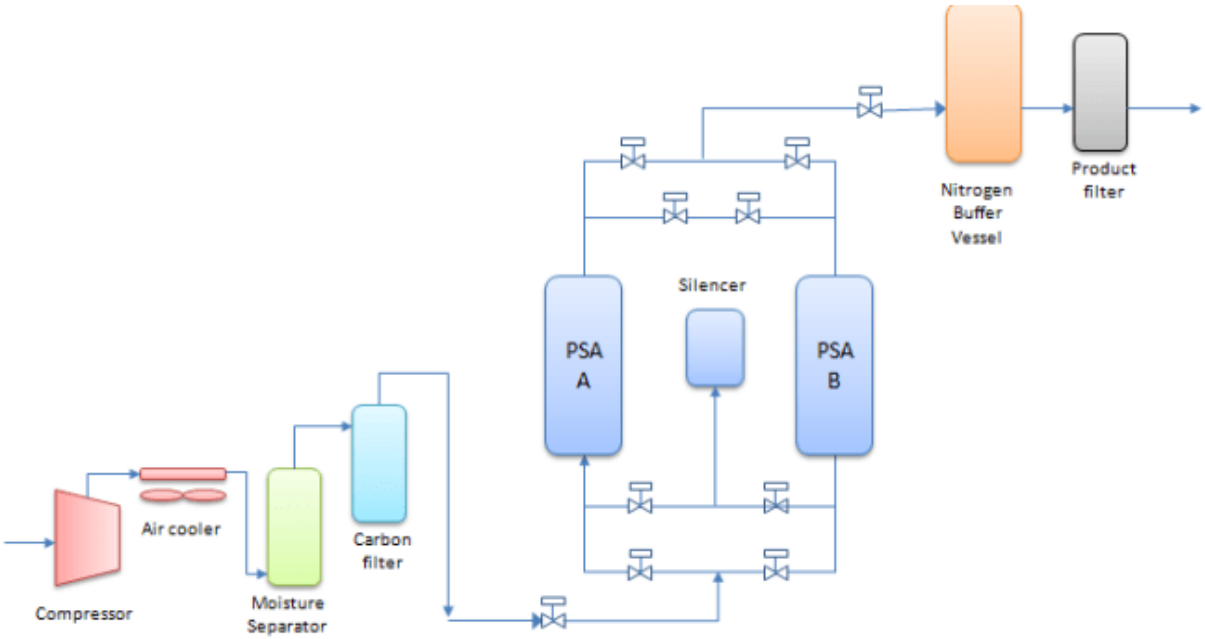
Regulated organizations should seek to maximize supplier involvement throughout the system life cycle in order to utilize knowledge, experience, and documentation, subject to satisfactory supplier assessment.

Best Practice for O&M

The compressed air is passed through a twin tower PSA module interconnected with automatic changeover valves. At the bottom of the PSA towers, activated alumina is provided, which has a tendency of adsorbing moisture from compressed air. After passing through this bed of activated alumina, air gets dried. Supply of dry compressed air from this layer of desiccant (activated alumina) will be continuous without any interruption. Dried compressed air will now come in contact with a bed of carbon molecular sieves (CMS). Carbon molecular sieves are a special grade of adsorbent which has the property of preferential adsorption of oxygen molecules. At any time, one tower remains under nitrogen production cycle, whereas the other tower undergoes regeneration, which is achieved through depressurization of the tower to atmospheric pressure.

The changeover between the two towers take place through pneumatic signal given by solenoid valve which, in turn, gets the electrical signal from the timer provided in the control panel. The changeover time cycle will be 1 + 1 minute. The outgoing nitrogen gas is sent to a surge vessel where the minimum nitrogen pressure will be maintained with the help of backpressure regulator. The product nitrogen will now be sent to the consumer point through a pressure reducing valve at the required pressure.

Basic P&ID of Nitrogen System:


Nitrogen
Buffer
Vessel
Product
filter
Silencer
PSA
A
PSA
B
Air cooler
Carbon
filter
Compressor
Moisture
Separator

PERIODIC MAINTENANCE

1	Daily checks
1a	Daily checks refer to religiously maintaining an hourly log sheet. Certain maintenance and check activities can neither be scheduled nor be anticipated, e.g., failure of a solenoid coil or seat leakage of a changeover valve. Maintaining a log sheet immediately reflects that there is an abnormality or change in operating parameter, compared to previous parameters; the required component of the system can be immediately located, and attended to by maintenance staff. Log sheet enables the monitoring of all the components of the plant, whether they are mechanical, electrical, and instrumentation or process components. To mention a few, log sheet ascertains the following: ❖ PSA sequence is working properly. ❖ Operations of changeover valves of PSA are in order. ❖ Operation of pressure control valves like nitrogen pressure holding valves are proper. ❖ Trip logics and alarm annunciations are working properly. ❖ System is producing gas as per desired quantity and quality.
1b	Check that auto-drain traps provided with air receiver are working properly as per specified time. At least once in a shift, operator should witness and record the drainage from all the automatic drain valves. Further, manual drain valves should be opened to drain out the moisture.
2	15 days checks, maintenance, and replacements
2a	Check and stop leakages of instrument air from any SOV or instrument air tubing.
3	Three-monthly checks, maintenance, and replacements
3a	Set points of all temperature controllers, pressure switches, drain valve timers, and overload relays should be checked for cross reference. Any change in set point should be verified for its reason of change.
4	Six-monthly checks, maintenance and/or replacements
4a	Open and clean pre-filter and after-filter to avoid excess pressure drop. Filter should be replaced after 3-4 cleaning.
4b	Condition of non-return valves should be assessed by change in operating parameters across the non-return valve. Any abnormality should be brought to the notice of maintenance personnel immediately. Even in case of no abnormality, condition of non-return valves should be checked in every six months. If required, non-return valves should be replaced.
4d	Check that all interlocks in the system are properly working.
4e	Check availability of spare parts in stock for smooth functioning of the system.
5	Yearly checks (and replacements)
5b	Replacements of following must be carried out strictly on the basis of 6000 hours of operation or 1 year, whichever is earlier: ❖ Elements of pre- and after- filters
5c	Following instruments should be calibrated every 6 months: ❖ Pressure gauges, pressure transmitter and temperature gauges. ❖ Temperature indicator and controllers. ❖ Oxygen gas analyzer (percentage type).
5d	Do testing of all change over valves of PSA unit. If change over valve/s is found leaking, arrange for servicing or replacement of such valves.
5e	Check proper working of pressure relief valves.
5f	Check availability of spare part in stock for smooth functioning of the system.
6	3-Year Checks
6a	The condition of the coir mattresses provided inside the PSA towers should be checked to avoid dusting of CMS. If required, the coir mattresses should be replaced or more mattresses should be added.

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25. CONCLUSION

1 Purpose

The purpose of this standard operating procedure is to provide guidance for handling of engineering drawings and documents for the pharmaceutical manufacturing sites

2 Scope

This procedure is applicable to provide guidance for engineering for drawings and document handling at plant.

3 Responsibility

- All employees/designated persons and personnel involved in GMP functions, e.g., manufacturing, quality, engineering, safety, etc., are responsible for following guideline documents.

- Site QA head and Engineering head shall be responsible for review and approval procedure followed as per guideline documents and take further action(s) as required.

4 Documentation Handling

4.1 Abstract

Do what is written and write what you do The basic rules in any good manufacturing practice (GMP) regulations specify that the pharmaceutical manufacturer must maintain proper documentation and records. Documentation helps to build up a detailed picture of what a manufacturing function has done in the past, and what it is doing now, and, thus, it provides a basis for planning what it is going to do in the future. Regulatory inspectors, during their inspections of manufacturing sites, often spend much time examining a company's documents and records. Effective documentation enhances the visibility of the quality assurance system. In light of the above facts, we have made an attempt to harmonize different GMP requirements and prepare a comprehensive guide to GMP requirements related to documentation and records, followed by a meticulous review of the most influential and frequently referred regulations.

4.2 Principle

Documentation is an integral part of good manufacturing practices. It defines a system of information and control so that risks so inherent in misinterpretation and/or error in oral communication are minimized. Handling documents and drawings efficiently is crucial for any organization. Proper management ensures easy access, improved collaboration, and compliance with regulations. The document and drawing life cycle involve several stages, including creation, review and approval, distribution, storage, retrieval, and destruction or archival.

4.3 Creation

Documents and drawings are created using various tools, such as word processors, design software, or CAD programs, etc. During this stage, it is important to follow standardized templates and naming conventions to maintain consistency and aid future retrieval.

4.4 Review and Approval

Documents and drawings often require review and approval from relevant stakeholders. This stage ensures accuracy, quality, and compliance with regulations. Collaborative tools and workflows can streamline this process, allowing multiple reviewers to provide feedback and make necessary revisions.

4.5 Distribution

Once approved, documents and drawings need to be distributed to the intended recipients. This can involve physical copies or digital distribution through email, file-sharing platforms, or document management systems. Proper tracking and version control are essential to avoid confusion, and ensure that everyone has the latest version.

4.6 Storage

Documents and drawings must be stored in a secure and organized manner. Physical documents can be stored in filing cabinets or archival boxes, while digital files can be stored on local servers, cloud storage, or document management systems. Implementing metadata and folder structures enables efficient retrieval and searchability.

4.7 Retrieval

Quick and accurate retrieval of documents and drawings is vital for efficient operations. Proper indexing, metadata, and search functionalities facilitate easy access. Document management systems often offer advanced search capabilities, making it easier to locate specific information within a large document repository.

4.8 Destruction or Archival

Depending on the document's retention period and legal requirements, it may need to be destroyed or archived. Destruction should follow secure processes, ensuring sensitive information is properly disposed of. Archiving involves transferring documents to long-term storage or preservation systems, ensuring their authenticity and integrity over time.

Throughout the document and drawing life cycle, maintaining proper version control is essential. This prevents confusion caused by outdated or conflicting versions and ensures that the most up-to-date information is used. Document security is also critical to protect sensitive data from unauthorized access or tampering. Compliance with regulations, such as data privacy and industry-specific standards, is necessary to avoid legal and reputational risks.

By effectively managing the document and drawing life cycle, organizations can streamline operations, enhance collaboration, and ensure regulatory compliance.

5 Objectives of Documentation

Documentation is the key to GMP compliance and ensures traceability of all development, manufacturing, and testing activities. Documentation provides the route for auditors to assess the overall quality of operations within a company and the final product. Hence, the objectives of documentation are:

1. To define the specifications and procedures for all materials and methods of manufactured and control.

2. To ensure that all personnel concerned with manufacturing know what to do and when to do it.

3. To ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale.

4. To ensure the existence of documented evidence, and traceability, and to provide records and an audit trail that will permit investigation.

5. It ensures the availability of the data needed for validation, review, and statistical analysis.

6 Scope

Good documentation encompasses practically all the aspect of pharmaceuticals:

1. Building and premises: installation, validation, cleaning, and maintenance.
2. Personnel: training, hygiene etc.
3. Equipment: installation, calibration, validation, maintenance, cleaning.
4. Materials: specification, testing, ware-housing, use, rejection/disposal.
5. Processing: individual steps in the process of manufacturing including controls thereof.
6. Finished goods: specifications, testing, storage, distribution, and rejection/disposal.
7. Complaints: investigation, actions (including recall, if necessary).

7 Characteristic of Documents

For effective use of documents, they should be designed and prepared with utmost care.
Each document shall:

i. Have a clear title.

ii. Have an identification number.

iii. Be approved by authorized person.

iv. Have the date of issue.

v. Have a due date of revision.

vi. List to whom it has been issued.

- Where the documents carry instructions (e.g., batch processing):

  i. The instructions shall be precise and not ambiguous.

  ii. They shall be for each individual step and not combined, e.g., weigh the materials; charge the weighed materials into the blend.

  iii. Instructions shall be in imperative mood.

- Where entry of any data (e.g., temperature, weight) is expected to be made by the person using the document:

  i. Sufficient space shall be provided for making the entry.

  ii. Heading shall clearly indicate what is to be entered, and who is responsible.

  iii. All entries shall be in ink.

  iv. All entries shall be clear and legible.

  v. Person making the entries shall confirm the entry by initialing/signing the same.

vi. An error in entry shall be so corrected that the original (wrong) entry is not lost. Such correction shall also be initialed and dated. Where necessary, reason for correction shall also be recorded, initialed and dated.

- Documentation system should provide for a periodic review, and revision, if necessary, of any document, or part thereof.
- Such revised versions shall also be approved by the authorized persons.
- Updated/revised versions shall also be superseding the previous edition, and the document shall clearly indicate this.
- Such revised versions shall also be approved by the authorized persons.
- Updated/revised versions shall also be superseding the previous edition, and the document shall clearly indicate this.
- Outdated/superseded document shall be immediately removed from active use, and copy retained only for reference.
- If documentation is through electronic data processing system (computerized system), there shall be adequate, reliable systems in place:
    1. To check and ensure accuracy of data.
    2. To record changes (addition/deletion).
    3. To ensure that the system meets other regulations and requirements, if any.
- For implementing efficient documentation practices, which meet full GLP/GMP/ISO and FDA requirements.
  Here is a hint from the 'Documents' model, which lists out the areas required for GMP document implementation:
    - D = Design, development, deviations, dossiers and Drug Master Files for regulated markets, distribution records.
    - O = Operational procedures/techniques/methods, Out of Specifications (OOS), Out of Trend (OOT).

- C = Cleaning, calibration, controls, complaints, containers and closures, contamination and change control.
- U = User requirement specifications, utilities like water systems, HVAC, AHU, etc.
- M = Man, materials, machines, methods, maintenance, manufacturing operations and controls, monitoring, master formula, manuals (quality, safety, and environment), medical records.
- E = Engineering control and practices, environment control, equipment qualification documents.
- N = Non-routine activities, new products and substances.
- T = Technology transfer, training, testing, trend analysis, technical dossiers.
- S = SOPs, safety practices, sanitation, storage, self-inspection, standardization, supplier qualification, specifications and standard test procedures, and site master file.

Record

Document which describes the evidence of past event.

Master Copy

Original approved or authorized document.

Controlled document

A photocopy of the master document which shall be distributed to the user department(s) as a part of document distribution procedure, and shall bear a stamp as 'CONTROLLED COPY'. These documents are controlled documents and are retrievable whenever superseded.

Uncontrolled document

A photocopy of master documents which shall be given to any customer/external agency for reference purpose only, and shall always possess the stamp 'UNCONTROLLED COPY' on every page. These documents are not controlled documents, hence are not retrievable.

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Obsolete document

A document which is discontinued from it is further uses. All the original/Master copy of previous version document which is discontinued shall be treated as obsolete document.

Superseded document

When a document has been revised, the old version shall be Superseded.

Archival

Data archival is the process of storage of document that is no longer actively used, in a separate storage area for long term retention. Documents archived consist of older documents that are still important and necessary for future reference, as well as documents that must be retained for regulatory compliance.

8 Specific Uses of Documents

Documents can serve a variety of purposes as part of a research undertaking. Let us consider five specific functions of documentary material. First, as indicated above, document scans provide data on the context within which research participants operate — a case of text providing context, if one might turn a phrase. Bearing witness to past events, documents provide background information as well as historical insight.

Advantages

1. Availability

Many documents are in the public domain, especially since the advent of the Internet, and are obtainable without the authors' permission. This makes document analysis an attractive option for qualitative researchers. As argued, locating public records is limited only by one's imagination and industriousness. An important maxim to keep in mind is that if a public event happened, some official record of it most likely exists.

2. Cost-effectiveness

Document analysis is less costly than other research methods and is often the method of choice when the collection of new data is not feasible. The data (contained in documents) have already been gathered; what remains is for the content and quality of the documents to be evaluated.

3. Lack of obtrusiveness and reactivity

Documents are 'unobtrusive' and 'non-reactive'—that is, they are unaffected by the research process. Therefore, document analysis counters the concerns related to reflexivity (or the lack of it) inherent in other qualitative research methods. With regard to observation, for instance, an event may proceed differently because it is being observed.

4. Reflexivity

Reflexivity is that which requires an awareness of the researcher's contribution to the construction of meanings attached to social interactions, and acknowledgment of the possibility of the investigator's influence on the research. This is usually not an issue in using documents for research purposes.

5. Stability

As a corollary to being non-reactive, documents are stable. The investigator's presence does not alter what is being studied. Hence, documents are suitable for repeated reviews.

6. Exactness

The inclusion of exact names, references, and details of events makes documents advantageous in the research process.

7. Coverage

Documents provide broad coverage since they cover a long span of time, many events, and many settings.

8. Insufficient detail

Documents are sometimes produced with insufficient details and information, which may lead to false results or conclusions, while using these for any procedure or investigation.

9. Low irretrievability

Documentation is sometimes not retrievable, or irretrievability is difficult. Sometimes, access to documents may be deliberately blocked.

10. Biased selectivity

An incomplete collection of documents suggests 'biased selectivity'. In an organizational context, the available documents are likely to be aligned with corporate policies and procedures, and with the agenda of the organization's principals. However, they may also reflect the emphasis of the particular organizational unit that handles record keeping (e.g., Human Resources).

TYPES

There are various types of procedures that a GMP facility can follow. Given below is a list of the most common types of documents, along with a brief description of each.

1. Quality manual

A global company document that describes, in paragraph form, the regulations or parts of the regulations that the company is required to follow.

2. Policies

Documents that describe, in general terms, and not with step-by-step instructions, how specific GMP aspects (such as security, documentation, health, and responsibilities) will be implemented.

3. Standard Operating Procedures (SOPs)

Step-by-step instructions for performing operational tasks or activities.

4. Batch Records : these documents are typically used and completed by the manufacturing department. Batch records provide step-by-step instructions for production-related tasks and activities, besides including areas on the batch record itself for documenting such tasks.

5. Test Methods

These documents are typically used and completed by the Quality Control (QC) department. Test methods provide step-by-step instructions for testing supplies, materials, products, and other production-related tasks and activities, e.g., environmental monitoring of the GMP facility. Test methods typically contain forms that have to be filled in at the end of the procedure; this is for documenting the testing and the results of the testing.

6. Specifications

That lists the requirements that a supply, material, or product must meet before being released for use or sale. The QC department will compare their test results to specifications to determine if they pass the test.

7. Logbooks

Bound collection of forms used to document activities. Typically, logbooks are used for documenting the operation, maintenance, and calibration of a piece of equipment. Logbooks are also used to record critical activities, e.g., monitoring of clean rooms, solution preparation, recording of deviation, change controls, and its corrective action assignment released for use or sale.

9 The 10 Golden Rules of Document Management

Number	The golden rule
1	Get the facility design right from the start.
2	Validate processes.
3	Write good procedures and follow them.
4	Identify who does what.
5	Keep good records.
6	Train and develop staff.
7	Practice good hygiene.
8	Maintain facilities and equipment.
9	Build quality into the whole product lifecycle.
10	Perform regular audits.

The management of each operational site should define its responsibility for origination, distribution, maintenance, change control, and archiving of all GMP documentation and records within that department or unit.

Document owners must ensure that all aspects of documentation and records management are specified in SOPs.

Requirements for specific documents or record, including ownership, content, authorization, and change control procedures, has to be described or cross-referenced in the quality modules which relate to the subject of the document.

10 Master Formula Record

Master formula record is a product specific document compiled, checked, authorized, and approved by competent technical personnel from different, but interlinked, functions such as development, production, packaging, and quality control as necessary and appropriate.
As with any other documentation, master formula record shall also be open for review. Changes, if any, shall also be approved by designated persons responsible for production and quality control.

1. Master formula record shall :
    a. Give patent/proprietary name of the product, and its strength.

    b. Give pharmacopeial/generic name of the product, and its strength.

    c. Give dosage form (e.g. tablet, ampoule) and physical characteristics of the product.

    d. Give sufficient, detailed information of product pack and primary packaging materials.

    e. Give identity, quality and quantity of every ingredient, including overages/assay value based quantities, if any, irrespective of whether, or not, the material:
        1. is an active drug substance in the formulation/product.
        2. is used as a pharmaceutical aid (excipient).
        3. appears, or is detected/tested in the final product.

    f. Briefly describe all the raw materials.

    g. Give broad outlines of the process of manufacture (as a flow-chart, for example).

    h. Give brief description of equipment/machinery used for manufacturing the product.
    i. Give step-wise manufacturing process.

    j. Give theoretical and practical (expected) yields at different stages of manufacture.

    k. Bring out in sufficient details precautions to be taken during manufacturing to ensure product quality and personnel safety.

    l. Give all analytical controls, including limits thereof, applicable to the finished product.

    m. Give stability test results covering the assigned shelf life.

    n. Have a product history data giving references in manufacturing/packaging introduced over the year.

    o. Preferably contain samples of printed packaging components.

11 Batch Manufacturing Record

Batch manufacturing record is a product and batch specific document designed to give a complete and reliable picture of the manufacturing history of each batch of every product.

Batch manufacturing record shall be essentially based on the master formula record and shall be compiled, checked, approved, and authorized by competent technical person/s responsible for production and quality control. Photo reproduction, or such other system (e.g., computer printouts) shall be preferred to avoid transcription errors, provided, however, there are adequate safeguards to prevent unauthorized re-production. The details in the record shall be:

- Name of the product:
- Batch number:
- Date of commencement and completion of significant intermediate stage:
- Name of the person responsible for each stage of production:
- Initials of operators who carried out significant processes and initials of persons who checked, wherever applicable.
- Quantity, batch number, quality control report number of each ingredient, actually weighed, and amount of any recovered material added.
- In-process controls carried out, their results, and signature of person who performed the controls.
- Theoretical yield and actual yield at appropriate stage of production together with explanation, if variation observed is beyond expectation.

12 Batch Packaging Records

Batch packaging record is a part of batch process record. These records are based on packaging instruction. One important operation that should be carried out before packaging operation is line purging. WHO guidelines require that following information should be recorded at the time of each action :

- The name, batch number, and quantity of the bulk finished product to be packed.
- Theoretical yield and actual yield and reconciliation.
- The date and time of the packaging operations.
- The name of the responsible person carrying out the packaging operations.
- Initials of the operators of the different significance steps.
- In-process control checks and the checks made for identity and conformity with the packaging instruction.
- Details of packaging operation, like equipment and the packaging lines used, also, when necessary, the instruction for keeping the product unpacked, or a record of unpacked product sent back to storage area.
- Sample of printed packaging material used, bearing the batch number, expiry date, and any additional overprinting.
- In any case of problem, if any deviation is made, written authorization for the same.
- Oquantity along with identification of different packaging materials issued, used, destroyed and/or returned to store and reconciliation.

13 Standard Operating Procedures (SOP)

The terms ‘standard operating procedure’ and ‘standing operating procedure’, both abbreviated by the initials, SOP, occur in a variety of different contexts, such as healthcare, education, industry, the military, etc.

One of the important activities in the implementation of GMP is preparation of SOPs. One of the objectives of GMPS is consistency in quality. Consistency in quality can be achieved by minimizing sources of quality variation. SOPs can be defined as written documents specifying the procedure that must be followed to carry out operation. One of the purposes of SOPS is to reduce the introduction of errors and variation in the operation. The other purpose of SOPs is to retain a historical perspective, i.e., how an operation was carried out.

A SOP is a written document or instruction detailing all steps and activities of a process or procedure. These should be carried out without any deviation or modification to guarantee the expected outcome. Any modification or deviation from a given SOP should be thoroughly investigated, and outcomes of the investigation documented according the internal deviation procedure.

All quality impacting processes and procedures should be laid out in SOPs.

13.1 Benefits of SOP

To provide people with all the safety, health, environmental and operational information necessary to perform a job properly.

Placing value only on production while ignoring safety, health, and environment is costly in the long run. It is better to train employees in all aspects of doing a job than to face accidents, fines, and litigation later.

1. **To ensure that production operations are performed consistently to maintain quality control of processes and products.**

   Consumers, from individuals to companies, want products of consistent quality and specifications. SOPs specify job steps that help standardize products, and, therefore, quality.

2. **To ensure that processes continue uninterrupted and are completed on a prescribed schedule.**

   By following SOPs, you help ensure against process shut-downs caused by equipment failure or other facility damage.

3. **To ensure that no failures occur in manufacturing and other processes that would harm anyone in the surrounding community.**

   Following health and environmental steps in SOPs ensures against spills and emissions that threaten plant neighbors and create community outrage.

4. **To ensure that approved procedures are followed in compliance with company and government regulations.**

   Well-written SOPs help ensure that government regulations are satisfied. They also demonstrate a company's good-faith intention to operate properly. Failure to write and use good SOPs only signals to government regulators that your company is not serious about compliance.

5. **To serve as a training document for teaching users about the process for which the SOP was written.**

   Thorough SOPs can be used as the basis for providing standardized training for employees who are new to a particular job and for those who need re-training.

6. **To serve as a checklist for co-workers who observe job performance to reinforce proper performance.**

   The process of actively caring about fellow workers involves one worker coaching another in all aspects of proper job performance. When the proper procedures are outlined in a good SOP, any co-worker can coach another to help improve work skills.

7. **To serve as a checklist for auditors.**

   Auditing job performance is a process similar to observation mentioned in the previous item, only it usually involves record keeping. SOPs should serve as a strong basis when detailed audit checklists are developed.

8. **To serve as an historical record of the how, why, and when of steps in an existing process, so there is a factual basis for revising those steps when a process or equipment is changed.**

   As people move from job to job within and between companies, unwritten knowledge, and skills disappear from the workplace. Properly maintained written SOPs can chronicle the best knowledge that can serve new workers when older ones move on.

9. **To serve as an explanation of steps in a process so they can be reviewed in accident investigations.**

Although accidents are unfortunate, they can be viewed as opportunities to learn about how to improve conditions. A good SOP gives a basis from which to begin investigating accidents.

Some guidelines are given below about how to prepare SOPS.

i. Give a clear and descriptive title to each SOP.

ii. Provide sufficient details. The SOP should meet the need of an individual; all the same, it should be general enough for more than one user.

iii. Flexibility should be written in the SOP wherever appropriate, but it should not be made too general; otherwise, it may be useless in meeting its intended purpose.

iv. Organize SOPs according to the sequence of events involved in performing the operation. Write the text in straightforward and easy to follow language and manner.

v. After drafting SOP, use it in performing the operation to ensure that it has sufficient details to perform the operation in intended manner.

vi. While drafting SOP, take into account the instructions from the manufacturer of the equipment that is employed in performing the operation..

vii. Indicate total number of pages so that user is certain that he is performing the complete operation.

viii. Indicate the effective date of the SOP.

The best way to prepare SOPs is to involve at least one person from each work area. The person selected should be asked to write down the procedure of the operation with details and the precautions to be taken. The written down procedure should be discussed by a group of persons intimately connected with the operation. Modifications, if any, should be made. This should be handed over to the person who has been designated as coordinator. The coordinator should rewrite it is needed to bring uniformity in style and format.

14 Equipment Cleaning and Use Record

1. Records of major equipment use, cleaning, sanitization and/or sterilization, and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

2. If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

15 Records of Raw Materials, Intermediates, API Labelling and Packaging Materials

1. **Records should be maintained including :**

    1. The name of the manufacturer, identity, and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for APIs; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt.

    2. The results of any test or examination performed and the conclusions derived from this.

2. **Records tracing the use of materials :**

    1. Documentation of the examination and review of API labelling and packaging materials for conformity with established specifications.

    2. The final decision regarding rejected raw materials, intermediates or API labelling and packaging materials.

3. **Master (approved) labels should be maintained for comparison to issued labels.**

16 Master Production Instructions (Master Production and Control Records)

1. To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).

2. Master production instructions should include:

   - The name of the intermediate or API being manufactured and an identifying document reference code, if applicable.

   - A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics.

   - An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included where they are justified.

   - The production location and major production equipment to be used.

   - Detailed production instructions, including the:

     i. Sequences to be followed.

     ii. Ranges of process parameters to be used.

     iii. Sampling instructions and in-process controls with their acceptance criteria, where appropriate.

     iv. Time limits for completion of individual processing steps and/or the total process, where appropriate.

     v. Expected yield ranges at appropriate phases of processing or time.

   - Where appropriate, special notations and precautions to be followed, or cross-references to these; and

   - The instructions for storage of the intermediate or API so as to assure its suitability for use, including the labelling and packaging materials, and special storage conditions with time limits, where appropriate.

17 Batch Production Records (Batch Production and Control Records)

1. Batch production records should be prepared for each intermediate and API, and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

2. These records should be numbered with a unique batch or identification number, dated, and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.

3. Documentation of completion of each significant step in the batch production records (batch production and control records) should include:

    - ❖ Dates and, when appropriate, times.
    - ❖ Identity of major equipment (e.g., reactors, driers, mills, etc.) used.
    - ❖ Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing.
    - ❖ Actual results recorded for critical process parameters.
    - ❖ Any sampling performed.
    - ❖ Signatures of the persons performing and directly supervising or checking each critical step in the operation.
    - ❖ In-process and laboratory test results.
    - ❖ Actual yield at appropriate phases or times.
    - ❖ Description of packaging and label for intermediate or API.
    - ❖ Representative label of API or intermediate if made commercially available.
    - ❖ Any deviation noted, its evaluation, investigation conducted (if appropriate), or reference to that investigation if stored separately.
    - ❖ Results of release testing.

4. Written procedures should be established and followed for investigating critical deviations, or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

18 Laboratory Control Records

1. Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

    - A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing.

    - A statement of or reference to each test method used.

    - A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents, and standard solutions.

    - A complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested.

    - A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors.

    - A statement of the test results and how they compare with established acceptance criteria.

    - The signature of the person who performed each test and the date(s) the tests were performed, and

    - The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

2. Complete records should also be maintained for :

- ❖ Any modifications to an established analytical method.
- ❖ Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices.
- ❖ All stability testing performed on APIs, and
- ❖ Out-of-Specification (OOS) investigations.

19 Batch Production Record Review

1. Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labelling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

2. Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Qualified production personnel or other units, following procedures approved by the quality unit, can review production and laboratory control records of non-critical process steps.

3. All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

4. The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

20 Document Required as per Regulatory Guideline

20.1 Principle

Good documentation is an essential part of the quality assurance system and as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and method of manufacture and control; to ensure that all personnel concerned with manufacturing know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale; to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation.
It ensures the availability of the data needed for validation, review, and statistical analysis. The design and use of document depend upon the manufacturer.

20.2 General Information

- Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant part of the manufacturing and marketing authorizations.

- Documents should be approved, signed, and dated by the appropriate responsible persons. No document should be changed without authorization and approval.

- Documents should have unambiguous contents; the title, nature, and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to use. Reproduced documents should be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

- Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specific period of time.

- Documents should not be hand written. Where documents require data to be entered, the entry should be clear, legible, and indelible. Sufficient space should be provided for such entries.

- Any alteration made to a document should be signed and dated. The alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

- Records should be made or completed when any action is taken, and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records should be retained for at least one year after the expiry date of the finished product.

- Data (and records for storage) may be recorded by electronic data processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available and the accuracy of the records should be checked.

- If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means, and the entry of critical data should be independently checked. Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs, or other means. It is particularly important that, during the period of retention, the data are readily available.

- Each specification should be approved, signed, and dated, and maintained by quality control, quality assurance unit or documentation center. This includes specifications for starting materials, intermediates, bulk finished products, and packaging materials.

20.3 Standard Operating Procedures, Specifications and Master Formulae

Descriptive documents give instructions on how to perform a procedure or a study, or give a description of specifications. Instructional documents are SOPs; protocols (for validation studies, stability studies, safety studies); and master formulae (manufacturing instructions). Each of these gives instruction on how to perform specific procedures. Specifications describe the required characteristics or composition of a product or material or test. These kinds of documents provide the specific details defining the quality of incoming materials, the quality of the production environment, the quality of the production and control process, and the quality of the final product.

20.4 Forms for Recording Data

Another type of documentation is the form used for recording data as it is taken during the performance of tasks, tests, or events. These are forms (datasheets, or data record forms), reports, batch processing records, and equipment log books. These documents provide the evidence that the raw materials, facility environment, the production process, and the final product consistently meet the established quality requirements.

20.5 Identification Numbers

There are also the identification systems or codes devised to number and track both information and documents. These are SOP numbers, equipment numbers, form numbers, receiving codes, and batch/lot numbers. These numbering systems should be designed so that procedures, processes, and materials can be traced throughout the data records.

20.6 Other Various Analysis Records

- Written release and rejection records should be available for materials and products, and, in particular, for the release for sale of the finished product by an authorized person.

- Records should be maintained of the distribution of each batch of a product in order, e.g. to facilitate the recall of the batch if necessary.

- Records should be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried out these operations.

- The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.

- There should be written procedures assigning responsibility for cleaning and sanitation, and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used, and facilities and equipment to be cleaned. There should be records as to whether such written procedures have been followed.

20.7 Device Master Record

- Each manufacturer shall maintain Device Master Records (DMRs). Each manufacturer shall ensure that each DMR is prepared and approved.

- The DMR for each type of device shall include, or refer to the location of, the following information.

    a. Device specifications including appropriate drawings, composition, formulation, component specifications, and software specifications.

    b. Production process specifications including the appropriate equipment specifications, production methods, production procedures, and production environment specifications.

    c. Quality assurance procedures and specifications including acceptance criteria and the quality assurance equipment to be used.

    d. Packaging and labelling specifications, including methods and processes used.

    e. Installation, maintenance, and servicing procedures and methods.

20.8 Device History Record

- Each manufacturer shall maintain Device History Records (DHRs). Each manufacturer shall establish and maintain procedures to ensure that DHRs for each batch, lot, or unit are maintained to demonstrate that the device is manufactured in accordance with the DMR and the requirements of this part.

- The DHR shall include, or refer to the location of, the following information:

    a. The date/s of manufacture.

    b. The quantity manufactured.

    c. The quantity released for distribution.

    d. The acceptance records, which demonstrate the device is manufactured in accordance with the DMR.

    e. The primary identification label and labeling used for each production unit.

    f. Any device identification(s) and control number(s) used.

20.9 Quality System Record

Each manufacturer shall maintain a Quality System Record (QSR). The QSR shall include, or refer to the location of, procedures and the documentation of activities required by this part. Each manufacturer shall ensure that the QSR is prepared and approved.

21 GMP Guidelines for Records and Reports

21.1 Equipment Cleaning and Use Log

- A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed.

- If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence.

- In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record.

- The persons performing and double-checking the cleaning and maintenance shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.

- This section requires written designation of which equipment is major. The intent of the regulations is not to include small items such as ladles, scoops, stirrers, and spatulas. The exclusion of no major items from the recordkeeping requirement does not, however, exclude them from the requirement that they be properly cleaned.

- Because the log is for a repetitive operation, the record may be initialed rather than signed. Note that, a separate log, which may be a completely separately bound volume, or consecutive pages in a bound or loose-leaf format, or a number of individual records or logs is required for each piece of major equipment that is not dedicated to the manufacture of a single product.

- The issue of signatures and initials has involved considerable industry and FDA interaction. As new computerized technology became available, it was possible to move to paperless control of manufacturing processes.

- These computerized controls had several advantages over manual systems:

    1. More consistent control.

    2. Only approved (trained) personnel could perform a process.

    3. Processing could be prevented until any prior steps or checks were performed.

    4. Precise recording of the times of operations were possible.

- Electronic signatures/initials frequently involve a personal password and a personal magnetic card with a secure system to manage allocation and review.

21.2 Distribution Records

- Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product. For compressed medical gas products, distribution records are not required to contain lot or control numbers.

- The primary purpose of this section is to ensure that adequate data are available to access trade customers should a recall be initiated.

- The recording of lot number to each order will certainly accomplish this purpose; other approaches can achieve the same result.

- The recording of dates on which a specific lot of products commenced and ceased distribution may be used.

- All customers receiving the product between these dates could then be contacted. Obviously on the first and last days of distribution, some of the customers may have received product from the end of the previous lot or the beginning of the next lot.

1. Complaint files

a. Written procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed. Such procedures shall include provisions for review by the quality control unit of any complaint involving the possible failure of a drug product to meet any of its specifications, and, for such drug products, a determination as to the need for an investigation. Such procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the Food and Drug Administration.

b. A written record of each complaint shall be maintained in a file designated for drug product complaints. The file regarding such drug product complaints shall be maintained at the establishment where the drug product involved was manufactured, processed, or packed, or such file may be maintained at another facility if the written records in such files are readily available for inspection at that other facility.

22 Development and Implementation in Documentation

The traditional records management model is based on cabinets, folder, and files. This physical model was given in a logical extension in the first electronic document management system, where files were placed into virtual cabinets and folders.

22.1 File room Model and Security

Security models for documents are all based on controlling who can see document, who can create or edit documents, and who can delete documents. Securing these rights is implemented at numerous levels. It is illustrative to consider these in terms of a physical library paper-based file room. First, one may need proper credentials simply to get in and browse the holdings. Second, once admittance has been gained to the filing area, one's ability to view certain kinds of records may depend on job title or departmental affiliation. Third, assuming one has rights to view a specific record, one may require to have permission only to view the final file under observation in the file room itself, and may not be permitted to make a copy. Finally, if one is permitted to check the document out of the file room for a limited time, he or she will be required to sign his or her name to a dated logbook.

22.2 Input–Output Model and Quality Control

Traditional document management rests on a very simple input-output model. An enterprise seeks to manage the storage of documents (input) in such a way that their retrieval (output) is simplified. The real goal is speedy retrieval of documents.

22.3 Electronic Documentation of Pharmaceutical Calibrations

Electronic documentation systems that do not require any paper were developed to overcome these disadvantages and reduce the amount of time technicians spend in complying with documentation regulations. However, electronic records do not inherently contain signatures that identify the person performing a calibration.

Multifunction calibrators can be integrated to provide automated documentation with less human intervention. This results in fewer human errors, improved work quality, and improved efficiency that can directly affect profit.

Moreover, locating the original electronic records in one database can not only reduce paper records into traceable electronic records with a history of change management, but can also turn the calibration system into a powerful repository of decision-making history that can be used to improve calibration procedures. Versatile security settings and multilevel user accounts help to ensure the security and integrity of the system, and track authorized and unauthorized database actions.

22.4 Web Document Management for the Pharmaceutical Industry

To achieve automation goals, most pharmaceutical companies would do well to start by investing in a web document management solution that can be launched from the same platform as other solutions designed for the life science industries (i.e., GxP process control, quality management and quality audit solutions).

The web document management software should also provide the following features and benefits:

1. History of Successful Validation

Quality assurance professionals and other pharmaceutical professionals know the importance of reputable software validation. When searching for a web document management solution, pharmaceutical professionals should pay close attention to its validation history.

2. Speed

The only reason any pharmaceutical company would even consider the purchase of a web document management solution would be to save money and time on the product-to-market pathway. If any given solution does not automate and increase the speed of document change processes, document approvals, notifications, and document distribution, then the solution is not worthy of consideration.

3. Time Required for Installation, Implementation and Validation - Effects on ROI

Some software vendors may promote the strengths of their software and its immediate capacity for providing a healthy ROI. However, it is possible that their installation, implementation, and validation processes may stretch into 6 months, a year or even longer, which the customer company may not have known prior to purchase. Pharmaceutical professionals need to search for a web document management solution that provides a healthy ROI, but that makes a clear statement regarding the time that will be required for installation, implementation, and validation. A clear statement will allow pharmaceutical companies to make transparent decisions and effective plan for the upcoming transitions that are inevitably linked with the switch to automated document control.

4. Configurable and 'Off-the-Shelf'

If pharmaceutical companies prefer an off-the-shelf web document management solution, it must still be configurable to the unique needs of every company that purchases it. For instance, some pharmaceutical companies, may not apply the same steps throughout a routing or collaboration process, and the web document management solution should be able to reflect that.

5. Tracking and Audit Trails

The web document management solution should also provide tracking and audit-trail features as well as sophisticated revision controls and reporting features.

6. Electronic Signature Controls

To comply with 21 CFR Part 11, pharmaceutical companies must employ electronic signature controls. A web document management software solution that automates document signings routing and collaboration is highly recommended.

7. Compatibility with other Existing Solutions

As mentioned earlier, the web document management solution should be launched from a platform that will allow for the future launch of other solutions. These solutions may include GEP process solutions such as software for deviations identification, non-conformance identification, quality audit, customer complaint handling, change control, and CAPA solutions. A submissions management solution particular to the pharmaceutical industry is also highly recommended.

23 Procedure Taking Document from QA

Upon receiving the various documents (quality records) from respective departments, QA person shall verify following, but not limited to:

- Title of document.
- Category of document.
- Total number of pages.
- Signature on all pages, etc.

After verification of received document, the QA person shall assign unique file number and location to each document for easy traceability of document.

23.1 Numbering of Compactor and files (Documents/Records/Other)

Numbering to compactor in document storage area shall be given as per the logic below:

XX/Y/ZZ

where

XX: Serial number of compactor, i.e., R1, R2, R3 ⋯...etc., so on starting from the entrance,

Y: Serial number of rack, i.e., A, B, C⋯...etc., so on starting from the entrance, for each new compactor in continuation for each rack,

ZZ: Sub rack number, i.e., A1, A2, A3 ...⋯etc., so on starting from top to bottom..

23.2 Numbering of File (Documents/Records/Other)

Numbering to file (documents/records/other) shall be given as per the logic below:

XX-Y-AA

where

XX : Serial number of compactor,

Y : Serial number of rack,

AA : Serial number of file, starting from 01.

For example:

If a file is placed in document room at compactor number R3, rack number is A, and file sequence number is 04, then file number shall be given as R3-A-04.

After assigning file number, QA document person shall scan the document and place the document at respective location of document store.

23.3 Entry/Exit Procedure for entering Document Storage Room

Entry to QA document store shall be controlled by biometric access system. Only authorized persons shall be allowed to enter QA document store.
Authorized person allowed into the document storage room show their identity card or use biometric access to release the door interlock and enter the document storage room.
To exit the room, the person escorting the visitor should show their identity card to release the door interlock and help the visitor exit from the room.

LOCATION OF FILES IN QA DOCUMENT STORE ROOM	Company Logo

Verification Done (Date) : _____ **Next Verification (Due Date) : _____**

Sr. No.	Date	Department	File Name	Document Name/Title	Document Number	File Number	File Location

Remarks : _____ **Verified By (Sign/Date) : _____**

LIST OF AUTHORISED PERSONS FOR BIOMETRIC SYSTEM OF DOCUMENT STORAGE ROOM	Company Logo
	Company Name
	REF SOP No.

Room Name : Document Storage Room : _____

Room ID No : _____

Sr. No.	Date	Name of Authorized Person	Employee Code	Designation	Remarks

Prepared By : _____

(Sign/Date)

Authorized By : _____

(Sign/Date)

24 Drawing Handling Procedure

24.1 Introduction

Qualification documents related to equipment and facilities are key for any organization, and one of the areas that auditors find interesting. Generally, auditors like to review equipment and facility qualification documents, and revision of drawings and qualification documents based on changes in equipment or facilities.

In the pharmaceutical industry, changes in equipment/facilities are covered under change management system, and thus, after completion of changes, engineering department has to ensure that all the changes are properly captured in qualification documents including all relevant drawings, with drawing revision number and document number mentioned in respective change documents.

24.2 Scope

The scope of this procedure is applicable for the preparation, review, approval, and management of the following drawings and layouts at the company's facility:

- Manufacturing facility plot plan.
- Facility floor plan.
- Facility Heating Ventilation and Air Conditioning (HVAC) system zoning layout.
- Facility area classification zoning layout.
- Facility pressure zoning layout.
- Facility man and material movement layout.
- Facility HVAC ducting layout.
- Facility equipment layout.
- Air Handling Unit (AHU) air flow diagrams.
- Water system drawings.
- Compressed air distribution line diagram.
- Nitrogen gas distribution line diagram.

24.3 Responsibility

❖ **Project department**

To prepare drawings (using an in-house team or with the help of a consultant) for plant design before plant construction.

❖ **Plant engineering department**

To prepare/revise the drawing and layout. Responsibility of plant engineering for preparation or revision of drawing usually starts once the plant is handed over to the site team by the project team after project completion.

❖ **Project head or Engineering head**

To check the drawing and layout for its adequacy.

❖ **Plant head/factory head**

To approve the drawing and layout.

❖ **Quality Assurance head**

To approve the drawing and layout.

24.4 Definitions

❖ **Engineering drawing or layout**

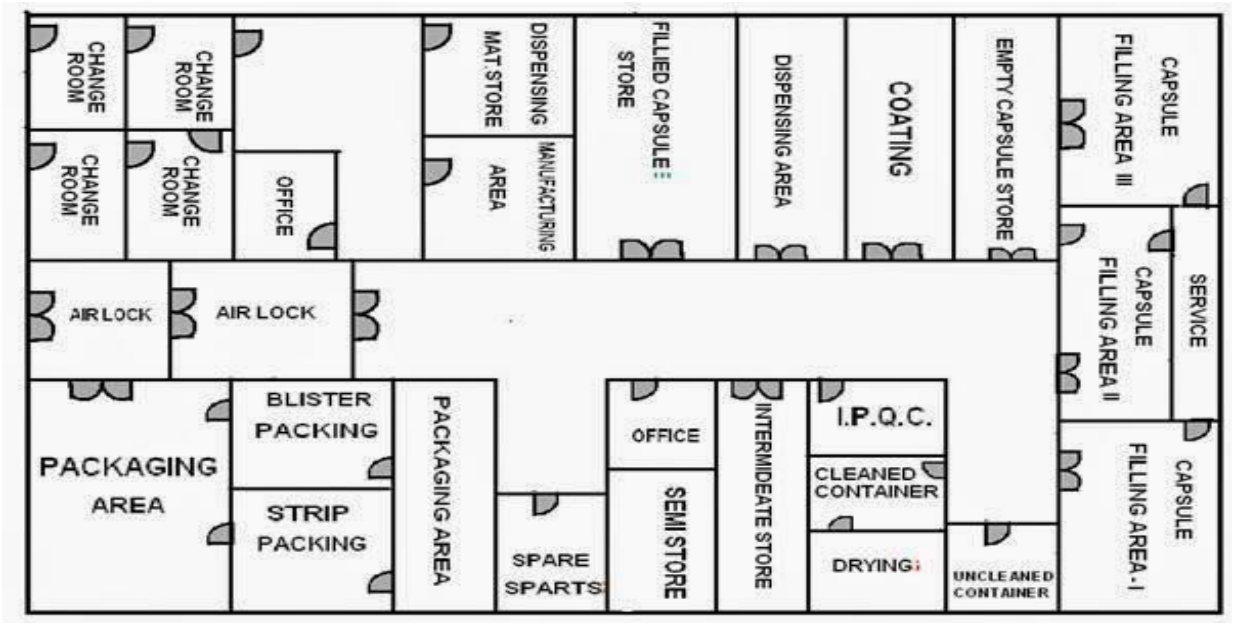
It is a technical schematic visual of a building, equipment, system, or object. The drawings or layouts provide information regarding the dimensions required for the construction and overview of a building, object, equipment, etc.

❖ **Manufacturing facility plot plan**

The plot plan provides information about the overview of the facility plot, walkways surrounding the facility, location of the facility, number of buildings/blocks available on the plot. It is good practice to cover the plot area and built-up area of the plant in the plot plan.

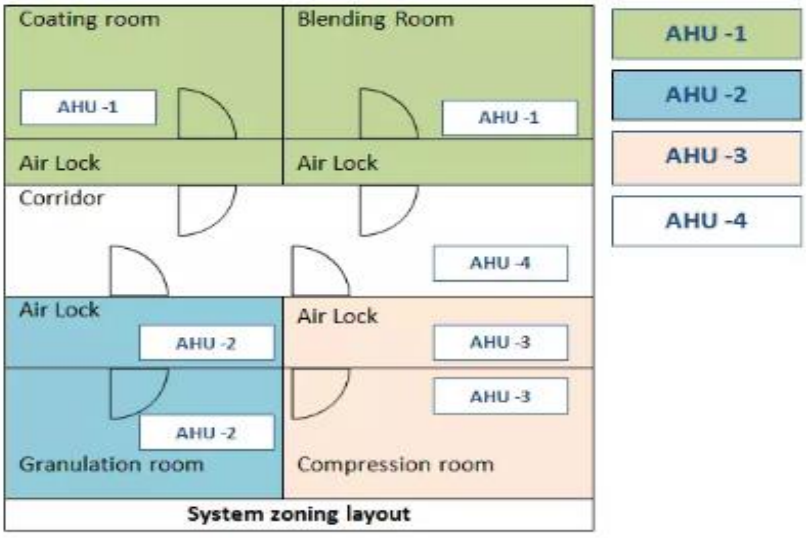
❖ **Facility floor plan**

The floor plan is a simple schematic layout of each floor of the manufacturing facility that provides an overview of the area, room names, room numbers, doors with opening direction, windows, pillars, etc.



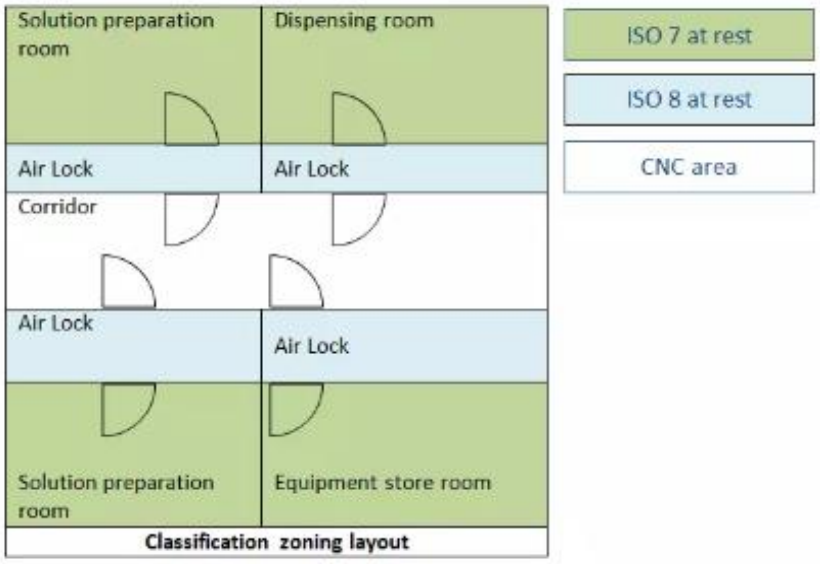
24.5 Facility Heating Ventilation and Air Conditioning (HVAC) system zoning layout

The drawing provides an overview of the HVAC systems design and AHU connections supplied to the respective areas. For example, the drawing will provide the information about which AHU is supplied to which rooms, which areas have common AHUs, and which areas have dedicated AHUs. Each area with different AHU connections should be demonstrated using different legends for easy understanding.



24.6 Facility area classification zoning layout

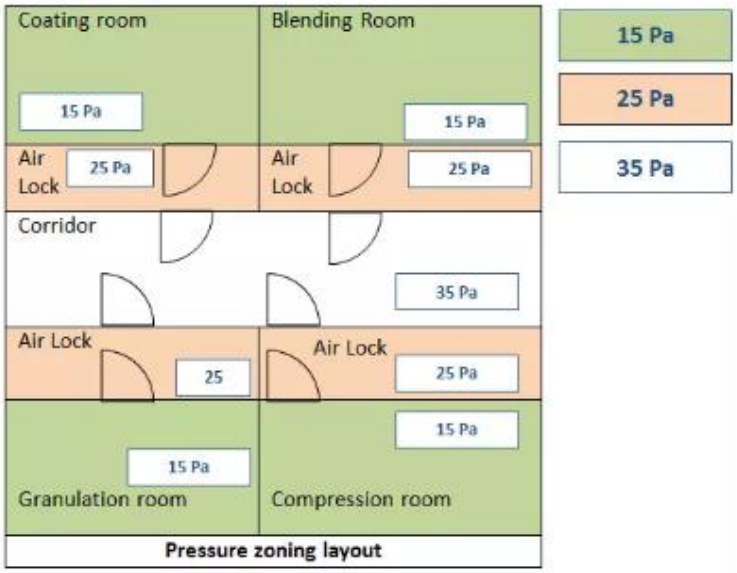
The drawing provides an overview of the room classification of different areas.



Classification zoning layout

24.7 Facility pressure zoning layout

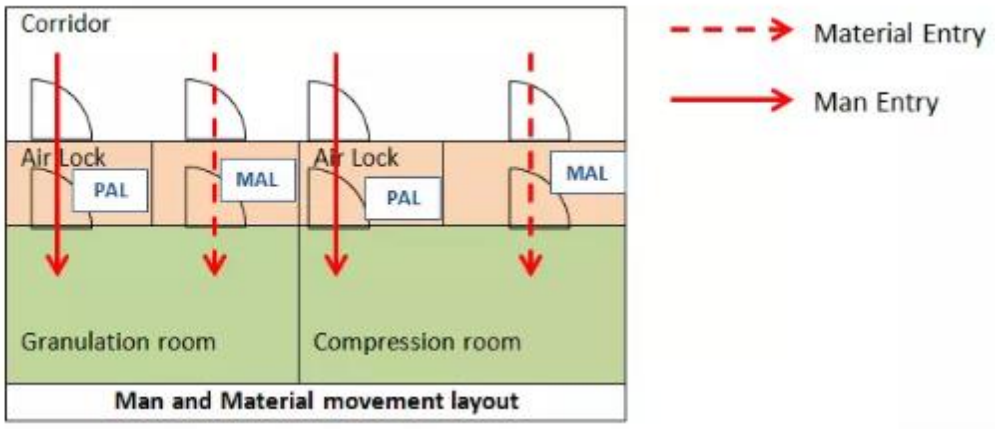
The drawing provides an overview of the room differential pressure of different areas.



Pressure zoning layout

24.8 Facility man and material movement layout

This drawing provides an overview of the man and material entry in the rooms.



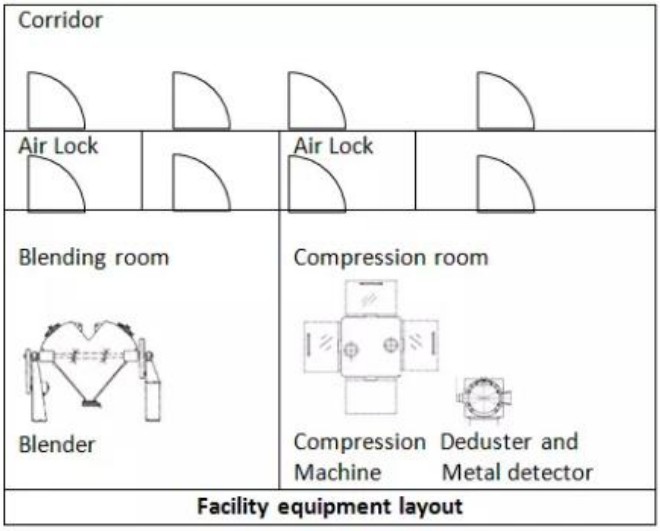
Man and Material movement layout

24.9 Facility HVAC ducting layout

This drawing provides an overview of the AHU ducting on the service floor and its entry to the respective rooms.

24.10 Facility equipment layout

This drawing provides an overview of the equipment placement in the room.



Facility equipment layout

24.11 AHU air flow diagrams

This drawing provides an overview of the individual AHU, where it describes the details regarding air filtration scheme, cooling and heating coil arrangement, percentage air mixing (fresh and recirculating air, bleed), airflow volume, air volume supplies to rooms, and air leakages from rooms, etc.

24.12 Water system drawings

Water systems generally consist of two parts - water generation system, and water distribution system. Water generation system drawings consist of different components of water system such as multigrade filter, softener, basket filter, UV, RO, ion-exchange units, sampling points, etc. Water distribution system drawings consist of piping distributions, sampling points, user points, distribution pump, UV light, instrumentation, areas where user points are available, etc.

24.13 Compressed air distribution line diagram

The drawing provides details of compressed air distribution from generation/storage to the user points. The drawing consists of details such as level of filtration, instrumentation, user points, areas where compressed air distribution has been reached, etc.

24.14 Nitrogen gas distribution line diagram

This drawing provides details of nitrogen gas distribution from generation/storage to the user points. The drawing consists of details such as level of filtration, instrumentation, user points, areas where nitrogen gas distribution has been reached, etc.

24.15 Procedure

24.15.1 Creation of Drawings in Project Stage

- After completion of project, it is the responsibility of Engineering/Project department to ensure as-built drawings are prepared as per site condition.

- Engineering/Project team can follow the procedure defined below.

  - **Preparation of As-Built Drawings**

    When the project is completed and ready for qualification, the engineer shall get the mark-up drawings compiled by contractor during execution stage.

    The contractor/site engineer will collate all the official notes and mark-up drawings regarding any change in the design issued during construction period and will submit this to consulting engineer to incorporate and make the final as-built drawings.

    The site engineer along with contractor must visit site to ensure all such changes are reflected in the drawings.

    The site engineer will verify the drawings with the official notes and mark-up drawings.

    Once all the drawings have been prepared, the site engineer will send the proposed as-built drawings to the Engineering/Project in-charge for approval.

    The as-built drawing must show all elements of the installation, for example, for technical areas like pathways, technical shafts, pipe rack, emergency exits, electrical panels etc., and for duct layouts like dampers, diffusers, terminal heaters, HEPA boxes, duct sizes, fire dampers, etc.

  - **Approval of As-Built Drawings**

    Upon receipt of the as-built drawing, engineering in-charge will verify the drawings. These drawings should also be checked on site against the work accomplished.

    Once satisfied with the submission, these drawings shall be archived.

  - **Preparation and Numbering of Drawings**

    The drawings related to the facility shall be prepared and reviewed by Engineering department in co-ordination with concern user department of the facility. The drawing shall be approved by QA department and shall be retained in QA department.

    Drawings shall be prepared and numbered as follows;

XXX-Dpt.-Drawing Code-Floor-00

where

XXX : Abbreviation of Company Name

Dpt. : Department Correspondence to,

FOR : for Formulation facility

ADMIN : for Administration

UTY : for Utility

SO : for Solvent yard (Peso & Non peso)

FI : for Fire pump house

CA : for Canteen

EO : for Engineering Office

QAQC : for Quality

ETP : for ETP (Effluent Treatment Plant)

HSE : for HSE (Health, Safety & Environment)

PA : for Production Area

Drawing Code: Refer table No 1 for different drawing codes.

Floor : GF- for ground floor drawings

FF-For first floor drawings

SF- for Second floor drawings, and so on.

00 : Corresponds to two numerical figures starting from 01 denoting the version number for the drawings.

Table No. 1

Drawing	Drawing code
Site plan	SITE
Men/material movement drawing	MEN-MAT
Civil layout	CIVIL
Area classification	CLASS
Pressure gradient layout	PG
Area wise AHU zoning	HVAC
Drain point drawing	DP
Schematic layout of DEX system	DEX
Container/waste flow	WASTE
Air flow diagram of HVAC	AHU ID
Technical area civil layout	TECH-CIVIL
Schematic layout of Equipment	EQUP
Schematic layout of Evacuation plan	EVACUATION
Schematic layout of light fixture	LIGHT
Schematic layout of insect-o-cutor	INSECT-O-CUTOR
Schematic layout of air curtain	AIR-CURTAIN
Schematic layout of fire Extinguisher	FIRE-EXTINGUISHER
Schematic layout of fire Hydrant	FIRE-HYDRANT
Air flow diagram of Process Equipment	EQUIPMENT ID (e.XXX-PA-001)
Single line diagram of Electrical	SLD

Site plan layout number can be given without adding department code and floor code; e.g., the first drawing of first floor formulation facility for area classification with first revision will observe the numbering system given below:

XXX-FOR-CLASS-FF-01

For the compressed air and nitrogen distribution system, the following numbering system can be followed, and an index of the same shall be maintained:

XXX-LOC-ZZZ-YY

Where, XXX : Abbreviation of Company Name
LOC : Abbreviation of Location Company
ZZZ , Corresponds to
CO

M : Compressed air distribution
NIT : Nitrogen distribution system
YY : Version number starting from 01

For the drawing to be submitted to local FDA, the following numbering system should be followed and the index of the same shall be maintained:

XXX-LOC -FDA-ZZ-YY

Where, XXX : Abbreviation of Company Name
LOC : Abbreviation of Location Company
FDA : Abbreviation of Food Drug Administration
ZZ : Drawing number starting from 01
YY : Version number starting from 01

Drawing number for water system shall be allocated as per the following pattern:

XXX-AA-BBB-YY

Where, XXX : Abbreviation of Company Name
AA :Corresponds to,
PW : Purified water
RW : Raw water
PT : Potable water
PS : Pure Steam

BBB: Refer Table No 2 for different drawing codes.

YY : Corresponds to version number starting from 01

Table No. 2

Drawing	Drawing code
P & ID of Generation system	GEN
P & ID of Storage & Distribution system	SDS
Schematic layout of purified generation & distribution system	SCM

24.15.2 Modification in Drawings due to changes in Equipment/Facility

- While initiating changes, a comprehensive list should be prepared of all documents and drawings which are affected due to proposed changes. There are certain drawings, which are not directly linked with proposed changes in equipment/facility, but they are indirectly affected with proposed changes.

- For example, while making changes in equipment or facility, there are chances that location of drain is not going to change, but due to change in equipment or facility, there may be need to change drain layout, which should match with revised equipment or facility changes.

1. The details of changes required on all the documents and drawings thus listed should be mentioned. (Refer Annexure – I).

2. While making changes, it must be ensured that all the listed documents and drawings are updated as per requirements. After the changes are done, the obsolete review sheet and layouts should be maintained by Quality Assurance to ensure better traceability.

3. After completion of changes, it should be ensured that all revised documents and drawings are verified by Quality Assurance, and record is kept of revision history with details of change management reference number for ease of traceability.

4. List of revised documents and drawings shall be part of closure of change management system.

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4. List of revised documents and drawings shall be part of closure of change management system.

24.15.3 Verification at Fixed Frequency

1. As review of documents and drawings are carried out after modification or changes, it is recommended to have fixed frequency (i.e., between 1 to 2 years) for review qualification of documents and drawings.

2. During this review, a cross-functional team consisting of Engineering, Quality, and User should re-verify documents and drawings, and ensure that these match on the current site condition.

3. In case of drawings that do not match site condition, deviations shall be captured, and all the drawings shall be updated based on procedure defined as per quality system.

4. It is recommended to maintain master list of all documents and drawings containing details of review period.

24.15.4 Application of Drawing and Layout

1. Facility approvals by government authorities.
2. Requirement of site master file.
3. To understand the facility at glance.
4. Requirement by regulatory auditors during inspection to understand the facility design.
5. Compliance.

24.15.5 Formats

1. Format for preparation of drawing.
2. Format for list of drawings.
3. Format for drawing revision history.
4. Format for drawing distribution.

24.15.6 Specimen for layout title

<table>
<tr><td colspan="2">Company LOGO</td><td colspan="2">Company Name</td></tr>
<tr><td colspan="2">Date of initial drawing</td><td>SIGN & DATE</td><td rowspan="6">TITLE:</td></tr>
<tr><td>PREPARED BY</td><td>Engg./Project Dept.</td><td></td></tr>
<tr><td>CHECKED BY</td><td>Engg./Project Dept.</td><td></td></tr>
<tr><td>CHECKED BY</td><td>User Department</td><td></td></tr>
<tr><td>APPROVED BY</td><td>QA</td><td></td></tr>
<tr><td colspan="2">DRG. No.</td><td>REV. No.</td></tr>
</table>

ANNEXURE : I

Details of Changes			
Change Control		Date	
Location of Changes		Responsible person & Department	
List of Drawings & Documents (Before Starting Modification)			

#	Drawing/ Document Title	Document Number	Changes required in document	Remarks
Prepared By :		Reviewed By :		Approved By :

#	Drawing/ Document Title	Document Number	Changes Incorporated	Verified By
Prepared By :		Reviewed By :		Approved By :

FORMAT FOR MASTER LIST OF DRAWINGS

MASTER LIST OF DRAWINGS	Company Logo
	Company Name with Location
	REF SOP No.

Revision No : _____

Page No. ____ : _____

Sr. No.	Date	Name of Authorized Person	Employee Code	Designation	Remarks

Prepared By : QA Department _____

(Sign/Date)

Authorized By : QA Department _____

(Sign/Date)

RECORD OF DISTRIBUTION DISPLAY COPY OF DRAWINGS

Sr. No.	Drawing Name	Drawing Number	No. of display copy of drawing handover by QA Department to concerned Department		No. of display copy of drawing received by concerned Department from QA Department		No. of display copy of drawing returned by concerned Department to QA Department		No. of display copy of drawing received by QA Department from concerned Department		Remark
			No.	Sign Date	No.	Sign Date	No.	Sign Date	No.	Sign Date	

Prepared By : Reviewed By : Approved By :

RECORD OF DISTRIBUTION DISPLAY COPY OF DRAWINGS

Sr. No.	Drawing Name	Drawing Number	No. of display copy of drawing handover by QA Department to concerned Department		No. of display copy of drawing received by concerned Department from QA Department		No. of display copy of drawing returned by concerned Department to QA Department		No. of display copy of drawing received by QA Department from concerned Department		Remark
			No.	Sign Date	No.	Sign Date	No.	Sign Date	No.	Sign Date	

Prepared By : Reviewed By : Approved By :

25 Conclusion

The documentation process gives a detailed picture of what the manufacturing function has done in the past and what it is doing now, thus, providing a basis for planning what it is going to do in the future. Effective documentation enhances the visibility of the quality assurance system.

The document and drawing life cycle involves several stages, including creation, review and approval, distribution, storage, retrieval, and destruction or archival.

Equipment, System and Facility Life Cycle

CONTENTS

1 Purpose

To provide a general procedure and guidance for deciding equipment, system, facility retirement, and factors to be considered to derive health check-up and its Life cycle managment

2 Scope

The scope of this document is applicable to all equipment, system, and facility in use across pharmaceutical industry.

3 Responsibility

- All employee/designated persons and personnel involved in GMP functions, e.g., manufacturing, quality, engineering, safety, etc., are responsible for following guideline documents.

- Site QA head or his designee and Engineering head shall be responsible for following review and approval procedures as per guideline documents, and taking further action(s) as required.

4 Introduction

Equipment life cycle management and maintaining regulatory quality standards over the life of critical equipment and facilities is critical. This will help the manufacturer to improve and sustain regulatory compliance in operations.

Pharmaceutical equipment and facilities are critical company assets. They reflect the final investment phase in the development of pharmaceutical products that take many years and hundreds of millions of dollars to bring to market.

Hence, management of plant asset information enables companies to enhance quality, reduce operating costs, and optimize the delivery of products to the consumers who need them.

The current regulatory climate of increased inspections and scrutiny from the FDA on manufacturing has elevated cGMP compliance to a long-term business strategy. The state of equipment needs to be ensured to comply with cGMP standard for its entire life cycle.

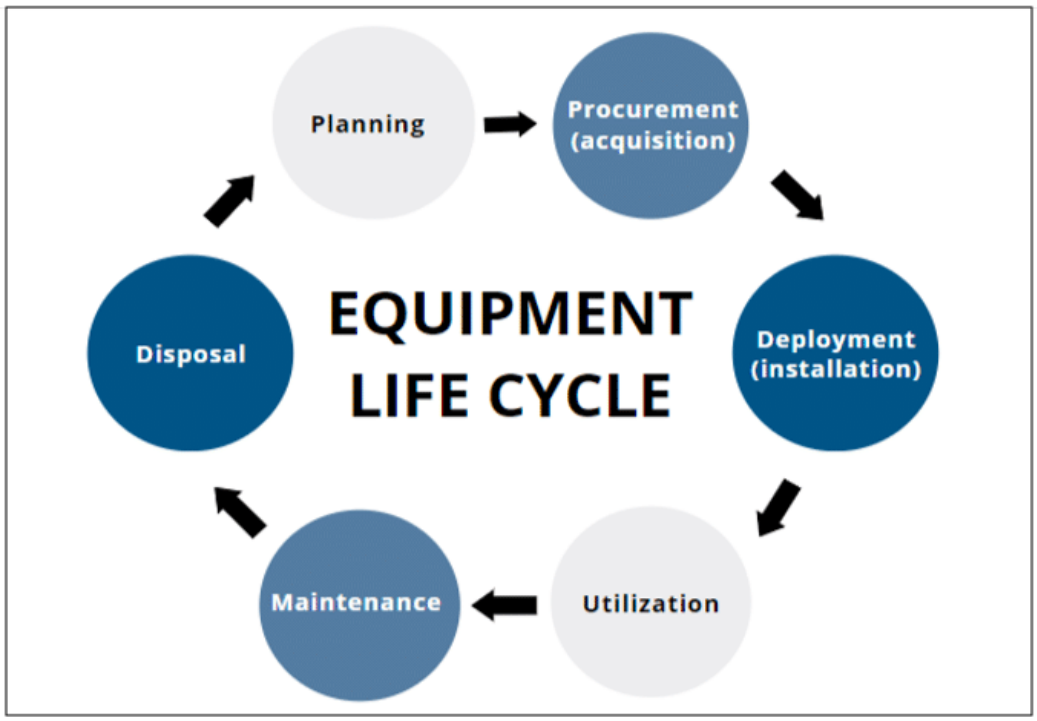
In pharma industry, state of equipment and facilities are generally ensured with qualification/validation and periodic re-qualification.

Qualification/validation can be defined as 'establishing documented evidence which provides a high degree of assurance that specific equipment procured will consistently produce its predetermined specification and quality attributes'. Validation was a term established by the FDA to obligate pharma companies to prove the control and reproducibility of their manufacturing equipment and processes.

The equipment life cycle consists of four phases:

1. Planning
2. Procurement/Acquisition
3. Operation/Maintenance (installation, qualification, utilization, periodic upgradation)
4. Disposal.

Each equipment life cycle phase is critical in supporting the longevity and performance of an asset.c



4.1 Planning

The first equipment life cycle stage is planning for replacing or acquiring a new piece of equipment. Proper planning involves assessing the organization's needs and determining the most cost-effective strategy for procuring a new asset.

Planning for new manufacturing capacity in the pharmaceutical industry is notoriously difficult. New potential blockbuster compounds are discovered that are predicted to have a big future, yet can fail at the last hurdle.

Older products coming 'off patent' may unexpectedly get a new lease of life meaning that existing production capacity must be increased. Consequently, many production facilities are built as multiproduct or general purpose manufacturing units to cater for the wide variety of compounds, processing characteristics, and volumes required.

This article focuses on the need for site master plans that form the basis for future manufacturing development, and addresses some of the early stage process development activities that influence the fundamental basis of the project.

Experienced external service providers can add value to the early stages of pharmaceutical facility planning and design by providing :

- An independent and objective viewpoint
- Methods and experience to analyse the process as a whole
- Modelling and simulation tools
- Benchmarking data
- Methods and procedures to formulate a robust basis for the project to proceed.

Site Master Planning

Despite the high-tech image of pharmaceutical facilities, many of today's manufacturing plants are over 20 years old and had been developed in an unstructured manner. Support services will often have been provided individually on a project-by-project basis, whereas, with hindsight, a more holistic approach would have been more cost-effective. Time pressures on new projects may have resulted in new facilities being located in the most convenient position rather than the best location for the overall site development.

Consequently, many companies have identified the need for a more structured planning approach to their future site developments, involving ;

- Rationalization of existing site facilities
- Reduction in operating costs in support services
- Surveying and census of newly acquired facilities
- Upgrading for good manufacturing practice (GMP), environmental health and safety (EHS), or to incorporate new technologies
- Improvements in flows and departmental relationships

Each pharmaceutical company understands its own business better than any other organization, and in this respect, the site master plan is best undertaken by the company's own resource. However, an external services provider can often add value by :

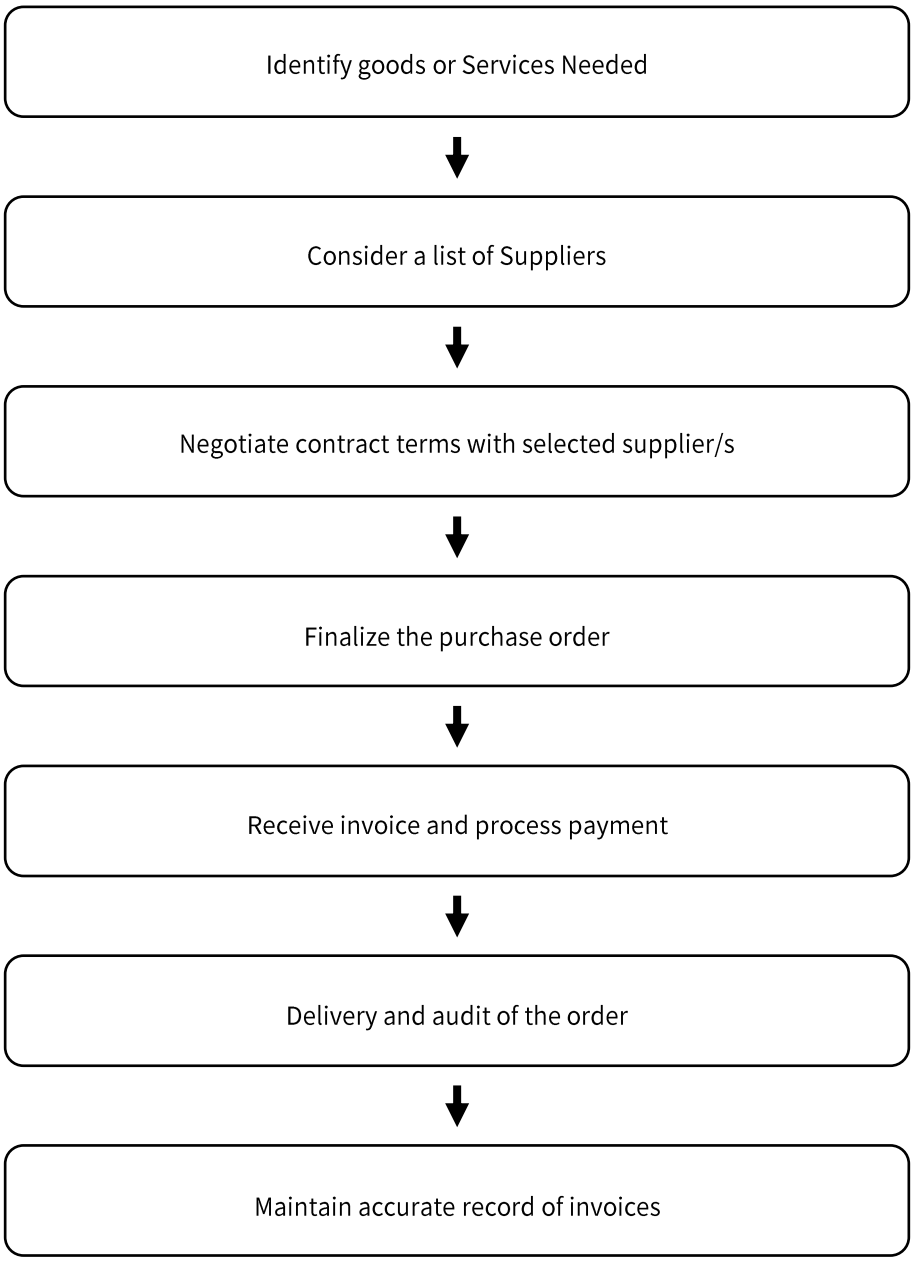
- Bringing an independent and objective approach
- Providing census techniques, questionnaires, and workshops
- Providing industry benchmarking
- Offering specialist knowledge in key technology areas
- Providing resources to enable the study

The resulting master plan will provide the cornerstone for future development of the manufacturing site, and a framework within which each future project can fit.

4.2 Procurement/Acquisition

The second phase of the equipment life cycle is procurement, which means acquiring or purchasing the asset. Before purchase, companies must budget for the asset and negotiate costs to ensure the purchase is as cost-effective as possible. Once the purchase is finalized, the asset is assembled and added to the company's inventory.

Flow chart of Procurement/Acquisition



Step 1

Procurement process should start when it required to obtain goods or services from an outsourced company. With this in mind, the first step should be looking at the whole business and recognizing the needs of each department.

By doing this, engineers can see and examine the totality of all the spending that is required in their company. Therefore, they can outline the areas of the business where they can look at saving money and cutting costs.

This stage of the procurement process is where the budget is set.

Step 2 : Consider a List of Suppliers

Finding the right supplier for a business is vital, so it is not a decision that the purchaser should take lightly. If they choose to work with the wrong supplier, it could have a knock-on effect throughout their whole business.

Not only purchaser could end up paying more than they should for their goods or services, but the delivery times may not be suited to their business; this could delay business operations.

Suppliers are partners, and buyers should not enter into a partnership without doing any research.

Therefore, when a company are looking at its suppliers, it should weigh up their options. It is recommended that the purchaser makes a list and compares all the different options on offer. That way, they can compare the competition against each other, and can see the different areas in which each potential partner excels.

A top supplier should have the following ideal traits :

- Accountability
- Production capabilities
- Ease of communication
- Ethics
- Prioritizing building relationships

Step 3 : Negotiate Contract Terms with Selected Supplier

Project/Engineering team should give technical recommendations based on rationale (previous work experience with supplier, technical comparison with other similar vendors, market updates, services, URS compliances, social media review, etc.), with approval from top authority of the department to purchase department.

After technical recommendation, the team should choose their supplier after negotiating the contract terms.

This stage is important as the buyer want to agree on a price that is fair to both parties, and which makes both happy to work together.

Contracts do not cover only the price/s part. The scope of the whole project – terms, conditions, delivery timelines – are all areas that should be taken into account. Purchaser should always keep a copy of their contract so that they can refer to it should anything fall short of their expected standard.

Analyzing previous contracts are a great way of scoping where they can streamline their costs and save money. If the purchaser feels that it has agreed to a too high a price point in the past, or have agreed on unrealistic terms, then these are mistakes from which the purchaser can learn from, going forward with future negotiations.

Step 4 : Finalize the Purchase Order

Once the purchaser has submitted their contract to the supplier and both parties have agreed to the details, than the purchase order can be finalised.

A purchase order is a document that outlines :

- A description of the goods or service being purchased
- Total costs,
- Quantity,
- Approval of workflow,

- When purchaser has approved their purchase order, it signals to the finance team to release the details to the supplier. Thus, the supplier has access to all the key pieces of information that they need. For example :
    - Reference number (should they need to follow up on any matter)
    - Agreement on payment terms
    - Any other key information they may require
- This document shows another level of agreement between the two parties. Whereas a contract covers the whole collaboration, purchase orders tend to contractually cover individual parts of the collaboration.
- A purchase order is typically sent via email.

Once approved, the finance team will then share the purchase order with the supplier, who will begin to prepare the order and sort payment details.

Step 5 : Receive Invoice and Process Payment

Once the supplier has received the purchase order, the purchaser will receive an invoice from the supplier detailing the agreed price and instructions on how to pay. This invoice will cover details of the order as well in order to make sure that the buyer keeps a record of them for any future reference as may be necessary.

Depending on what the purchaser has agreed in their contract, it will have a certain number of days in which to make the payment. A lot of businesses offer thirty (30) days credit notice, which gives them some leeway to make the payment if they cannot do so at the time of the order. However, this depend on what has been agreed between the buyer and the supplier, and the strength of the relationship between both parties.

It is recommended that purchaser pays their invoices when they are received. This saves any potential problems in paying late or not paying through forgetfulness, and maybe incurring extra costs for being late. In addition, their supplier will appreciate the fact that the purchaser pays on time, every time. This will stand the purchaser in good stead, and will establish a high quality of rapport between both parties.

Step 6 : Delivery and Audit of the Order

Depending on what terms purchaser have agreed in their contract with the supplier, deliveries will arrive at some point in time after their purchase order has been sent in. The purchaser should always keep a record of when the order is delivered in relation to when it was ordered. Thus, the purchaser can keep track of whether the supplier is sticking to the agreed delivery times.

If vendor is not doing so, the purchaser has a proven record of the supplier not holding up to their side of the bargain.

Purchaser should always double-check the order upon arrival in terms of ensuring that what is delivered is exactly what has been ordered in every respect. If there is a mistake in terms of delivery, it could lead to the purchaser letting down their customer base.

Hence, when the order arrives, the purchaser should take the invoice and inspect the delivery. If it notices that something is missing, the supplier should be contacted as quickly as possible to rectify the problem and reduce potential downtime.

Step 7 : Maintain Accurate Record of Invoices

It is essential to keep a record of all invoices and payment records. In case of any audit being carried out, the company will know exactly how much the purchaser have spent throughout the allotted time, and can analyze the spending in more detail. Keeping all invoices is key to working out whether purchaser is staying within budget, or overspending

4.3 Operation/Maintenance

This next stage is, ideally, the longest stage of the equipment life cycle. 'Operation' means using the asset for its intended purpose, and 'maintenance' means carefully maintaining an asset to support its performance over time.

After FAT and SAT are done at vendor site and user site, the equipment shall be installed at the respective location. Qualifications shall be done as URS, DQ, IQ, OQ, and PQ. After successful qualifications, the machine shall be released for its intended usage.

During its utilization, robust periodic maintenance, and health checkups shall be done by engineering or through OEM AMCs. Periodic reviews of each equipment shall be done considering the breakdown trends, and/or any major part replacement after going through its history card. Based on these records, re-qualification of the respective equipment shall be decided in consultation with user and QA department.

On a day-to-day basis, periodic technology upgradation shall be considered in the maintenance program, while tracking through new software technologies available in market. The equipment should be capable of producing with its defined efficiency with qualitative output of products so as to comply with regulatory markets and 21 CFR compliances.

There are many influences in the industry that demand higher quality, more efficient practices, greater industry collaboration, and superior manufacturing design. But as a pharmaceutical manufacturing facility advances to stay competitive and cost-efficient, executive management and frontline leadership must pay close attention to the organization's maintenance performance. While often overlooked or operating under a 'run till it breaks' approach, maintenance performance is crucial in many industries, but it is critically important for pharmaceutical manufacturing. One of the most important things to avoid in a pharma plant is contamination, which can easily occur if old equipment is not maintained correctly.

It is imperative that plant and facility directors, and everyone involved in plant management and leadership, follow Good Manufacturing Practices (GMP) in their manufacturing facilities. If they do not, it can result in tragedy.

4.4 Disposal

The final stage of the equipment life cycle involves properly disposing of the asset. This stage cannot be overlooked, as many organizations are required to follow certain environmental and safety regulations when discarding equipment. The equipment disposal phase entails safely dismantling and disposing of the asset while adhering to important regulations to protect employees and the surrounding environment from any hazards.

5 Replacement of Equipment

Disposal of equipment is often important due to several reasons:

1. Technological Obsolescence

Over time, technology evolves, and older equipment may become outdated. Upgrading to newer technology ensures high efficiency, reliability, and compatibility with modern systems.

2. Energy Efficiency

Newer equipment is often designed to be more energy-efficient, helping organizations reduce energy costs and environmental impact.

3. Maintenance Costs

Older equipment may require more frequent maintenance, leading to higher operational costs. Upgrading can result in lower maintenance expenses and increased reliability.

4. Compliance and Regulations

Changes in industry standards and regulations may necessitate the replacement of outdated equipment to ensure compliance with safety, environmental, and other regulatory requirements.

5. Security Concerns

Older equipment may lack the latest security features, making it more susceptible to cyber threats. Upgrading can enhance cybersecurity measures and protect sensitive data.

6. Improved Performance

Newer equipment often comes with enhanced performance capabilities, enabling organizations to meet growing demand and stay competitive in their respective industries.

7. Warranty and Support

As equipment ages, warranties may expire, and manufacturers may discontinue support. Upgrading ensures access to warranties and ongoing support, reducing the risk of extended downtime.

8. Environmental Impact

Discarding outdated equipment responsibly through recycling or proper disposal methods helps minimize the environmental footprint associated with electronic waste.
In summary, discarding equipment after a long period of installation is crucial for staying technologically competitive, reducing operational costs, ensuring compliance, enhancing security, and minimizing environmental impact.

6 Why Equipment Life Cycle Management Matters

For plants, factories and similar enterprises, the performance of their physical assets is directly correlated to profitability. The longer a physical asset can be used, the greater the return on investment.

However, utilization only goes so far without optimization, which is where equipment life cycle management comes into play.

Strategic asset lifecycle management requires analysing equipment performance and making adjustments accordingly to optimize assets for results.

By taking advantage of software tools and other asset management solutions, companies can take a proactive, hands-on approach to asset management and gain a better understanding of how to effectively support the equipment life cycle.

7 Life Cycle Of Equipment Documents

The document life cycle refers to the various stages that a document goes through from its creation to its eventual disposal or archival. This life cycle typically involves stages such as creation, review and approval, distribution, storage, retrieval, and destruction.

- Creation: in this stage, the document is initially generated, either in a physical or digital format. It may involve writing, typing, or designing the document using appropriate software.

- Review and approval: after creation, the document may need to go through a review and approval process. This involves checking the accuracy, completeness, and compliance of the document with relevant policies or regulations. Any necessary revisions or modifications are made during this stage.

- Distribution: once the document is approved, it needs to be distributed to the intended recipients or stakeholders. This can be done through various means, such as email, printing and mailing, or uploading to a shared drive or document management system.

- Storage: after distribution, the document is stored for future reference or retrieval. This can be in physical filing cabinets or digital repositories such as document management systems or cloud storage platforms. Proper organization and indexing are essential for easy retrieval.

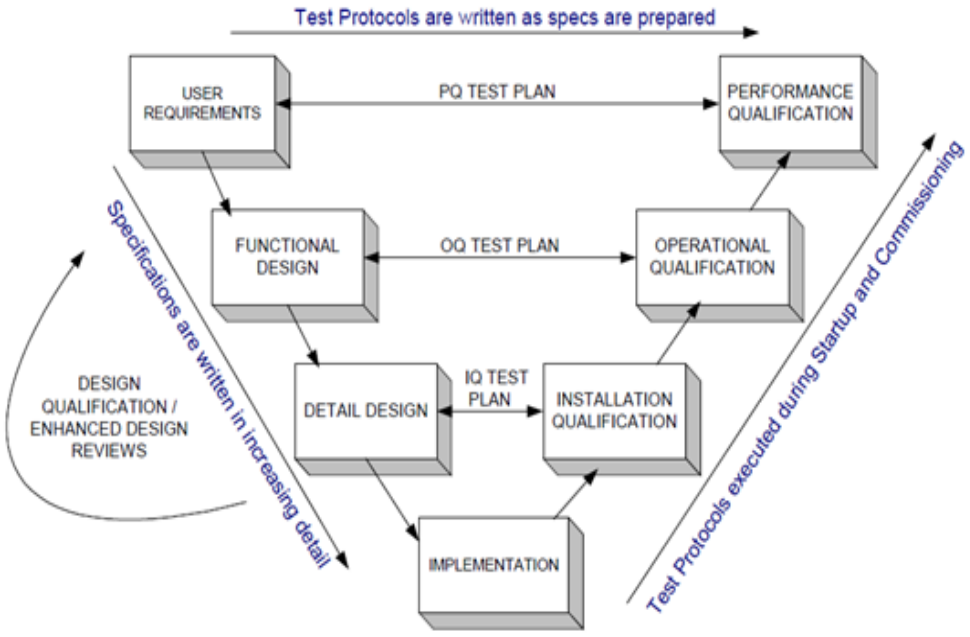
- Retrieval: when needed, the document is retrieved from storage. This can be done by searching for keywords or metadata associated with the document. Quick and efficient retrieval is crucial for effective document management.

- Destruction or Archival: at some point, the document may no longer be needed or relevant. In such cases, it can be securely destroyed following the organization's retention and disposal policies. Alternatively, if the document holds historical or legal value, it may be archived for long-term preservation.

  Throughout the document life cycle, it is important to maintain proper version control, ensure document security and confidentiality, and adhere to relevant regulatory requirements. Document management software and systems can streamline and automate many of these processes, improving efficiency and compliance within an organization.

8 Life Cycle of Equipment Qualification/Validation

In pharma, the equipment life cycle starts with qualification. It is divided into following steps:



- The equipment life cycle ends with retirement of the equipment. Prior to retirement of any equipment, the following parameters must be evaluated:
    - An appropriate change request should be in place.
    - Calibration needs to be performed prior to equipment decommissioning to confirm the performance of previous operations.
    - Filter integrity (if any).
    - Removal of equipment from VMP and master schedules.
    - Update respective layouts.
    - Data migration/availability of application in case data migration is not feasible.
    - Deactivation of all user ids.
    - Backup, archival, and restoration of data.
    - Archival of qualification documents, SOP, and records with meta data.

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    - Archival of qualification documents, SOP, and records with meta data.

- **Objectives of Equipment Qualification:**

    1. To review the requirements of equipment
        - Selection
        - Design
        - Use
        - Maintenance

    2. To discuss the equipment qualification principles, specifically focusing on
        - The different stages of qualification
        - Re-qualification
        - Qualification of in-use equipment

    3. To form the basis for written procedures for production and process control which are designed to ensure that the drug products have the SISPQ (Safety, Identity, Strength, Purity, and Quality).

4. To improve and control overall production reliability and availability.

5. To ensure safety of products.

Qualification requirements of established equipment are decided on the basis of available historical data of that equipment.

As per good laboratory practice, rules and regulations impose similar requirements; hence, assets used for the generation, measurement, or assessment of data shall be adequately tested, calibrated, and/or standardized.

❖ **Documentation**

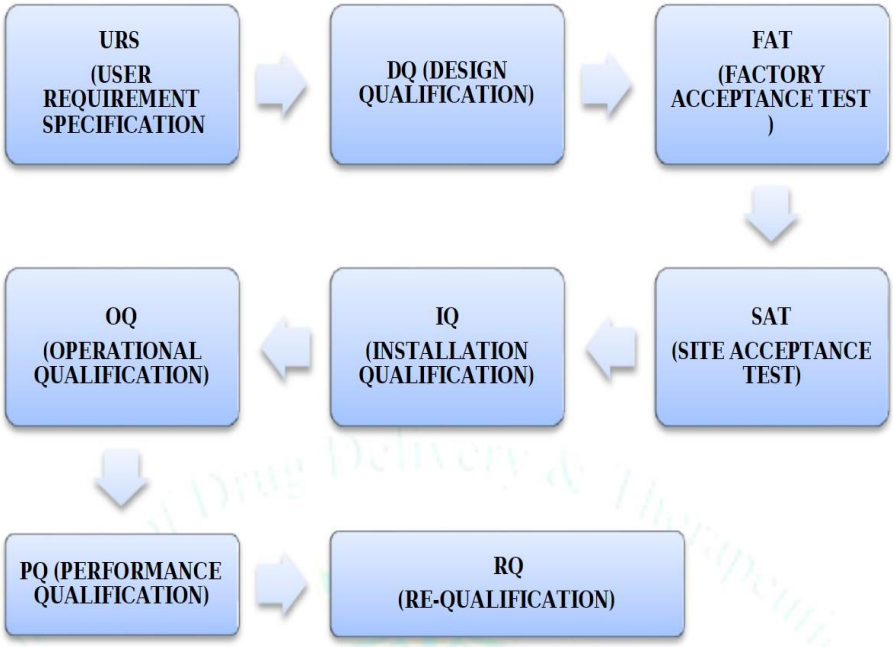
This section provides guidelines on those requirements relating to documentation covering the equipment qualification process.

Appropriate documentation of the qualification program is very important as lack of the documented evidence does not give any meaning to qualification (not documented means not done).

It should not be intended to cover other documentation and reports relating to operation or servicing (e.g., manuals) of the instrument :

- ❖ User Requirement Specification (URS)
- ❖ Design Qualification (DQ)
- ❖ Risk Assessment/Risk Management (RA/RM)
- ❖ Factory Acceptance Test (FAT) and Site Acceptance Test (SAT)
- ❖ Installation Qualification (IQ)
- ❖ Operational Qualification (OQ)
- ❖ Performance Qualification (PQ)
- ❖ Preventive Maintenance
- ❖ Calibration
- ❖ Periodic Re-qualification

9 Stages of Equipment Qualification



Responsibilities

1. URS

i. User department: to prepare URS
ii. Engineering department/Vendor: to verify

2. DQ

i. Engineering department/Vendor: DQ Protocol
ii. User department: to verify

3. IQ

i. Engineering department/Vendor: IQ Protocol
ii. User department: to review
iii. QA department: to approve

4. OQ

i. Engineering department/Vendor: OQ Protocol
ii. User department: to review
iii. QA department: to approve

5. PQ

i. Engineering department/Vendor: PQ Protocol
ii. User department: to review
iii. QA department: to approve

9.1 Gap Analysis

Gap analysis includes the responsibility of applicable personnel, characteristics of equipment to be evaluated, the model number, manufacture serial number, serial asset number, purpose of using, location, document or SOP, number, equipment logs, date of last calibration, personnel training records, a validation certificate, system controls, data storage methods, risk type, the level of the responsible person, and validation by specialist qualification study director.
Gap analysis offers an easy and convenient information for the validation process. The qualification study director wishes to work with the manufacture or vendor, and to notify any abnormality of the facility to them.

Gap Analysis Record

Sr. No.				
Equipment (Asset)				
Make				
Model No.				
Serial No.				
Inst. ID.				
Software				
21 CFR compliance status				
Critical/-Non-Critical Calibration				
IQ/OQ/PQ				
SOP No.				
Document Archival				
Location				
Remark				

9.2 User Requirement Specification

The specification for equipment shall be defined in a URS.

This is the set of owner, user, and engineering requirements necessary and sufficient to create a feasible design meeting the intended purpose of the system, and any GMP risks mitigated to an accepted level. The URS shall be a point of reference throughout the validation life cycle. The URS may be considered as the first initial and important step in the qualification 'flowchart'.

The URS shall cover the specific requirements of the equipment to be procured.
The user department shall prepare the URS for the new equipment, utility and system considering the principles, requirements and precautions that should be followed to safeguard product quality, EHS objectives, GMP and GEP on site.

9.3 Design Qualification

The DQ confirms that the design of the equipment is appropriate and meets with the URS. DQ shall be done based on the product/process requirements.

The compliance of the design with cGMP shall be demonstrated and documented during design review. Design qualification is a combination of user requirement specification, design specification, and functional requirement specification.

Design qualification is used when a design that has been developed from the URS is reviewed and commented on by competent persons to ensure that the designed equipment, while built properly, will satisfy all the detailed specified requirements.
It can also be used to review of the shelf item to ensure it will satisfy the URS.

Flow chart of Design Qualification

URS consisting of design and functional specifications for the equipment shall be verified with the actual equipment details (design and functional) offered by the Supplier. This is called design qualification, and this is a documentation activity and recommended to be completed before the PO is placed (if applicable).

The design qualification protocol shall be given by vendor, and in case vendor does not provide the DQ document, engineering department shall prepare the DQ in coordination with user department and manufacturer/supplier in reference with URS.

The DQ protocol shall be prepared for each equipment based on the quotation/proposal and technical discussions between supplier and user department. The DQ protocol must cover all the necessary diagrams, layouts, location suitability and desired special feature of components, equipment components and their specification, desired material of construction (MOC), location of control panel, electrical requirement, and utility requirement.

The compliance of the design with cGMP and also with the specification must be introduced and documented as per general guidance mentioned in a given qualification protocol.

9.4 Factory Acceptance Test (FAT)

Equipment, especially if incorporating novel or complex technology, shall be evaluated at the vendor site prior to delivery. A team from user engineering and QA shall perform the FAT at Vendor's site after fabrication of equipment and before dispatch to company site, to ensure that the equipment is built/fabricated with the required functionality as specified in URS/DQ.

The FAT shall be documented in supplier's document and the contents of FAT documents shall include at least the following but limited to;

1. **Visual inspection of components:**

   This includes the verification of dimensions, motor, blower specification, MOC, valves (size/no) and safety requirements (alarm/interlocks).

2. **Critical operational requirements:**

   This includes the verification of critical operations based on URS.

3. **Operational test (if applicable):**

   The critical operations shall be performed under FAT. If equipment is identified as critical/sophisticated, FAT shall be performed depending upon the complexity of equipment.

9.5 Site Acceptance Test (SAT) :

SAT shall be applicable for major customized machines. Vendor shall provide the SAT documents, and if vendor does not provide the SAT protocol, in-house protocol shall be prepared by engineering department in coordination with user.

- SAT shall be performed by relevant subject matter experts of different functional areas like Engineering, Production, QA and QC at company site, after the receipt of equipment, with the following objectives ;

    1. To inspect and ensure that the equipment received at company site is in good state and no components are damaged during transportation.

    2. To provide documented evidence that the equipment received at company site is in good state and meeting specifications as designed.

- The main contents of SAT shall include, but is not limited to, the following :

    1. Equipment details,

    2. Receipt of consignment,

    3. Inspection of equipment consignment,

    4. Inspection of equipment,

    5. Inspection of major components,

    6. Accessories/spare parts

    7. Master documents: maintenance/user's manual/calibration certificate.

9.6 Installation Qualification

Documented verification that all aspects of the system, facility, utility or equipment that can affect product quality installed or modified, comply with the approved design and the manufacturer's recommendations.

IQ applies to a new, pre-owned, or an existing onsite instrument, but not to already existing qualified instrument. The activities and documentation associated to IQ are as follows:

IQ shall be performed on new or modified equipment, for establishing the evidence that all key aspects of the process equipment and ancillary system installation are as per the requirements of company's approved specifications and recommendations.

The main contents of IQ include but are not limited to, the following :

- Physical verification of equipment
- Manufacturer specification verification
- Purchase order specifications
- Piping and installation drawing (P&ID)
- Construction and installation
- Component verification
- Test equipment instrument calibration
- Critical component calibration requirements
- Required spare parts
- Cleaning/Passivation
- Weld inspection
- System installation compliance to cGMP

- Change/replacement spare parts
- Physical verification of area
- Verification of material of construction
- Identification of instrument to be calibrated
- Verification of utilities
- Verification of safety features
- Identification/preparation of SOPs for operation, cleaning, calibration, and preventive maintenance

Identification/preparation of SOPs for operation, cleaning, calibration, and preventive maintenance IQ protocol shall be provided by vendor and shall be reviewed and approved from user and engineering departments. After approval, QA department shall authorize the protocol for further execution.

After completion of an execution by vendor, documents review of executed protocol, raw data shall be done by user, engineering, and QA. After successful completion of the protocol execution activity, proceed for the post approval of the document/protocol..

In case the vendor is not providing the installation qualification document, user department shall prepare the in-house protocol in coordination with engineering and QA.
After successful completion of the protocol activity, all instruments associated with the equipment shall be identified and shall be added in the master list of instruments as applicable.

- Installation qualification to be re-qualified in case of :
  - Transfer of the equipment from one location to another (excluding portable type).
  - In case of major changes or to address the qualification of newly added component.

9.7 Operational Qualification

After successful completion of the IQ protocol activity, operational qualification shall be performed to verify that the equipment operates in accordance with design specifications, manufacturer recommendations, and meeting the operational cGMP requirements.

This provides documented verification that all angles and functions of a system, facility, utility, or equipment that can affect quality of product, operate properly within all anticipated operating ranges as required by the process, capability, procedures, and design specifications.

- The OQ phase focuses on following parameters :

  All testing equipment shall be identified and calibrated before use. Test methods shall be authorized, implemented and the resulting data shall be collected and evaluated. It is important at this stage to ensure that all operational test data conforms to predetermined acceptance criteria for the studies undertaken.

  OQ protocol shall be provided by the vendor, and shall be reviewed and approved from the user and engineering department. After approval, QA department shall authorize the protocol for further execution.

  After completion of an execution by vendor, documents review of executed protocol, raw data shall be done by user, engineering, and QA. After successful completion of the protocol execution activity, proceed for the post approval of the document/protocol..

  The OQ shall be performed in accordance with the preapproved written protocol.

- The contents of OQ shall include at least the following but not limited to :
    - Calibration review of critical instruments/components.
    - Calibration review of reference test equipment/instrument.
    - Methodology for operational procedure to includes the tests that have been developed from knowledge of processes, systems, and equipment to ensure the system is operating as designed.
    - Test including the conditions encompassing upper and lower operating limits, and/or 'worst condition'.
    - Testing of safety features and alarm testing.
    - Power failure verification.
    - Computer system validation.
    - Verification of SOP.
    - Verification of PM.
      OQ shall be performed as a combined installation/operational qualification, i.e., IOQ and IOPQ. If IOPQ needs to be performed, the same format shall be used for protocol preparation, and PQ test shall be incorporated as required.
      The completion of a successful OQ shall allow the finalization of SOP and cleaning procedures, operator training, and PM requirement.
- Operational qualification should be re-qualified in case of
    - Transfer of the equipment from one location to another (excluding portable type).
    - In case of major changes or to address the qualification of newly added component, where RQ shall be required.

9.8 Performance Qualification

After successful completion of the IQ protocol activity, operational qualification shall be performed to verify that the equipment, or equipment under anticipated conditions, is providing consistent performance required to produce a product that meets all predetermined requirements.

This provides documented verification that all aspects of a system, facility, utility, or equipment that can affect product quality, does produce the required output over an extended period under typical operating conditions and interferences.

PQ shall be carried out in accordance with a pre-approved written protocol. The specific PQ attributes developed from the finished product specifications, R&D data, cGMP requirements, and other specific documentation shall be verified along with the acceptance criteria.

SOP of 'operation and cleaning of equipment' and 'PM procedure' must be approved prior to starting the PQ.

The data generated under PQ shall not be considered for routine production and for human use. It shall be restricted to the qualification purpose only.

The PQ test shall be considered successful if all the test results meet the acceptance criteria.
If vendor provided PQ protocol is available, then it shall be reviewed and approved from user and engineering department. After approval, QA department shall authorize the protocol for further execution.

After completion of an execution by vendor, documents review of executed protocol, raw data shall be done by user, engineering, and QA. After successful completion of the protocol execution activity, proceed for the post approval of the document/protocol..

In case the vendor does not provide the PQ document, user department shall prepare the in-house protocol in coordination with engineering department and QA.

- PQ must include the following but not limited to :
    - Prerequisite for PQ
    - Tests, with production materials, qualified substitutes, or simulated products, that have been developed from knowledge of the process and the equipment
    - Tests including the condition or set of conditions encompassing upper and lower operating limits (worst case)
    - Qualification done or documented by the equipment supplier shall be also accepted after reviewing it for adequacy and approval by responsible personnel from the company
    - After successful completion of PQ, QA shall release the equipment for routine operation
    - During PQ, equipment shall be qualified for the entire operating range as per DQ. However, PQ can also be performed simultaneously with process validation of product to cover the complete range of product manufactured
    - For such qualification, summary report of validation activity shall be prepared, and this report shall be attached with qualification documents
- Performance qualification to be re-qualified in case of :
    - Replacement/modifications of existing equipment/component in the equipment with a new one, which can have a direct impact on the performance of the equipment
    - Any major changes to the existing equipment/system, which can affect the overall performance of the equipment
    - If system is found to be malfunctioning during performance qualification.

9.9 Re-qualification

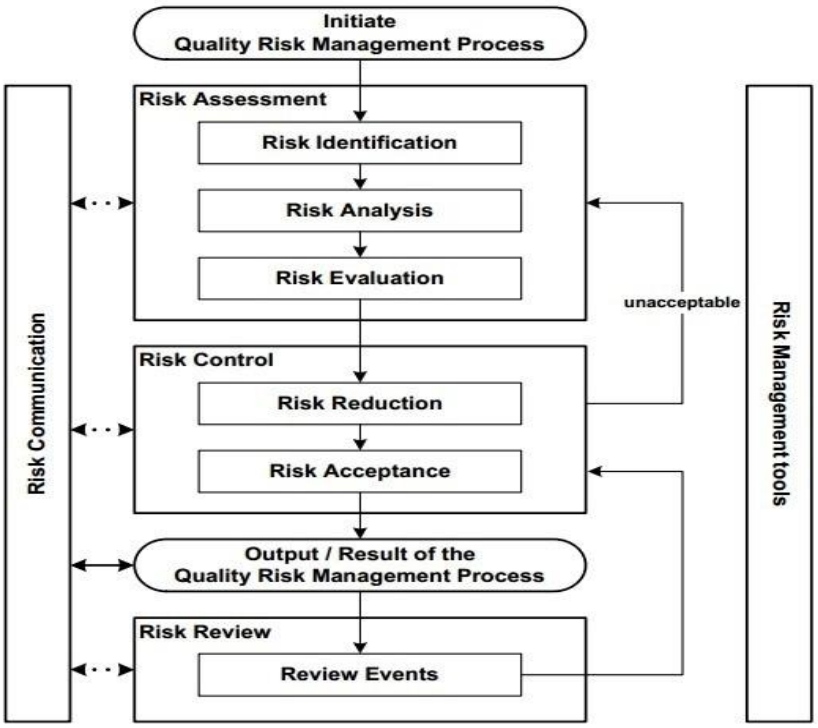
Re-qualification is an activity involving complete, or portions of of qualification activities, like IQ, OQ and PQ.

Re-qualification is carried out for the following reasons :

- To overcome deficiencies observed in qualification
- Need for any new additions in qualification tests
- To qualify the modifications done in equipment or process due to equipment failure,
- Findings/recommendations from inspections/audits/PQR, etc.
- Inputs from preventive maintenance/calibration program
- Equipment upgradation
- During testing of the elements impacted by the changes or qualification parameters found to be deficient, all critical components of the equipment verified for functionality during Re-Qualification.

10 Stages of Equipment Qualification

Flow of Risk Assessment/Risk Management



Qualification is to produce written evidence that processes and equipment work within their specifications to get quality products.
Working with processes and equipment, there are always risks that may or may not be acceptable.
To ensure the product quality, a crisis evaluation or quality risk management shall be performed.

- This requires rigorous assessment of the potential critical and non-critical points of the process or equipment.

Critical Equipment

These are equipment that comes into direct contact with product which may affect the SISPQ (Safety, Identity, Strength, Purity and Quality) of products. Critical equipment often impacts safety, regulatory conformity, cost, or operational procedures output.

Examples are laminar air flow, PH meter, HPLC, PCR, chromatographic system, etc.

Non-critical Equipment

These are the equipment that do not come into direct contact with product and, thus, do not affect SISPQ (Safety, Identity, Strength, Purity and Quality) of products.

Examples are refrigerator, centrifuge, weighing balance, CO2 incubator, etc.

- Using three-dimensional risk factors like severity, probability and detectability, risk shall be quantified. A risk probability number (RPN), is calculated based on these three factors.

- Risk priority number (RPN) assessment is a function which indicates the severity of the effect of failure, the probability of occurrence, and the ease of detection for each failure mode. RPN is calculated as per the formula below :

  RPN = S × O × D
  where
  S - the severity of the effect of failure,
  O - the probability of occurrence, and
  D - the ease of detection.

  In the choice of action against failure modes, RPN may not have any role, but it will help in indicating the threshold values for determining the areas of greatest concentration. In other words, a failure mode with a high RPN number should have the highest priority in the analysis and corrective action.

- Risk based approach impact assessment should focus on product impact. Every equipment needs to be classified between direct impact, indirect impact, or no impact to the product.

- Purpose of the equipment impact risk assessment

  - Determine equipment criticality based on impact to product safety.

  - Determine level of qualification required for new direct impact equipment.

  - Determine level of qualification required when changes are made in qualified equipment.

11 Preventive Maintenance

To sustain the equipment condition and achieve the accepted life with smooth functioning of the machine, it is very important to emphasize the preventive maintenance of each equipment and calibration thereof. In PM, the facility staff are performing health check of equipment/system/instrument at predefined frequency, so as to ensure optimum functioning and to minimize breakdown.

- Each equipment or system or instrument shall have preventive maintenance procedure in the shape of a SOP.
- Each preventive maintenance SOP can be equipment/system/component specific, or depending upon its application, there can be a single SOP or common SOP for carrying maintenance of different equipment/ system/component.
- Rationale shall be prepared for preparation of the check list and SOP for each equipment/system/instrument. The rationale shall contain :
    - Original equipment manufacturer recommendation
    - The performance specification of the equipment/system/component
    - Meeting of regulatory requirement
    - Details of maximizing uptime and minimizing corrective maintenance

Check list shall be dynamic in nature. Based on observations during PM/breakdown maintenance, deviations, etc., new check points may be added/upgraded so as to ensure reduction in down time/smooth operation of machine.

- Just like validation master plan, the preventive maintenance program shall be developed to ensure online and continuous preventive maintenance.

Category of Equipment	Minor Check Frequency	Major Check Frequency
Primary Equipment	Quarterly ± 7 Days	Half-Yearly ± 10 days
Secondary Equipment	Half-Yearly ± 10 days	Yearly ± 15 days
Ancillary Equipment	Half-Yearly ± 15 days	Yearly ± 15 days

All equipment is to be divided into three categories

- **Primary**

Those that have significant impact on the quality of product.

- **Secondary**

Those that have less impact, compared to primary equipment on the quality of product.

- **Ancillary**

Those that have no significant or direct impact on the quality attributes of the product.

Primary, secondary and ancillary equipment should be considered for preventive maintenance as per the following frequencies and tolerances:

- Preventive maintenance SOPs of all equipment define the frequency and activities in two categories, as shown below;

Minor Check

This includes the visual observation of assembly or parts of the equipment against operational checks of the equipment.

All the minor check observation shall be recorded in in form of preventive maintenance SOP of respective equipment.

Major Check

These are required due to dismantling/servicing of the assembly or parts of the equipment based on the observations of checks, which are subjected to day-to-day wear and tear.

As per defined procedure, preventive maintenance should be carried out and all the major check should be recorded in the form of preventive maintenance SOPs of respective equipment.

Equipment shall be evaluated based on following logical factors, in order to derive appropriate frequencies, tolerances, and check points for preventive maintenance, as applicable.

a. Based on equipment category, considering the impact on the product quality and criticality of the equipment.

b. Recommendations provided in operational and maintenance manual by the Original Equipment Manufacturer (OEM).

c. Based on learning and experience of existing preventive maintenance procedure.

d. Based on investigation finding of deviations, CAPA of market complaints, root cause and CAPA of breakdowns of equipment.

e. Based on Health, Safety and Environment (HSE) concerns.

f. Based on evaluation of Change Control Form (CCF).

g. Based on evaluation of yearly periodic review of the equipment and performance throughout the life of the equipment.

- Steps for Accessing Data of Equipment for Preventive Maintenance

  - **Registration and PM Check List for Equipment Preventive Maintenance**

  - All equipment that required preventive maintenance in the organization or plant can be included in the software with an auto generated number or existing manual numbers. All types of PM checklist for the activity, like daily, weekly, fortnightly, monthly, quarterly, half-yearly and yearly checklists can be generated in the software.

  - PM Scheduler E-Mail Notifications

    PM schedule should be created based on the plant level requirements for the year.

  - Work Sheet Generation for the User for PM

    Work sheet will be generated for the required user to perform the PM activity on the day of activity.

  - PM Check List Results Approval

    The completed checklist can be sent for approval process and status approval.

  - Performance Management

    Pie Chart view is available for the senior level users to know the overall status of the calibrations.

  - MIS Reports

    Management Information Reports are generated automatically for online status and it will be generated as a PDF copy.

    Advantages Comply with all regulatory requirements like 21 CFR Part11, Annexure 11 of MHRA and GAMP-5.

    - Scalable installation and use across plant or enterprise. .
    - Automatic notifications to all users.
    - Work assignments to the required personnel.
    - Automatic tracking status.
    - Online approvals of PM checklist.

12 Calibration

- Calibration is a process that demonstrates that a particular instrument or device produces results within specified limits, as compared to those produced by a traceable standard over an appropriate range of measurements.

- Every equipment has instruments which ensures the accuracy of critical process parameters of equipment. All such instrument need to be accurate in its measurement and perform consistently during its intended use.

- Hence, calibration of all such instruments is critical for optimum equipment performance and for enhancing its life cycle.

- Calibration master plan shall be prepared and periodic calibration shall be performed for all such associated instruments.

13 Importance of AMC

An equipment's Annual Maintenance Contract (AMC) refers to the agreement for property repair and maintenance. It is an agreement between a company and a service provider.

The service may be for any property that is company-owned, and may include many equipment from large manufacturing machines to printers and computers.

Maintenance is a key factor to extend the life of an equipment

Having a set of AMCs covering plant and equipment results in a lot of advantages. Downtime is reduced and the overall costs are also lowered. However, many times it is overlooked at the operational level, and units pay attention to AMC only when it becomes an emergency.

- There are many reasons for this oversight, such as:
    - Inconvenient timing,
    - Lack of resources,
    - Lack of planning or disorganization.

In many cases, all these factors become a problem all at once, such that there is a huge maintenance deficit. It needs immediate addressing, and may add up to a huge sum of money in emergency repairs, operations, and facility safety and part defects. Most of such costs are avoidable, since with a little bit of foresight, AMCs could have been entered into, and these would have saved equipment and product from major loss.

- How do manufacturers address these issues?

In order to ensure proper and regular maintenance manufacturers enter into equipment AMC contracts with external service providers.

The annual maintenance contract, or the agreement for maintenance, is an ongoing maintenance agreement agreed by a service provider or by the manufacturing facility through the service provider. The industrial contract maintenance protects the plant's most critical aspect, by arranging;

- Regular diagnostics and check-ups
- Scheduled preventive maintenance
- Documentation and process development
- Dedicated certified and skilled technicians

A comprehensive AMC includes implementation of smart technology, safety training, existing workforce training, procedure implementation, and many more aspects.

❖ **Equipment Life Cycle Optimization for Enhanced Results**

Thanks to modern technology, equipment life cycle management has never been easier to harness, with tools such as Enterprise Asset Management software (EAM software), CMMS (Computerized Maintenance Management System), etc.

With maintenance software and other intelligent solutions, organizations can take better control of the enterprise asset management process to maximize equipment performance over time.

Here are just a few examples of asset management solutions that help support asset life cycle management.

EAM software :

Enterprise Asset Management (EAM) incorporates the management and maintenance of physical assets owned by a company throughout the entire life cycle of an asset, from capital planning, procurement, installation, performance, maintenance, compliance, risk management, through to asset disposal.

EAM software helps organizations to plan, optimize, execute, and track the necessary activities, priorities, skills, materials, tools, and information associated with an asset.

Failure to manage and maintain enterprise assets can lead to unplanned downtime, suboptimal asset performance, and supply shortages.

Some organizations also rely on EAM systems to demonstrate compliance with regulatory bodies to preclude liability if a failure occurs.

❖ **How does an EAM system work?**

Although traditional EAM systems were installed on the premise, the technology has evolved, with modern systems running in the cloud.

A cloud platform provides a range of benefits including larger data storage capacities, stronger security, and easier integration with complementary applications such as supply chain management systems, mobile workforce management systems, Internet of Things (IoT) sensor systems, GIS (Geographic Information Systems), GPS, and other applications.

❖ The main steps in enterprise asset management

1. **Collect and store asset data in the cloud.**
   Leverage the agility of the cloud to collect and track asset information in a centralized data repository. Use powerful analytics and extract detailed insights to understand how assets are performing and where attention is needed.

2. **Use the data to guide asset strategy and optimize productivity.**
   Assess risk and identify potential equipment failures before they can happen, using machine learning, digital twin technology, and predictive analytics.
   Identify and carry out maintenance requirements in advance so that asset availability is maximized.

3. **Proactively schedule inspections and maintenance work.**
   Use integrated processes and data to plan, schedule, and execute maintenance work and inspections. Prioritize critical assets to minimize downtime. Detect, report, and resolve issues quickly.

4. **Extend EAM system capabilities to assets and workers in the field.**
   Manage work orders and asset processes online or offline, with rich visualizations and location services.
   Integrate GIS data to provide a map-based user experience for remote workers and assets. Track and manage maintenance processes, data, and work orders from anywhere.

❖ **Benefits of EAM systems**

With an EAM system, companies can centralize all their asset information in one place, making it easier to monitor and optimize the assets and proactively inspect and maintain them. Planning and scheduling of tasks and workers are streamlined and automated, leading to increased productivity, while also safeguarding both workers and the environment.
Key benefits include :

1. **Integrated data stores**
   A centralized view of the operation incorporates data from all types of assets, regardless of source or location.
   This single blueprint can be used to coherently monitor asset performance, plan for inspection and maintenance work, and minimize disruptions to productivity.

2. **Real-time decision-making**
   Time-consuming, paper-based reporting and stale or inaccurate information is replaced with real-time data. Predictive analytics support proactive maintenance and repairs, with the necessary work automatically scheduled.
   Critical assets can be prioritized to optimize productivity, and resiliency is augmented when responding to or managing emergencies and unexpected scenarios.

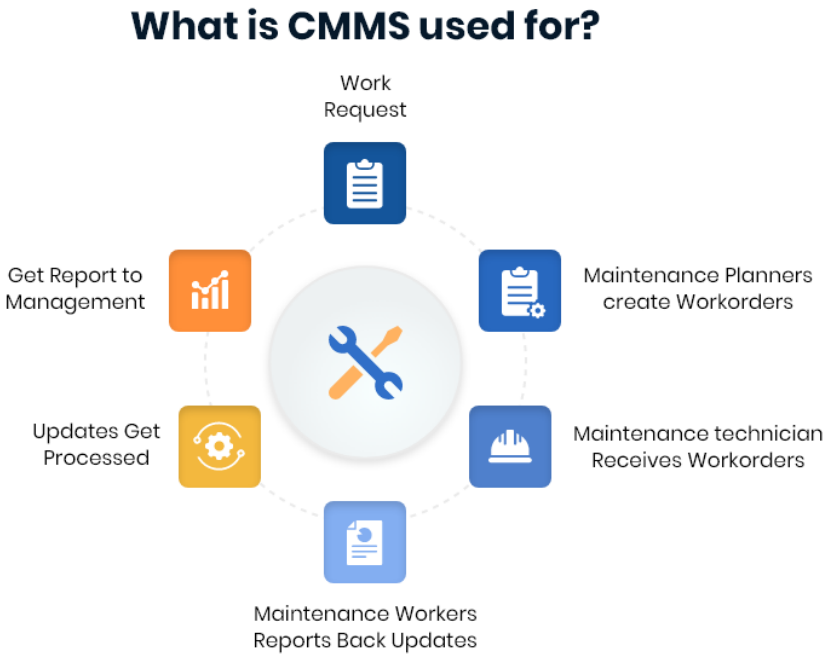
3. **End-to-end life cycle management**
   The entire life cycle of an asset is managed. Data from assets can be integrated with maintenance processes to predict and visualize asset status and behaviour from cradle to grave. Performance benchmarks are clearly defined, highlighting when immediate attention is needed for equipment that is underperforming.

4. **Improved environmental, health, and safety measures**
   Potential outcomes can be identified proactively and action can be taken before an asset failure causes worker injuries and accidents. Spills, fires, and other harmful outcomes are avoided, safeguarding the environment.
   Carbon footprints are reduced by running equipment optimally and minimizing resources used in maintenance cycles such as truck rolls and other heavy equipment.
   Compliance with regulatory bodies can be easily proven to preclude liability.

❖ **CMMS software :**

Pharmaceutical companies are held to strict standards by the United States Food and Drug Administration (FDA) and other international standards. Ensuring compliance with regulations like 21 CFR Part 11 is essential to keep manufacturing operations running smoothly and protect the health and safety of the end user.

A Computerized Maintenance Management System (CMMS) software is a powerful tool for compliance. The best CMMS software for pharmaceuticals will also provide maintenance teams with countless other benefits.



❖ **21 CFR Part 11 : What Pharmaceutical Companies Need to Know**

FDA Title 21 CFR Part 11 is a fundamental compliance requirement for pharmaceutical companies. 21 CFR Part 11 is enforced on biotechnology, biomedical, and pharmaceutical suppliers in the public health sector. For these highly regulated industries, every step of the manufacturing and maintenance process must be carefully and accurately documented to protect the end users' health and safety.

21 CFR Part 11 establishes the standards for ensuring that electronic records are just as complete, accurate, and authentic as traditional paper-based records. The regulation outlines requirements for record storage and retrieval, electronic signatures, system validation, and more.

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❖ **Complying with International Pharmaceutical Regulations like ISO 13485, EudraLex Annex 11, and GLP**

In addition to FDA compliance, pharma companies that do business outside of the United States must also comply with international laws and standards for the manufacturing and distribution of over-the-counter medications.

For example, ISO 13485 is the international standard that specifies controls for quality management systems. In addition, the EU version of 21 CFR Part 11, known as EudraLex Annex 11, discloses how medical device manufacturers should validate their software systems.

Good Laboratory Practices (GLPs) are fundamental to confirming the identity and quality of a drug.

Every plant must adhere to Good Manufacturing Practices (GMP) under the appropriate conditions, where equipment is properly maintained, the necessary controls are in place, and employees are qualified to do the job.

GMPs are characterized by the reliability of testing procedures, detection of quality deviations, and sourcing of raw materials. GMPs are meant to eliminate traces of contamination or mistakes in labelling containers.

❖ **Benefits of a CMMS for Pharmaceutical Manufacturing**

1. Reduce Maintenance Costs

Leveraging a life sciences CMMS software and incorporating best practices for equipment maintenance gives organizations a competitive edge while reducing costs. For example, a well-executed maintenance strategy reduces time and costs associated with unplanned maintenance and downtime.

2. Keep Complete and Accurate Maintenance Records

A centralized maintenance platform helps plant supervisors schedule and document maintenance duties, keep track of individual assets, and document methods to continue moving items through the pipeline. CMMS software seamlessly handles work order approvals, and can even deliver predictive maintenance abilities that alert staff about equipment malfunctions ahead of time. It schedules days for cleaning duties and testing of machinery.

3. Ensure Product Safety and Integrity through Computer Systems Validation

A CMMS combines maintenance, documentation, and compliance into a maintenance management dashboard.

It aligns with Computer Systems Validation (CSV) standards for product safety and data integrity to demonstrate to auditors that your software has been validated for its intended use and will perform the necessary functions.

4. Approach Audits with Confidence

A CSV service speeds up CMMS validation under GxP guidelines to guarantee audit readiness. It includes features for operational qualifications, accessing records on demand, and acquiring functional specifications.

5. Maximize Uptime and Throughput

Company maintenance staff can get access to streamlined reports and audited records from nearly any location.

For example, a CMMS solution can be used to notify staff about equipment maintenance requirements before they lead to failure, unplanned downtime, or damaged product.

❖ **What is the difference between EAM and CMMS?**

A computerized maintenance management system (CMMS) consists of maintenance and operational functions that focus predominantly on the management of asset uptime.

Decision-making is insular and limited to the maintenance and operations personnel that use these systems. A CMMS allows asset-intensive industries to focus on driving asset uptime.

An EAM system is designed to address the total life cycle management of an asset, from capital planning, procurement, installation, performance, maintenance, compliance, risk management, through to asset disposal.

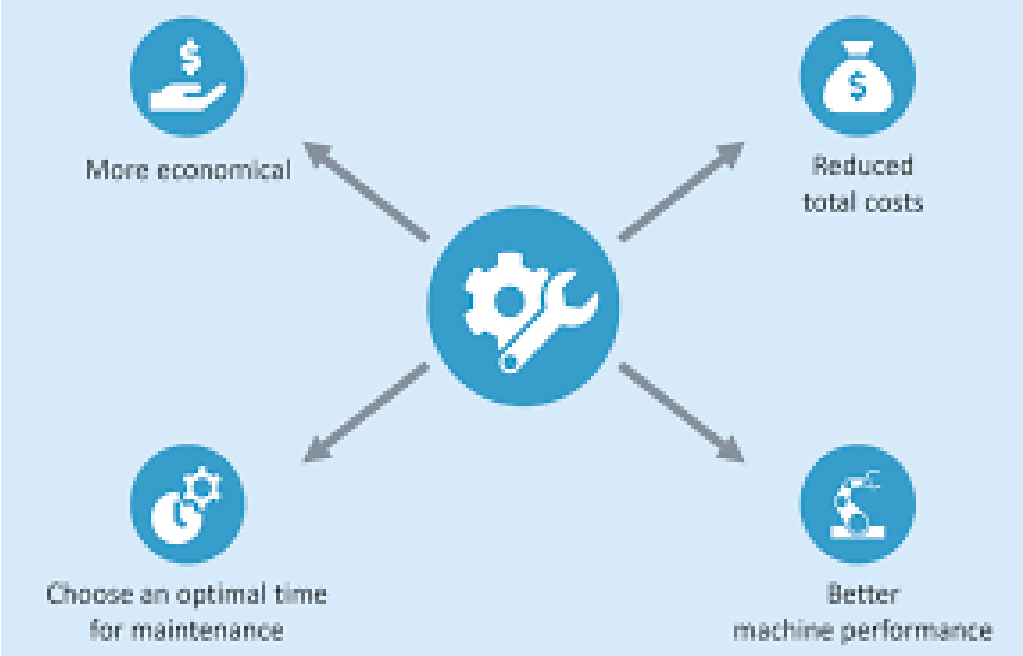
Along with maintenance and operations, users include finance, production, compliance, and other business stakeholders. With such a broad base of capabilities, decision-making extends beyond the maintenance and operations teams to include senior leadership and C-suite personnel. An EAM system allows asset-intensive industries to manage the life cycle of an asset in its entirety.

❖ **Predictive Maintenance Tools**

Predictive maintenance is a data-driven approach that collects and analyses machine health and performance data, in order to predict when an asset will fail.
Maintenance and reliability professionals are notified as assets start to show initial signs of failure, thereby giving enough time for engineers and technicians to schedule repairs.

This prediction and notification help to identify developing issues, preventing unplanned downtime in the future.
It offers organizations the potential to produce better products at a faster rate without sacrificing quality or consistency.

Automated AI-based predictive maintenance in pharmaceutical industry consists of wireless industrial IoT sensors and analytics platform, that crunches complex machine data to provide meaningful and actionable insights. Improved condition monitoring of industrial assets using automated AI-based predictive maintenance helps to maximize the uptime of machines and equipment sets.



❖ **Benefits of Predictive Maintenance in Pharmaceutical industry**

Predictive maintenance can have significant impact on a business in the pharmaceutical industry. It can allow for production to stay consistent and predictable, which in turn means companies can maintain a competitive edge in an ever-changing market.

Intelligent predictive maintenance solutions enable manufacturing plants to work more efficiently and generate higher yields. Investing in predictive maintenance solutions helps maintenance and reliability professionals identify areas that require attention before they become problems.

Predictive maintenance is also an excellent way to reduce downtime and increase productivity in the pharmaceutical industry. When downtime is reduced from hours to minutes, it can be translated into huge savings for the business, thereby improving the bottom-line.

AI-based predictive maintenance allows maintenance personnel to optimize the resources, by identifying faults at an early stage. This ensures that the maintenance technicians/engineers are dispatched only after a particular defect has been identified in an asset, thereby eliminating the need for a time-based maintenance strategy.

In the end, predictive maintenance is not only good for the company's bottom line; it also reduces risk. Manufacturers can avoid costly shutdowns or emergency repairs because the predictive maintenance solution will notify the maintenance personnel about potential issues before they become serious problems.

The benefits of wireless predictive maintenance technologies have heightened the interest of the pharmaceutical industry professionals, mainly due to its potential to prevent unplanned downtime and improve operational efficiency.

A single hour of downtime can potentially cost millions of dollars in lost productivity, and predictive maintenance promises to make maintenance practices more efficient and effective.

Real-time insights about the health and performance of various equipment sets and machinery enables personnel to make smarter and accurate decisions that help the overall productivity of the manufacturing unit.

❖ **Equipment Aging, Possible Upgradation and Replacement :**

Generally, replacement of equipment is simply linked with ageing of equipment. Ageing is not about how old the equipment is; it is about its condition, and how that is changing over time.

Ageing is the effect whereby a component suffers some form of material deterioration and damage (usually, but not necessarily, associated with time in service) with an increasing likelihood of failure over its remaining lifetime.

The significance of deterioration and damage relates to the potential effect on the equipment performance, viz. functionality, availability, reliability, and safety. Just because an item of equipment is old does not necessarily mean that it is significantly deteriorating, damaged and needs replacement. All types of equipment can be susceptible to ageing mechanisms. The equipment's intended usage shall be proportional with the life cycle of that equipment.

Possible technology upgradation shall be done with OEM support in accordance with the current regulatory requirements and 21 CFR compliances. Periodic review shall be done with respect to breakdown data, equipment availability, performance for efficiency and good quality products.

Age of facility or plant can no longer be the sole reason for retiring the facility or plant. 'Ageing' is not directly related to chronological age. There are many examples of very old plant remaining fully fit for purpose, and of recent plant showing evidence of accelerated or early ageing, e.g., due to corrosion, fatigue, or erosion failures.

To increase the life of the facility or plant, regular maintenance of the facility shall be carried out by applying suitable paint to walls and structure, filling of cracks by suitable material, and water proofing the terrace.

Inspection of the facility shall be carried out by competent person and the observations shall be implemented to increase the life of the facility or plant.

Depends on the geographical condition of the area and climatic condition, stability certificate shall be taken at regular intervals from the competent agency.

❖ **Procedure**

1. Indicators to determine if an equipment/facility is aging

It is often difficult to detect the signs of aging, since the aging process occurs over a continuum that may not be obvious at first glance. When evaluating an equipment/facility to determine if it is aging, there are three main areas of impact to consider – regulatory/quality, facility/equipment, and process/supply – that may present potential indicators.

Regulatory/Quality

- ❖ Increase in number of deviations, out of specification (OOS) results, CAPAs, changes (e.g., process, equipment, or facility), customer complaints, increase in audit/inspection observations, etc.

Facility/Equipment

- ❖ Physical deterioration of systems (e.g., HVAC systems, utilities) and surface finishes.
- ❖ Inability to procure parts or services for existing equipment.
- ❖ Obsolete technologies (vendors no longer provide support).
- ❖ Increasing maintenance or metallurgical issues and related costs.
- ❖ Increasing contamination issues.

- Increasing operational overhead cost.

Process/Supply

- Manufacturing capacity issues and resulting inability to meet market demand.
- Increasing process deviations, downtime, failures, variability, re-work.
- Proportional increase in maintenance.

Apart from the above indicators, following are other key indicators to decide equipment retirement :

- Depreciation.
- Obsolescence (age/vendor support/spare part/technology).
- Maintainability cost (as percentage of cost of machine).
- Loss of efficiency.
- Quality compliance (CGMP).
- Mean time between failure (MTBF).
- Equipment criticality.

While these are not the only indicators that can be used to determine if an equipment or a facility requires reconditioning, or moderniza¬tion, examining these areas will provide an objective overview of the current status of the equipment or facility and its capabilities. If the equipment is having a negative impact on the safety and quality of the products produced there, replacement or up-gradation of equipment is definitely needed.

The statistical evaluation of process parameters and quality attributes provide an insight that the process and equipment are suitable of producing a product with consistent quality. In case the statistical assessment is acceptable, it can be inferred that the equipment used in the processing is suitable for its intended use. Continuous process verification shows whether the variability within batches is within control or this needs an evaluation.

If any critical process parameter and critical quality attribute is observed to be out of trend, the same should be investigated in order to check whether the equipment ageing is leading to the failure or not. Equipment breakdown trend also needs to be verified.

If repetitive breakdown is observed, the preventive maintenance procedure should be reviewed for its adherence to schedule, and adequacy of preventive maintenance check points. Continuous process verification can be evaluated by determining the process capability (CpK).

This formula can be used to determine CpK.

$$Cpk = min\left(\frac{USL - mean}{3\sigma}, \frac{mean - LSL}{3\sigma}\right)$$

where
σ is standard deviation,
USL is the upper specification limit,
LSL is the lower specification limit.

The higher the CpK, the better is the capability of the process to meet its requirements. In common practice, a CpK of less than 1.66 needs a closer look. ACpK that is less than 1.33 needs some action to make it higher, and a CpK of less than 1.0 means that the process is not capable of meeting its requirements.

Any equipment gradually faces mechanical problems and requires maintenance activities. While the operating cost per equipment usage hour increase over a period of time, the ownership cost per hour declines because the depreciation makes the monetary value of the equipment decrease with time.

Generally, the ownership cost per hour decreases exponentially during the initial ownership period. The economic useful life ends when the total hourly cost reaches its minimum amount.

Retaining the equipment after this time indicates high operating costs and a low trade-in value, which is not an efficient situation. The equipment finally finishes its physical life when the equipment is worn out, no longer works properly, and it is not worth the cost of repair.

Regression equation can be used to determine the correlation between the operating cost and equipment usage hours.

The formula below can be used to determine linear regression function.

$$Y = a + bX$$

where

b = slope of regression line

a = (Y) intercept of regression line

$$b = r \text{ (Std. Dev. of Y) / (Std. Dev. of X)}$$

$$r = \Sigma (X - \bar{X}) (Y - \bar{Y}) / \sqrt{\{ \Sigma (X - \bar{X})^2 \Sigma (Y - \bar{Y})^2\}}$$

$$\text{Std. Dev. of Y} = \sqrt{\{ \Sigma (Y - \bar{Y})^2 / (n-1)}$$

$$\text{Std. Dev. of X} = \sqrt{\{ \Sigma (X - \bar{X})^2 / (n-1)}$$

$$a = \bar{Y} - b \bar{X}$$

2. Checklist for Evaluating Requirement of Equipment Replacement

Equipment and facility condition shall be evaluated for healthiness. This shall be based on routine maintenance, quality notification and expected equipment life (given in Table 1);

If any of the equipment/facility is giving signs of ill health according to the indicators mentioned above, the following checklist should be used to evaluate replacement or upgradation.

- For any equipment the following data shall be recorded, which helps us to decide the age and condition of the equipment :

    1. Name of the equipment/machine/apparatus.
    2. Manufacturers name/model no/type of identification.
    3. Serial no of the equipment/machine/apparatus.
    4. Date on which equipment/machine/apparatus received at site.
    5. Date of usage of equipment/machine/apparatus.
    6. Location of the equipment/machine/apparatus.
    7. Condition when received (new/used/reconditioned).
    8. Operation log book of the equipment.
    9. History of any major breakdown, malfunctioning, modification, or major upgradation,
    10. Preventive maintenance schedule,
    11. AMC of the equipment/machine/apparatus.

❖ **Recommended Evaluation Frequency**

a. On completion of 50 % expected life: once in 2 years.

b. After completion of 75 % expected life: every year.

The following checklist needs to be reviewed jointly by ESD, Production, Safety and Quality team. Based on site condition, this checklist should be modified.

Points	Yes	No	Remarks
Is equipment/facility not meeting with safety requirement?			
Is equipment having frequent breakdown, resulting in production loss?			
Is equipment not able to repair (spares/vendor support not available)?			
Is equipment/facility having quality issue, resulting in major non-compliance or audit observation?			
Is software life cycle support nearing end or non-compliance to CGMP and electronics hardware nearing life cycle end?			

If Answer of any of above points comes 'YES' and reconditioning / up-gradation / In case, going with reconditioning / up-gradation / modification check cost effectiveness and decide further action.

In case of Operating system, for old OS no support will be available in market, so need to change OS of equipment/ system.

1. Expected Equipment Life

Every equipment has its expected life, after which equipment shall be replaced based on evaluation of its condition, as mentioned above. This is an indicative figure, and it depends on utilization/application, maintenance, connected services, external environment, manufacturing quality, and other factors related to the equipment.

For equipment for which expected life is completed, requirement of replacement should be evaluated, as discussed above. In case the equipment is found fit for use, the concerned team can continue utilization of equipment, and evaluate its condition as per defined frequency.

Table 1 : Expected Equipment Life for Major Equipment (In OSD Plant)			
Sr. No.	Equipment Type	Product Contact MOC	Expected Equipment Life (in years)
Key Process Equipment			
1	Fluid bed equipment	SS 316	15
2	Tablet coater machine	SS 316	15
3	Rapid mixer granulator	SS 316	15
4	Tablet compression machine	SS 316	15
5	Capsule filling machine	SS 316	15
6	Dry granulator/compactor	SS 316	15
7	Steam kettles	SS 316	20
8	Blenders	SS 316	15
9	Blister pack machine	SS 316	15
10	Bottle filling machine	SS 316	15
11	Sachet filling machine	SS 316	15
12	Packing line equipment and conveyors	--	20
13	LAFs/RLAFs	--	15
14	Sifter	SS 316	15
15	Sizer mill	SS 316	15
16	Quadra mill	SS 316	15
17	Lifter and positioner	SS 304	15
18	Peristatic pump	---	15
19	Lifter and tippler	SS 316	15
20	Planetary mixture	SS 316	15
21	Metal detector	SS 316	15

Table 1 : Expected Equipment Life for Major Equipment (In OSD Plant)			
Sr. No.	Equipment Type	Product Contact MOC	Expected Equipment Life (in years)
Key Process Equipment			
22	Tablet deduster	SS 316	15
23	Tablet capsule inspection	SS 316	15
24	Tablet/capsule check weigher	SS 316	15
25	Tablet printing machine	SS 316	15
26	IP /conta bin washing machine	SS304	10
27	Vacuum transfer system	SS 316	10
28	Stirrer	SS 316	10
29	Homogenizer	SS 316	10
30	Cotton inserter	SS 316	15
31	Induction sealer	---	15
32	Retorquer	SS 304	15
33	Labelling machine	SS 304	15
34	Track and trace	SS 304	15

Table 2 : Expected Equipment Life for Major Equipment (In Injectable Plant)			
Sr. No.	Equipment Type	Product Contact MOC	Expected Equipment Life (in years)
Key Process Equipment			
1	Double door autoclave	SS 316	15
2	Dry heat sterilizer	SS 316	15
3	Vial/ampule washing machine	SS 316	15
4	Sterilization tunnel	SS 316	15
5	Vial filling machine	SS 316	15
6	Bung machine	SS 316	15
7	Capping machine	SS 316	15
8	Leak testing machine	SS 304	15
9	LAF	SS 304	15
10	Sip station	SS 316	15
11	Preparation tanks	SS 316	15
12	Holding tanks	SS 316	15
13	Filter assembly	SS 316	15
14	Labelling machine	SS 304	15
15	Ampule filling machine	SS 316	15
16	Ultra sonic machine	SS 316	15

Table 1 : Expected Equipment Life for Major Equipment (In API plant)			
Sr. No.	Equipment Type	Product Contact MOC	Expected Equipment Life (in years)
Key Process Equipment			
1	Reactor	SS 316	20
		MSGL	15
		Hastelloy	30
2	Centrifuge	SS 316	18
		Halar lined	5
		Hastelloy	30
3	RCVD	SS 316	20
		MSGL	18
		Hastelloy	20
4	ANF / ANFD	SS 316	20
		Hastelloy	20
5	Sparkler Filter	SS 316	20
6	Tray Dryer	SS 316	20
7	VTD	SS 316	20
8	FBD / FBP	SS 316	18
9	Spray Dryer	SS 316	18
10	Sifter	SS 316	12
11	Miller	SS 316	12
12	Compactor	SS 316	12
13	Micronizer	SS 316	10
14	Blender	SS 316	18
15	Isolator	SS 316	15
		Hastelloy	15

Table 1 : Expected Equipment Life for Major Equipment (In API plant)			
Sr. No.	Equipment Type	Product Contact MOC	Expected Equipment Life (in years)
Key Process Equipment			
16	Rota vapour	Glass	10
17	All glass equipment	Glass	10
18	Heat exchanger/condenser	SS 316	20
		Hastelloy	18
19	Receivers	SS 316	20
		SS 304	20
		MSGL	15
		Hastelloy	20
		MS	18
20	Pumps	SS 316	10
		PP	5
		PVDF	5
21	Distillation kettle and column	SS 316	20
22	Weighing machine	SS 316	15
23	Lyopholizer	SS 316	25
24	TFF	--	25
25	Synthesizer	--	20
26	Preparative HPLC and column	--	25
27	Ion exchange	--	25
B	**Utility equipment**		
28	Boiler	--	30
29	Chiller	--	20
30	Cooling tower	--	15

Table 1 : Expected Equipment Life for Major Equipment (In API plant)			
Sr. No.	Equipment Type	Product Contact MOC	Expected Equipment Life (in years)
	Key Process Equipment		
31	Air compressor	--	18
32	Nitrogen generator	--	18
33	Water treatment (other than ETP)	--	15
34	Dry vacuum pump	--	15
35	Dg set	--	18
36	Ups	--	15
37	Transformer	--	30
38	HVAC	--	20
39	Pumps	CS	15
C	**Laboratory Equipment**		
40	HPLC	--	8
41	GC	--	8
42	KF titration	--	8
43	Stability chamber	--	15
44	PSD	--	10
45	Oven	--	10
46	Polarimeter	--	10
47	Analytical balance	--	15
48	RLAF	--	15
49	Autoclave	--	20
50	Incubators	--	10
51	XRD	--	15

Table 1 : Expected Equipment Life for Major Equipment (In API plant)			
Sr. No.	Equipment Type	Product Contact MOC	Expected Equipment Life (in years)
Key Process Equipment			
D	**Other Equipment / Instruments**		
52	Electrical panel (MCC/PCC)	--	25
53	Field instruments (PT, TT, FT, PG, VG)	--	15
54	DAS/DCS/PLC/BMS: main panel, RIO panel, hardware	--	20
54	HMI	--	10

The expected life of the above equipment has been estimated based on experience and discussion held with suppliers. Based on site condition, expected life shall be reviewed and finalized by team from Engineering, Quality and Safety departments.

3. Criteria and Methodology for Deciding Equipment Retirement

List of equipments to be considered/not considered for retirement shall be assessed as per the table below.

All equipment/machinery (including equipment which are not in use) that could be considered for retirement shall be evaluated as per the methodology given below.

The factors listed shall be considered for evaluation of an equipment as per Table 1.

By considering table no.1 & table no.2 equipment evaluation shall be done and retirement shall be decided.

Further, OEM health check-up shall be done to derive the ROI for the modification.

Based on the decision, the decommissioning process shall be carried out.

Mean Time Between Failures (MTBF) is the average time between system breakdowns.

If the MTBF is low, based on the observation period under consideration, then OEM shall be consulted to carry out the health check of the equipment.

The criticality of the equipment and the accessibility of the equipment vendor shall also be an important factor impacting the equipment retirement.

OEM heath check report of equipment shall be also taken under consideration as an important factor.

OEM shall be contacted in an event of doubt, to seek clarification on the equipment.

Table 1 Methodology for Retirement of Equipment

Criteria							
Score	Depreciation	Obsolescence (age/vendor support/spare part/technology)	Maintainability Cost	Loss of Efficiency	Quality Compliance (CGMP)	Mean time between failure (MTBF)	Equipment Criticality
5	< 20%	Equipment age < 40% of design life / Available same day in person or cloud connect/ Spare part available / Latest technology and latest version of software	1-3%	< 5%	Easy to clean within the desired time and CGMP compliant / No Scratch on process equipment	>90 Days	Non-critical equipment (<30% utilization)
4	21% to 33%	Equipment age in between 40% to 60% of design life/ Available within 1-3 days in person or cloud connect/ OEM has stopped mfg. spare part / 1~3 version old software	3-5%	5-10%	Longer time to clean the equipment (greater than 20% than the desired time) / Scratch on process equipment	45-90 Days	Non-critical equipment (30% to 50% utilization)
3	34% to 67%	Equipment age in between 60% to 80% of design life / Telephonic or mail availability or Available within a fortnight (3-14 days) in person or cloud connect / Spare part cannot be mfg. / Easy to upgrade the software	5-7%	10-15%	Takes more than 20-40% time to clean the equipment than the desired time / Corrosion observed on process equipment	30-45 Days	Production Critical (50% to 80% utilization)
2	68% to 94%	Equipment age > 80% of design life / Available after fortnight to 1 month (14 days to 30 days / Spare part are not available with alternate vendors / Software upgradation possible through hardware modification	7-10%	15-25%	Takes 40-70% time to clean the equipment than the desired time / Many corrosion spot observed on process equipment	15 - 30 Days	Production Critical (>80% utilization)
1	>=95% depreciate of the original cost	Equipment cross the design life / Available after 1 month / Spare part cannot be mfg. with anyone / Software cannot be upgraded	> 10%	>25%	Takes more than 70% time to clean the equipment than the desired time/Not CGMP compliant /Surface roughness not repairable	< 15 Days	Safety Critical/ Statutory requirement not met
Weightage	1	2	1	1	2	2	2

Table for Declaring Retirement Status of Equipment

Sr. No.	Equipment Name	Equipment Code	Considered for Equipment Retirement/Not	Justification	Remarks (If any)

❖ **Conclusion**

Equipment or facility age is not the only critical parameter for replacement of the equipment or facility; other factors also need to be considered, such as effect on quality, safety, and productivity.
The life cycle of equipment or facility depends on the quality of equipment installation, as well as qualification, periodic maintenance, overhauling, periodic operational usage verification, timely technology upgradation, etc.

In summary, discarding equipment after a long period of installation is crucial for staying technologically competitive, reducing operational costs, ensuring compliance, enhancing security, and minimizing environmental impact.

Pharma Maintenance Strategy

CONTENTS

6. RCM (RELIABILITY CENTERED MAINTENANCE)

Measures Of Reliability

7. ANNUAL TURN AROUND

8. PLANNING AND SCHEDULING OF MAINTENANCE

9. STANDARD OPERATING PROCEDURES (SOP)

10. FAILURE MODE AND EFFECR ANALYSIS (FMEA)

1 Definitions

PREVENTIVE MAINTENANCE (PM)

Systematic planned inspection, detection, correction, and prevention of equipment failures, before they become actual or major failures. Preventive Maintenance can be time base or condition base.

BREAKDOWN MAINTENANCE (BM)

Breakdown maintenance is maintenance performed on equipment that has broken down and is unusable. It is based on a breakdown maintenance trigger. Either it may be planned, or it can be unplanned

EQUIPMENT

Any individual machine, integrated set of machines, mechanical systems or other mechanical objects that are maintained within the plant.

CRITICAL EQUIPMENT

These are equipment whose operation, contact, control, alarm, or failure will have direct impact on product quality.

NON-CRITICAL EQUIPMENT

These are equipment whose operation, contact, control, alarm, or failure will not have direct impact on product quality.

NOTIFICATION

A form in SAP PM Module assigned to engineering by user department for intimation of need for repair or maintenance activities.

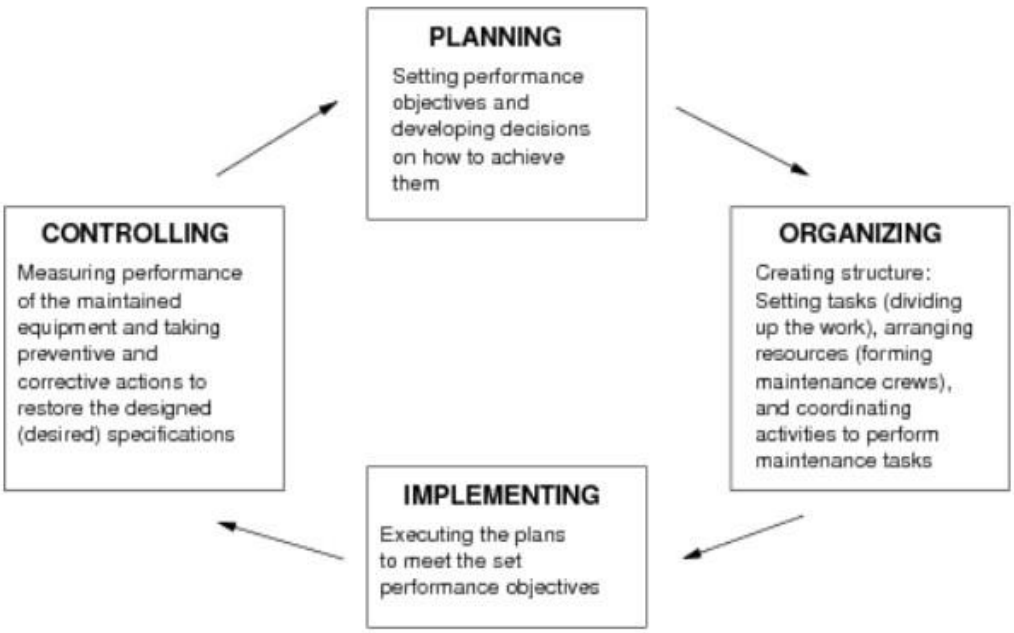
2 Purpose

The purpose of this manual is to serve as a guideline for the maintenance functions. By providing this guidance the manual serves to meet the following objectives:

- Definition and understanding of the maintenance strategy, which in turn is predicated on manufacturing strategy.
- Clarity of roles and responsibilities in maintenance along with knowledge and skills requirements and enhancement.
- Promotion of Good Engineering Practices (GEP)/Good Maintenance Practices (GMP) in maintenance functions, so as to enhance compliance, safety and productivity.
- The purpose of the Maintenance function is to maximize equipment availability, within the boundaries of cGMP and SHE standards.

3 Maintenance Management

Maintenance management involves formulating and implementing maintenance strategies. Maintenance strategy implementation is concerned with logistical issues, such as spare parts inventory, restocking policies and scheduling, as well as deciding on maintenance policies that determine specific maintenance actions and replacement intervals of the maintained equipment. The process of maintenance management can be broken down into a four-step loop as illustrated below



The steps are similar to the perhaps more familiar OODA loop, used to describe the decision making process in military strategy (Boyd 1995); OODA stands for Observe, Orient, Decide and Act. Controlling involves observation of the data from the maintained equipment and calculation of performance measures.

Planning involves setting performance objectives and developing a plan for how to achieve them.

Organizing involves realization of the plan into a work structure.

Implementation is the execution of maintenance tasks in order to meet the set performance objectives.

The maintenance management process should be driven by the idea of achieving continuous improvement.

3.1 MAINTENANCE MANAGEMENT DECISION LEVELS

- Maintenance management is a cross-disciplinary area involving many different types of tasks, deciding on maintenance strategies, setting policies for maintenance and inventory management, scheduling specific tasks with regard to staff, resources and scheduled production, etc. To structure the area, maintenance management is frequently divided into different categories. One approach is to divide it into three decision levels, which can be done in different ways.

- Top-level management responsibilities include deciding on economic and investment related issues, such as in-house or outsourced maintenance as well as providing required resources. The task also includes creating an organizational culture that fosters closer interaction between different business units (production, maintenance, marketing, etc.).

- Middle-level maintenance management deals with the planning of optimal maintenance strategies, analysis of collected data, and monitoring/controlling the implementation of maintenance actions carried out by lower-level management.

- Junior-level management responsibilities include implementing maintenance actions and collecting relevant data.

- Other ways of structuring maintenance into three levels are also followed.

- Strategic planning is concerned with the provision of production resources to ensure the company's competitive capabilities. This involves equipment replacement decisions along with capacity considerations, monitoring technological changes, and weighing economic factors and investment criteria.

- Tactical planning addresses effective resource utilization and involves ensuring the availability and reliability of production equipment, as well as finding optimal maintenance policies.

- Operational planning deals with day-to-day operational and scheduling decisions. This involves prioritizing jobs and considering the availability of workers, spare parts, tools, and the equipment to be maintained.

- The performance objectives that a maintenance manager focuses on are different depending on what decision level the maintenance manager is working on. For example, a strategic level decision maker may focus on overall equipment effectiveness or life cycle cost, while an operational level decision maker will focus on minimizing down time or number of breakdowns. The design and nature of maintenance organization varies depending on their environment. For example, a labor-intensive production environment is different from that of a maintenance support provider focusing on highly technical and complex military equipment. Maintenance organizations may also be designed with different objectives in mind. Profit maximization may be a common criterion in manufacturing, where the maintenance organization in a nuclear power plant or other safety critical settings will more likely be focused on providing the best possible equipment reliability.

- This means that different maintenance management processes will focus on different performance objectives.

4 Maintenance Processes

This is a routine and continuous activity required to keep facilities and equipment in a safe and effective condition enabling it to be utilized at original design capacity and efficiency.

It is maintenance that keeps processes and equipment on-line, thereby enabling the direct work force to be productive. Quality, customer service, energy conservation, regulatory compliance, employee safety, loss prevention, business interruptions, and property damage are all maintenance dependent.

In general maintenance activities encompass the following:

1. **TPM (Total Productive Maintenance)**

2. **Scheduled Maintenance**

    - ❖ Preventive.
    - ❖ Modifications.
    - ❖ Impairment and Replacement of Assets.

3. **Un-scheduled Maintenance**

    - ❖ Breakdown/Corrective maintenance.
    - ❖ Predictive Maintenance.

4. **RCM Reliability Centered Maintenance.**

In order to ensure that these activities are adequately performed, it is important to put processes in place that ensure a standardized approach and deliver the required results.

5 Maintenance Planning

A. MAINTENANCE MASTER PLAN (MMP)

The Maintenance Master Plan of any manufacturing site is a document that outlines the basic strategic context and the basic policies of operation in the maintenance function of the site. The Maintenance Master Plan should prioritize, schedule, and provide for resources that enable the site to drive towards a state of maintenance excellence and realize the associated cost savings. The MMP is a long-term document and must be reviewed every five years. All maintenance processes and practices, facilities, and resources must be aligned to the MMP.

DEVELOPMENT OF MAINTENANCE MASTER PLANNING

MMP must be developed based on the site maintenance objectives:

- Culture
- Quality
- EHS needs
- Supply of product to the market
- Efficiency of plant equipment
- Defect rate
- Financial
- Leadership
- Colleagues and competencies
- Reliability
- Specific metric objectives

The above maintenance objectives are largely derived upon the manufacturing site vision of the organization, mission, and 5-year objectives.

These maintenance objectives are a quantifiable set of objectives that are drilled down to all sections of the Maintenance department. On the basis of these objectives, a strategy should be created in order to achieve the defined objectives, and a plan drawn up which would define the actions that must be taken to close the gap between the current state and the defined objectives. The current state of maintenance shall be captured by doing an assessment on the current maintenance practices. Refer Annexure – I for the Basic Format for the Master Maintenance Plan.

5.2 TOTAL PRODUCTIVE MAINTENANCE

What is TPM?

Total Productive Maintenance (TPM) is a method of physical asset management, focused on maintaining and improving manufacturing machinery, in order to reduce the operating cost to an organization.
TPM is designed to disseminate the responsibility for maintenance and machine performance, improving employee engagement and teamwork within management, engineering, maintenance, and operations.

TPM in pharmaceutical industry

At present, pharmaceutical organizations face strong competition in a highly competitive, dynamic and challenging environment. Hence, it is necessary for any organization to integrate the maintenance function with technical, and other manufacturing functions, in dealing with the issues of equipment availability, maintainability, and reliability. According to the principles of reliability engineering, the causes of equipment failures change with the passage of time. A good and effective preventive maintenance (PM) system alone cannot eliminate breakdowns, and it is necessary for an organization to follow a maintenance technique along with PM to achieve higher degree of equipment performance. Many studies and research reveal that in place of conventional maintenance systems, the organizations should also practice efficient maintenance strategies like Total Productive Maintenance (TPM), Condition Based Maintenance (CBM), Computerized Maintenance Management system (CMMS), and Reliability Centered Maintenance (RCM) techniques so as to improve their performance.

TPM is a collaboration between production and maintenance functions to improve product quality, reduce manufacturing cost, and waste.

Objectives of TPM

The goal of TPM is the continuous improvement of equipment effectiveness through engaging those that impact on it in small group improvement activities. For TPM to be effective, the full support of the total workforce is required. This should result in accomplishing the goal of TPM:

The main objective of TPM is to increase the Overall Equipment Effectiveness (OEE) of plant equipment. TPM addresses the causes for accelerated deterioration while creating the correct environment between operators and equipment to create ownership.

The objective finally is to identify, prioritize, and eliminate the causes of the losses.

Principles of TPM

TPM has eight pillars which are shown in the figure below.

1. It includes Sort out, Set in order, Shine the workplace, Standardize, and Self-discipline.

2. Jishu Hozen (Autonomous Maintenance): it means maintaining one's equipment by oneself.

3. Kobetsu Kaizen (Continuous Improvement): it includes continuous improvement even by taking small steps

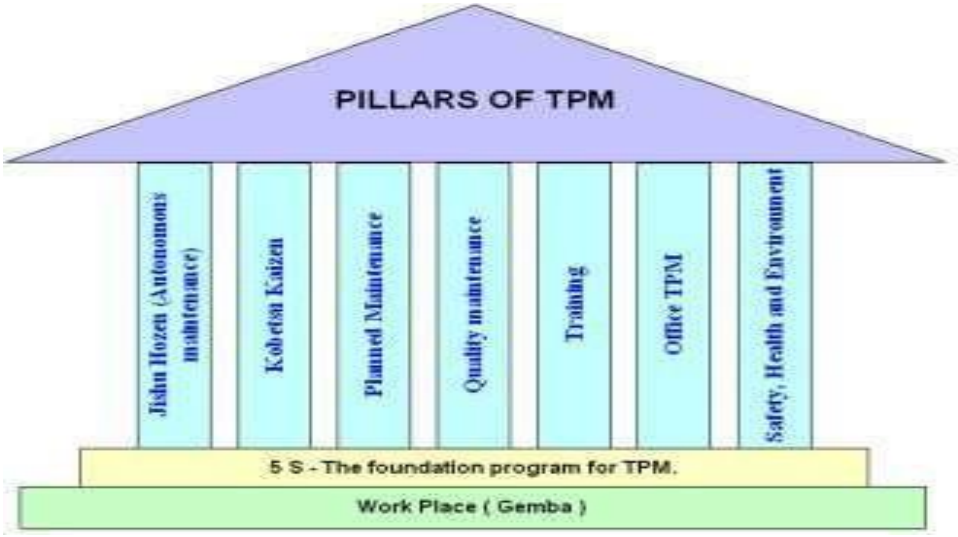
4. Planned Maintenance: this focuses on increasing the availability and reducing the breakdown of machines.

5. Quality Maintenance: this is aimed towards customer delight through highest quality. The highest quality can be achieved through defect free manufacturing.

6. Education and Training – this is aimed to having multi-skilled invigorated employees with high morale who are eager to perform all required functions effectively and independently. Education is given to operators to upgrade their skills.

7. Office TPM: this must be followed to improve productivity and efficiency in the administrative functions, and to identify and eliminate losses.

8. Safety, Health, and Environment Control: here the focus is to create a safe workplace.



Overall Equipment Effectiveness (OEE) and Six Major Losses

OEE is the main goal or benchmark of the any TPM process and is used to measure the equipment effectiveness. OEE is a measurement used to determine how efficiently a machine is running. The OEE calculation is quite general and can be applied to any manufacturing industry. The OEE formula measures availability, performance rate, and the quality rate, as shown below:

OEE = Availability x Performance rate X Quality rate where

Availability = [(loading time - downtime) ÷ loading time] ×100

Performance rate = [(standard cycle time x units produced) ÷ operating time] x 100

Quality rate = [(units produced - defective units) ÷ units produced] x100

OEE combines the operation, maintenance, and management of manufacturing equipment and resources.

The six major losses which affect the overall performance of the equipment are :

1. Breakdown losses: these are the time and quantity losses caused by defective products.

2. Set-up and adjustment losses: these are the time losses resulting from downtime and defective outputs that occur when production of one item ends and the machine is adjusted to meet the requirements of another item.

3. The above two losses are termed as down time losses and they are used to calculate availability of a machine.

4. Idling and minor stop losses: they occur when a machine is idling, or the production is interrupted by a temporary malfunction.

5. Reduced speed losses: it is the difference between designed speed of the machine and actual operating speed.

6. The third and fourth loses are termed as are speed losses and they are used to calculate the performance rate.

7. Reduced yield losses: these losses occur from machine start up stage to stabilization stage.

8. Quality defects and reworks: these are the quality losses due to the malfunctioning of production machine.

9. The fifth and sixth losses are considered to be losses due to defects in the products. OEE is measured in terms of these six losses, which are the function of availability, performance rate and quality rate of the machine.

TPM is a holistic approach and requires extensive support of all the workforce present in the manufacturing site. One of the major pillars that can be adopted in a pharmaceutical manufacturing site which is absent as of now is 'Autonomous Maintenance' pillar. Other pillars such as planned maintenance, quality maintenance, education and training, and EHS are indirectly implemented in pharmaceutical manufacturing sites as a part of cGMP requirements and compliance. The next section gives a brief introduction to the autonomous maintenance concept. Refer Annexure – III for extensive details on TPM.

5.3 AUTONOMOUS MAINTENANCE

General maintenance approach by operators: “I run, you maintain.” Autonomous maintenance approach by operators: “I run, WE maintain.”

Autonomous maintenance (AM) is performed by the operators and not by dedicated maintenance technicians. It is a crucial component of the TPM. The core idea of autonomous maintenance is to provide the operators with more responsibility and allow them to carry out preventive maintenance tasks.

According to conventional maintenance programs, a machine can run until it breaks or reaches its maintenance date. The maintenance department is then responsible for handling and fixing it. In contrast, autonomous maintenance allows machine operators to directly carry out simple maintenance works (lubrication, bolt tightening, cleaning, and inspection) to prevent breakdowns, and react faster if a certain failure has been detected.

Since TPM gives operators much more responsibilities, dedicated training is required as well as some modifications on the machines to ease operations of cleaning and maintenance. This will significantly increase the operators’ skill levels and help to them better understand how to maintain and even improve the equipment.

Autonomous maintenance requires operators to develop and master certain skills:

- Detect abnormalities and make improvements.
- Understand the functions and the components of the machines and detect the causes of abnormalities.
- Recognize possible quality issues and identify their causes.

The machine operator should be able to provide fast and reliable initial diagnosis and troubleshooting in a certain number of failure cases. The best way to impart this knowledge is through dedicated training, and even an entire methodical implementation program.

Whenever the failure requires the intervention of the maintenance department, the operator may be asked to assist the maintenance engineer.

A. Education of Operator

Sometimes called “step 0”, the education required is about imparting basic knowledge of machine components and functions. In order to perform properly, the most important task – machine cleaning - operators should fully understand the objectives of autonomous maintenance, and even be able to deliver improvements in equipment reliability.

B. Initial Cleaning and Inspection

The initial cleaning of the machines is essential for high-quality maintenance. It is usually performed by all the involved members of the production, maintenance and engineering teams, and includes the thoroughly cleaning of the equipment and surroundings. The purpose is to ensure that the machines’ performance is fully restored by identifying and eliminating all signs of deterioration.

- Leak detection.
- Control of loosened bolts.
- Lubrication.
- Detection of non-apparent cracks; contamination rate and decrease in level of oil or other fluids.
- Correction of defective items.
- Removal of material rests from oil or water.
- Removal of dust and dirt and, therefore, reduction of paint corrections.
- Suppression of conductibility of trouble in the electric manufacturing due to oil deposits or dust on the contact points.

- Suppression of electrical incidents related to conductivity contact points covered with oil deposits or dust.
- Elimination of micro-stoppages due to accumulation of dust, waste.
- Prevention of fire in the waste and dust accumulated in inaccessible places.
- Better precision adjustments especially when changing production levels.

C. Eliminating Contamination and Inaccessible Areas

After the initial cleaning has been performed and the equipment has been restored again, it is very important to make sure that it does not deteriorate again. This can be taken care of by eliminating all possible contamination sources, and improving accessibility for cleaning and maintenance.

At that point, the machine operators can be given the freedom to control the root causes of contamination directly at source, especially given the fact that they know the machine better, and were the ones who performed the initial cleaning.

This step also considers all possible security issues that could happen during autonomous maintenance. Cleaning a running machine is quite dangerous and the frequent changing of operators only increases the difficulties.

A maintenance manager should consider the following possible solutions:

D. Develop Standards for Cleaning, Lubrication, and Inspection

The establishment of standards for operations of cleaning, inspection and lubrication starts from the current documentation and follows the suggested lubrication and inspection schedule. This is the step which can be individually adjusted by the operators to fit every machine. In this phase, one develops own standards indicating the items to be cleaned and/or lubricated, the methods to be used and the responsibilities to be assigned.

In this case, two complementary methods should be followed:

- In case of non-critical machines, operators can be trained in-house to follow the established general standards, and then be given the opportunity to set up their own rules, led by an experienced technical maintenance engineer.

- In case of critical machines, a special working group, dedicated to maintenance methods and production, can be created.

The outcome of this phase is a set of established standards, which are also the best evidence for the successful implementation of autonomous maintenance at a plant.

5.4 SCHEDULED MAINTENANCE

5.4.1 ANNUAL MAINTENANCE PLAN

Purpose

This is an exercise to plan and provide resources for coming year's maintenance program for the site. The output is document called the Annual Maintenance Plan (AMP), done before the start of every New Year.

It has to be in consonance with both the MMP and the production and financial outlook for the year. The AMP is a medium-term document, drawn up every year, and forms the basis for the annual maintenance budget as well as ensuring that the plant uptime is maintained in the coming year.

Process:

1. Estimated utility generation is calculated for the year.

2. Based upon the operating hours of the production, utility, and other equipment, the schedule of PM (including annual shutdowns, if any), for the next year is drawn. Assets replacement/discard plan for the year is also drawn up.

3. Provisions for unscheduled activities, i.e., breakdown maintenance, are prepared based on thumb rules

4. The AMP is then challenged by the Plant Head and representatives of Engineering department, and any changes made thereof are incorporated into the AMP.

5. The AMP is now circulated and explained to all sections of the Maintenance functions.

6. It forms the basis for all activities relating to maintenance processes and facilities requirements for the year.

This is an exercise to plan and provide resources for coming year's maintenance program for the site. This exercise captures the following components:

1. Projected production volume for the year.

2. Projected operating hours of equipment.

3. Scheduled preventive maintenance programs.

4. Scheduled asset replacement programs.

5. Scheduled training programs for colleagues.

6. Provisions for unscheduled activities.

Refer Annexure – II for the Basic Format for the Annual Maintenance Plan.

5.4.2 PREVENTIVE MAINTENANCE

The main objective of PM is to service and maintain plant equipment and systems, in order to minimize breakdowns and maintain equipment in its validated state.
Defined PM procedures are intended to ensure that maintenance activities are carried out with low product risk, planned in agreement with production schedules, and to ensure the product strength, identity, quality, safety, and purity. Preventive maintenance can be time based, condition based, or based on running hours.

DEFINITION

The PM plan shall define the responsibilities, criteria, and documentation requirements for the PM of direct impact equipment, buildings, and utilities used at the site. PM refers to more than just preventive maintenance, but includes any proactive routine activity that is performed to assure that the equipment continues to operate as required by operations by avoiding, delaying, or identifying the onset of failure.

EQUIPMENT OWNER and RESPONSIBILITY

The equipment owner is a person/position who uses and operates the equipment to produce products/form of the products. He/she is responsible for ensuring that PM has been established for direct impact equipment, buildings, and utilities.

MAINTENANCE PERSONNEL

Qualified and trained personnel only shall perform PM. Records of the training for the maintenance personnel shall be maintained.

LIST OF EQUIPMENT

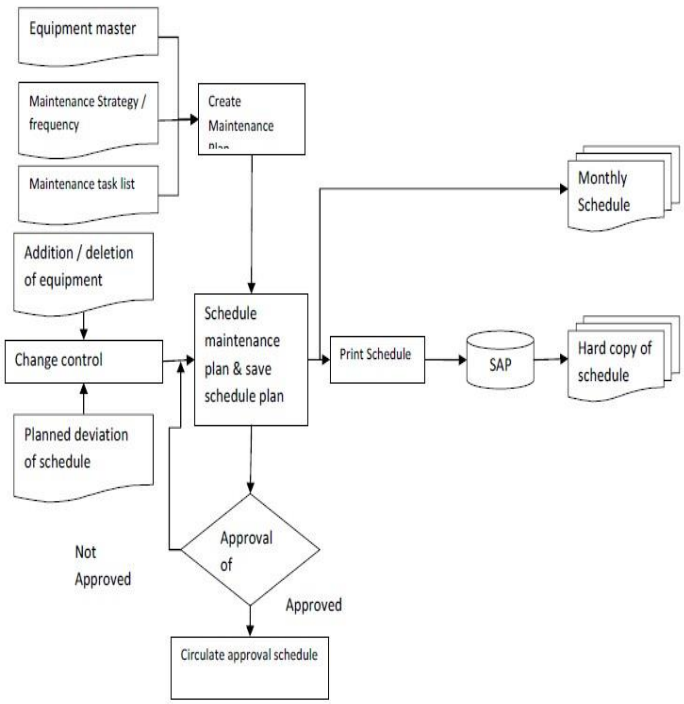
List(s) of all direct impact equipment, buildings, and utilities requiring PM shall be maintained, updated, and kept current at each site.

These equipment shall have a unique identification number and an asset number which should be tagged to it for tracking and easy identification.

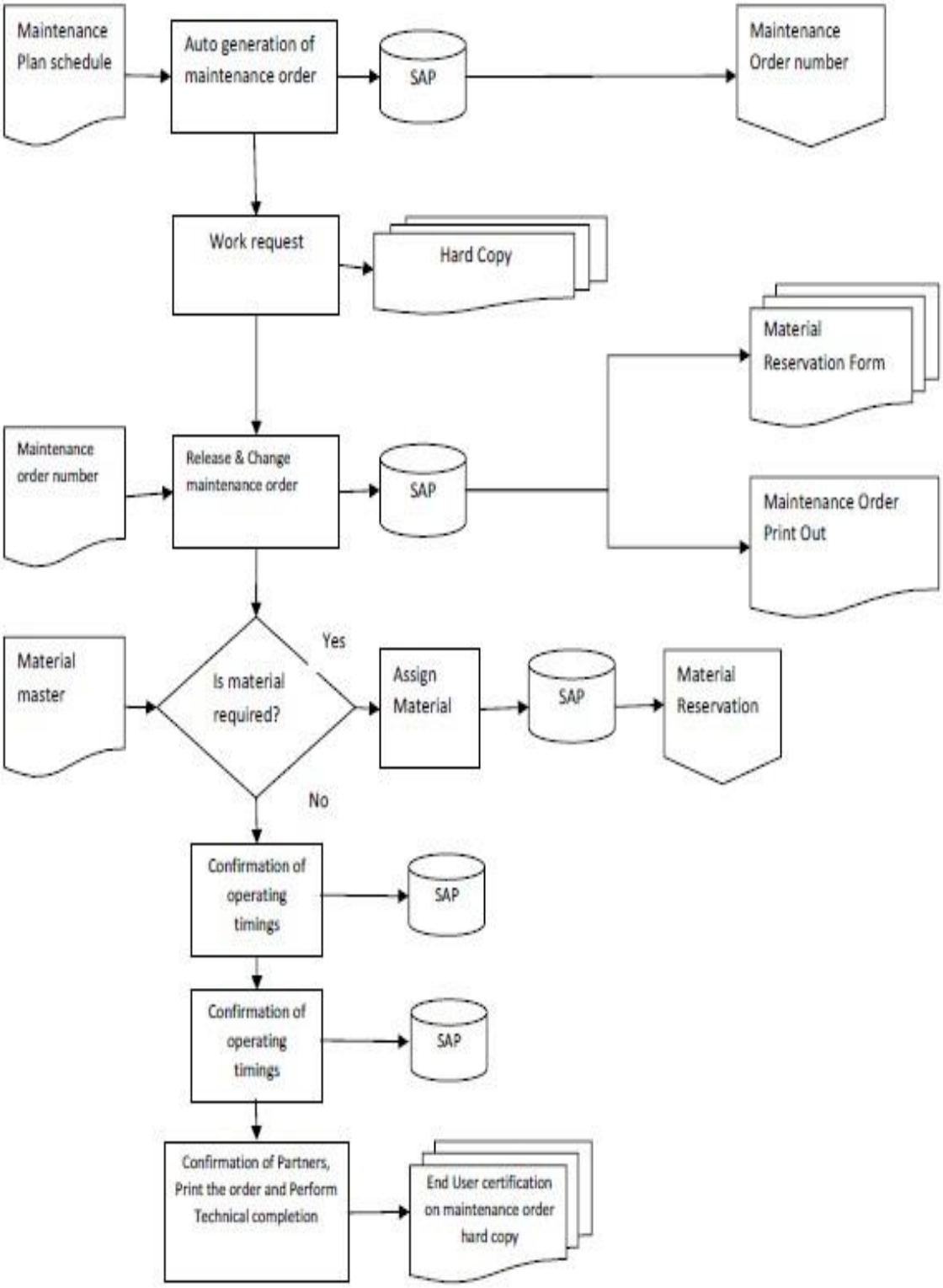
UTOMATION OF MAINTENANCE

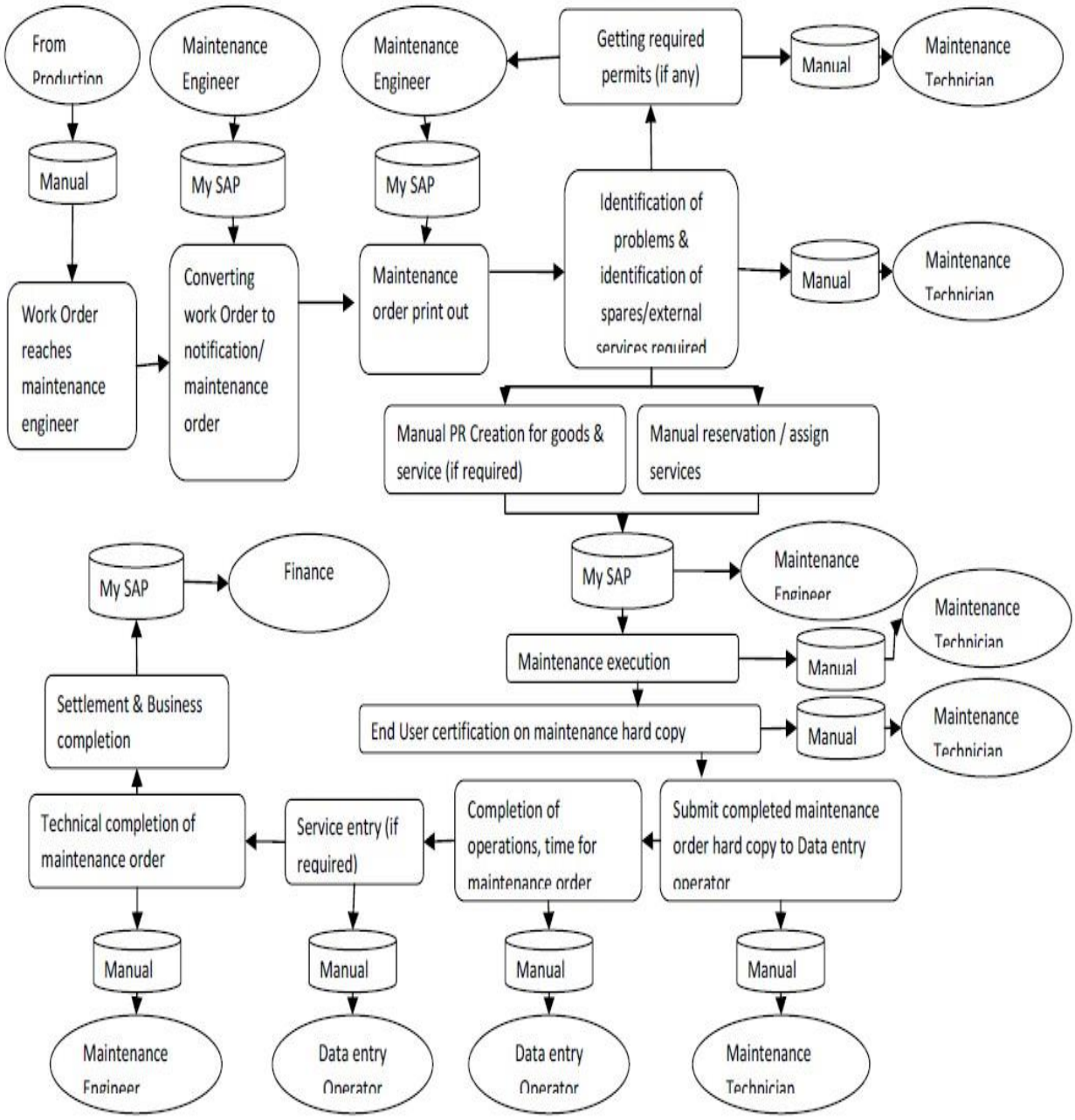
There are a number of ERP software available, such as SAP, Microsoft Dynamics, Oracle E-Business Suite, Sage Intaact, etc., out of which, the most popular and 21 CFR compliant software is SAP, which has user requirement customization.

SAP system can be used for planning and scheduling PM jobs and activities.



The flow charts given below explains how PM is addressed through SAP.


Maintenance Plan schedule
Auto generation of maintenance order
SAP
Maintenance Order number
Work request
Hard Copy
Material Reservation Form
Maintenance order number
Release & Change maintenance order
SAP
Maintenance Order Print Out
Material master
Is material required?
Yes
Assign Material
SAP
Material Reservation
No
Confirmation of operating timings
SAP
Confirmation of operating timings
SAP
Confirmation of Partners, Print the order and Perform Technical completion
End User certification on maintenance order hard copy


From Production
Maintenance Engineer
Maintenance Engineer
Getting required permits (if any)
Manual
Maintenance Technician
Manual
My SAP
My SAP
Identification of problems & identification of spares/external services required
Work Order reaches maintenance engineer
Converting work Order to notification/ maintenance order
Maintenance order print out
Manual
Maintenance Technician
Manual PR Creation for goods & service (if required)
Manual reservation / assign services
My SAP
Finance
My SAP
Maintenance Engineer
Maintenance Technician
Maintenance execution
Manual
Settlement & Business completion
End User certification on maintenance hard copy
Manual
Maintenance Technician
Technical completion of maintenance order
Service entry (if required)
Completion of operations, time for maintenance order
Submit completed maintenance order hard copy to Data entry operator
Manual
Manual
Manual
Manual
Maintenance Engineer
Data entry Operator
Data entry Operator
Maintenance Technician

Maintenance Approach for PLC/HMI/SCADA and DAS/BMS

Information Technology function should have specialized maintenance approach for all the PLC/HMI/SCADA and DAS/BMS with respect to data backup, software backup, application related maintenance, upgradations of relevant patches, ROM and battery replacements, etc. The maintenance activities need to be carried as per scheduled plan.

5.5 UNSCHEDULED MAINTENANCE

5.5.1 BREAKDOWN MAINTENANCE

If any breakdown happens in the plant, they need to be addressed on priority. Manufacturing department raises a maintenance work request and sends the same to the Maintenance department.

On account of any equipment being taken out of service due to equipment failure or suspected systems failure, the user department shall inform the Engineering department through malfunction notifications.

On receipt of the notification, the Engineering department shall execute and organize necessary repairs including verifying safety considerations.

Upon primary inspection and diagnosis, the Engineering personnel shall take area clearance from user and label the equipment with an “UNDER MAINTENANCE” tag at a prominent location, or at the control switch ensuring prominent visibility.

Based on the criticality of Maintenance activity, product/material should be removed from equipment/machine/area, and this will be decided by user and Engineering before starting the activity.

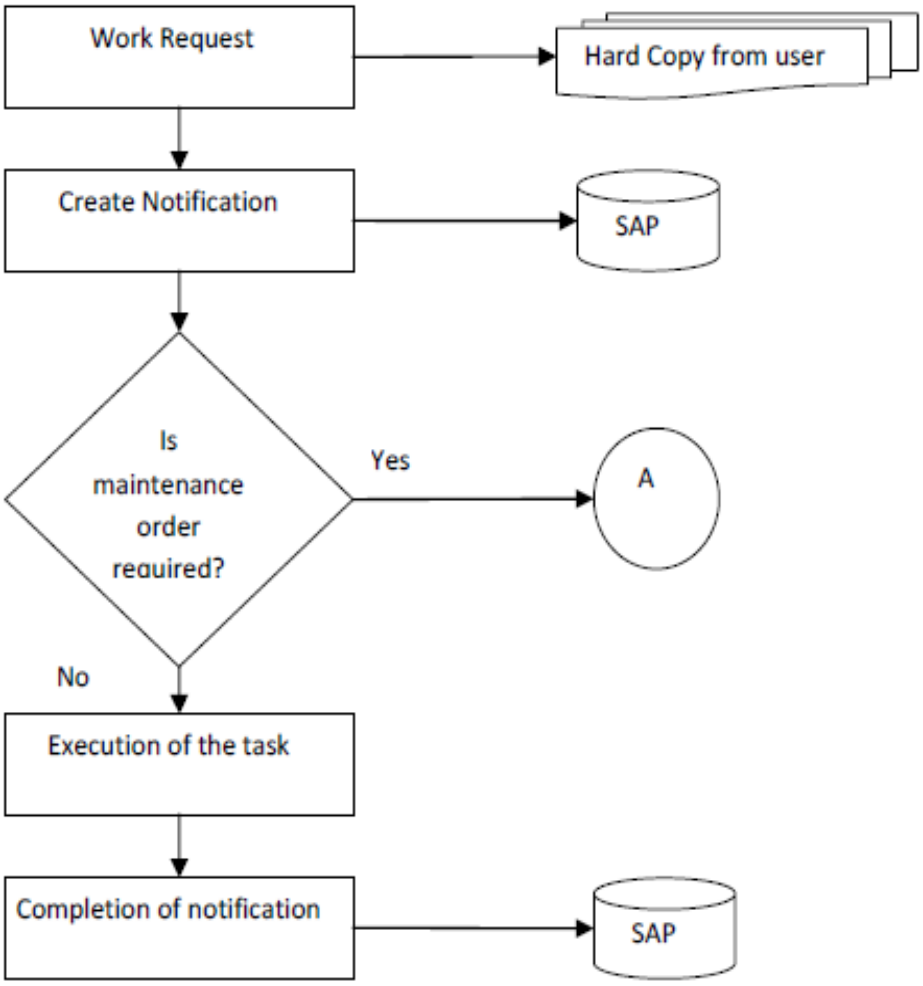
Systems or equipment shall be attended as per technical know-how of Engineering department. If required, technical assistance may be requested from a competent approved external service provider.

On completion of work, it should be ensured that the equipment is inspected and tested for optimum performance.

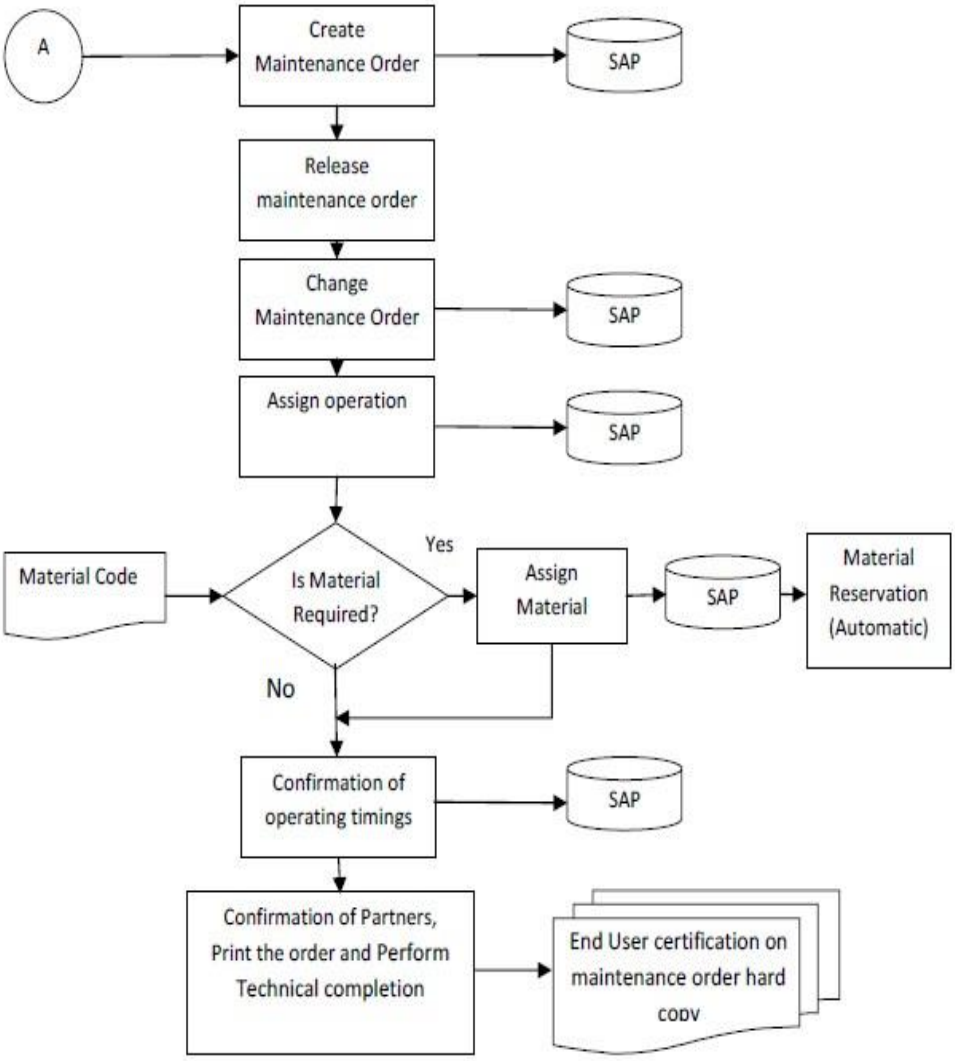
On successful completion of work and performance testing of the System/ Equipment to be done and complete the BM (breakdown maintenance) activity and close the Notification in SAP PM Module.

All breakdown maintenance carried out is reviewed yearly, and all reviews shall be documented as per Annual Maintenance Plan. Based on the annual review, the scope and periodicity of the maintenance activities shall be revised, if required.

Flow charts for the process of handling break down maintenance are given below.



Flow charts for the process of handling break down maintenance are given below.



5.5.2 CONDITION BASED MONITORING/PREDICTIVE MAINTENANCE (PDM)

PDM refers to maintenance action based on actual condition obtained from in-situ, non-invasive tests, and operating and condition measurements. One of the advantages of the PDM program is that it can be performed without affecting the manufacturing schedule, since the systems are monitored at their operational conditions by high tech instruments.

TYPES OF EQUIPMENT TO MONITOR

- Centrifuges pumps.
- Chillers
- Air compressors air handlers
- Exhaust fans motors
- Gearboxes

Basically, all types of rotating equipment can be monitored in this way.

CONDITIONS THAT ARE DETECTABLE

- Unbalance (Imbalance).
- Misalignment.
- Structural looseness.
- Bearing defects.
- Bent shaft resonance.
- Gear problems.
- Belt and chain wear and looseness.
- Cavitation and airflow problems.
- Electrical problems.

VIBRATION ANALYSIS

This measures the mechanical vibration of a machine to check if amplitude, frequency, and phase are outside a baseline range. The overall level of vibration indicates the general condition of the machine; vibration analysis can be used to determine the cause of vibration including such factors as unbalance, misalignment, or bearing defects.

THERMOGRAPH

It uses an infrared camera designed to monitor the emission of infrared energy. By detecting thermal anomalies, i.e., areas that are hotter or colder than they should be, an experienced technician can locate and define incipient problems within the plant.

This measures the surface temperature of the equipment to check for:

- Hot electrical connections.
- Insulation defects.

- Overheated bearings.
- Steam trap failures.
- Facility heat loss.

LUBRICANTS ANALYSIS

This measures the viscosity, acidity, or particulate particle count to check for deterioration and likely wear of the mechanism.

ULTRASONIC MONITORING

This technique uses principles like vibration analysis. Such types of analysis monitor the noise generated by plant machinery or system to determine their actual condition. The principal application for ultrasonic monitoring is leak detection, making it ideal for detecting leaks in valves, steam traps, piping, and others process systems. Two types of ultrasonic systems are used for predictive maintenance, structural and airborne. Most of ultrasonic monitoring systems are typically scanners that do not provide any long-term trending or storage of data. They are in effect a point-and-use instrument that provides an indication of overall amplitude of noise within the bandwidth of the instrument (20,000 to 100,000 KHz).

EQUIPMENT MONITORED BY ULTRASONICS

- Electrical power substation.
- Transformers.
- Electrical switchgears, electrical panels.
- High vacuum systems.
- Steam traps.
- Compressed air piping.

6 RCM (Reliability Centered Maintenance)

RCM is a concept of maintenance planning that ensures that systems continue to do what their user require in their present operating context. Successful implementation of RCM will lead to increase in cost effectiveness, reliability, and machine uptime.

It is defined by the technical standard SAE JA1011, Evaluation Criteria for RCM Processes, which sets out the minimum criteria that any process should meet before it can be called RCM. This starts with the seven questions given below, worked through in the order that they are listed:

1. What is the item supposed to do and its associated performance standards?
2. In what ways can it fail to provide the required functions?
3. What are the events that cause each failure?
4. What happens when each failure occurs?
5. In what way does each failure matter?
6. What systematic task can be performed proactively to prevent, or to diminish to a satisfactory degree, the consequences of the failure?
7. What must be done if a suitable preventive task cannot be found?

Measures of Reliability

Mean Time To Failure (MTTF)

The time that a system is available for operation . Often referred to as 'uptime' in the industry, the length of time that a system is online between outages or failures can be thought of as the 'time to failure' for that system.

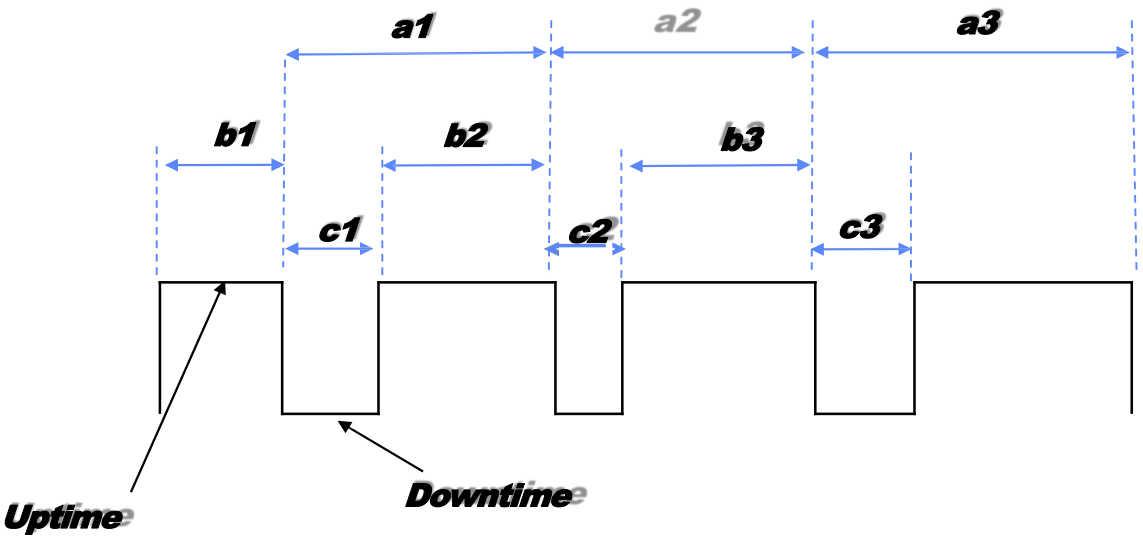
Mean Time To Repair (MTTR)

The amount of time required to repair a system and bring it back online is the 'time to repair'.

Mean Time Between Failure (MTBF)

This is the amount of time that elapses between one failure and the next. Mathematically, this is the sum of MTTF and MTTR, the total time required for a device to fail and that failure to be repaired.

Calculation for MTBF, MTTF and MTTR



$$MTBF = \frac{(a1+a2+a3)}{3} \qquad MTTF = \frac{(b1+b2+b3)}{3} \qquad MTTR = \frac{(c1+c2+c3)}{3}$$

The main objective of RCM is to improve or increase MTTF and MTBF and reduce MTTR. In this way, the user can rely on the equipment more, since there is higher probability of machine uptime. The maintenance measures that are taken to achieve this goal of increasing MTTF and MTBF, and reducing MTTR, comes under the RCM umbrella.

7 Annual Turnaround

Unscheduled outage, that is breakdown, is up to ten times more expensive than a scheduled outage. Equipment will fail without scheduled maintenance outages. It is, therefore, important to plan annual turnaround or planned shut down for plant and machinery.

PLANT TURNAROUND PHILOSOPHY

A plant turnaround philosophy has to be developed and be incorporated in the strategies of the company. These philosophies have to be simple and should be applicable to all facilities. The philosophy should be clear and concise with a descriptor of both plant turnaround management and plant shutdown. The philosophy has to address the business needs and provide a suitable plant turnaround management process, which can be approved and executed.

PLANT TURNAROUND MANAGEMENT PROCESS

Each unit needs a plant turnaround management process document made to their specific needs, which include the types of plant and machinery involved, the spares and people requirement, and the general complexity of the expected plant outage. The document is dynamic and should be reviewed at the end of each plant turnaround to ensure that it is consistent with the needs of the facility.

The plant turnaround management process document should generally encompass the following:

- Strategic planning.
- Organizing and execution.
- Closeout and start up.
- Training to people to increase the skill sets.
- Formation of the turnaround team.

8 Planning and Scheduling of Maintenance

Planned maintenance reduces the wait and delay times which technicians encounter when doing unplanned work. Without effective planning and scheduling, it is impossible to properly manage the widely varying scope and diversity of activities performed by the maintenance organization.

The planning and scheduling function form the communication center from which all maintenance activity is coordinated. The basic goal of planning and scheduling is to avoid delay. The objective of job planning is to allow maintenance tradespersons to prepare for, perform, and complete each job without encountering time-wasting delays, and to see that the job is safely performed to the satisfaction of the requester at optimal cost.

SOME FACTS ABOUT PLANNING

Most maintenance departments do not plan to fail - they just fail to plan. Failing to prepare is preparing to fail. Every rupee invested in planning saves three to five rupees during work execution. Every hour of effective planning typically returns 3 hours in saved maintenance time.

A planned job requires only half as much time during execution as does an unplanned job.

In each maintenance office, the Sectional Head does the planning and scheduling for the maintenance operations. The head gets the job notification through the SAP module.

WHO PLANS THE WORK?

Planning should be a function, separate from work execution. Planning performed by a separate staff has the added advantage of an overall functional perspective. Priorities, labor loading, and management reports are better coordinated through a controlled planning function. Several jobs can be planned more efficiently by a focused function than by an assigned tradesperson planning one job at a time.

Everyone contributes to the function of planning; however, it is the responsibility of the Sectional Head to lead and implement the process.

PLANNING PROCESS STEPS

JOB REQUIREMENTS - EXTENSIVE PLANNING JOBS

- Performed at the jobsite.
- Scope job and perform field inspection.
- Troubleshoot problem if needed.
- Interview and review with requestor/-operations.
- Refine the description if needed.
- Definition of the problem.
- Determine what corrective action is required.
- Determine actual job scope.
- Location of the job.
- Review proposed priority.

DEVELOP PLAN

- Visualize job execution.
- Outline requirements.
- Record the steps necessary to execute the job.
- Consider both repair and replacement if applicable.
- Prepare sketches or take pictures to clarify intent of the work order.

- Take exact measurements as necessary.
- Determine required conditions to execute; coordinate with Production.
- Determine if other equipment will be impacted by performance of this job.
- Check for safety hazards.
- Identify alarms and remote monitoring.
- Determine if technical assistance, extensive troubleshooting. or diagnosis is required. Reassign if needed; either issue work order, or ask informally.
- Depending on level of reassignment determine scoping, troubleshooting, planning, estimating, execution, etc. Review equipment history: SAP, hard copy, logs, etc.
- Has the job been previously performed? Was the previous way the best way? How recently was the job performed? Is it repeating too frequently?
- Should additional work be performed in the interest of a longer term solution? Is it better to repair or replace?

LABOR AND JOB DURATION

- Estimate labor requirements.
    - The actual hours to be worked on the job by the technicians. This will usually reflect what will be written on timecards.
    - Specify if multiple technicians or craftsmen are required for the job.
    - Estimate job duration.
    - Estimate how long the job should take from start to finish.
    - Estimate required downtime.
- Estimate job duration, i.e., equipment will remain out of service.

PARTS AND MATERIALS

- Determine if parts or materials replacement is required; identify such parts and materials, and link to plan.
- Assess difficulty in accessing for future replacement.
- Assess probability of failure in current condition.
- Assess consequence of failure if it should occur.
- Include a BOM as a contingency.
- Technician may find that other unanticipated parts are needed. Estimate how quickly such parts can be acquired.
- Determine which items are in stock.
- Reserve in SAP.
- Develop materials acquisition plan.
- Decide whether to make direct purchase or make parts.
- Decide whether to make in house or send out for making.
- Open work order for in-house fabrication.
- Create PO for contractors and outside equipment rental. Consider disposal of used parts.
- Consider recondition, special needs, time required, expense, etc.

SPECIAL TOOL REQUIREMENTS

- Determine if special tools are required, including tools that technician would not possess in pouch or toolbox.
- Determine which tools can be useful including common tools from Tool Room, Shop or Stock Room.

PPE AND SAFETY HAZARDS

- Determine PPEs (Personal Protective Equipment) required.
- It is the planner's responsibility to verify standard list and identify other potential PPE needs, depending on identification of other potential safety hazards, like hot surfaces, pinch points, sharp edges, chemicals, flammability, fall hazards, tasks requiring lockout locks to be removed, etc.
- Identify utilities requiring lock out/tag out.
- Identify required safety inspections and standby positions for special conditions.
- Identify required safety equipment, e.g., safety signs, barricades, safety tape, etc.

9 Standard Operating Procedures (SOPs)

SOP for the PM of direct impact equipment, buildings, and utilities shall be reviewed and approved by equipment owner, responsible department heads so as to ensure that the SOPs are technically correct. The site quality assurance shall review and approve PM SOPs to ensure that the SOPs are following applicable regulatory requirements.

The PM Plan shall include, and is not limited to, the following:

- Master list of direct impact equipment, buildings, and utilities that require PM.
- Responsibilities for performing PM.
- PM frequency.
- Materials to be used.
- PM SOPs, instructions, and checklist.
- List of approved lubricants.
- Reference to approved drawings, e.g., floor plans.
- Piping and Instrument Drawing (P&ID).
- SOPs on PM change control.
- SOPs for returning equipment to service after performing PM.
- SOPs on handling overdue PM.
- Qualification and training requirements of personnel who execute the PM.
- Documentation requirements.

PM SOPs or Instructions shall include, and are not limited to, the following:
Identification of equipment, building, or utility and Instructions for performing PM, including Equipment assembly and disassembly.

- Adjustments and/or replacements and functional testing.
- Identification of any tools and/or standards to be used.
- Inspection for equipment wear, damage, or failure.
- Identification of documentation required.
- Scheduling information.
- Description of measurements to be taken.
- PM frequency and rationale for frequency shall be established for each piece of direct impact equipment, each building, and each utility and shall be based on the following considerations :
    - Manufacturers recommendations on equipment use and criticality.
    - Frequency of use.
    - Environmental conditions to which equipment is exposed.
    - Equipment location.
    - Performance history including failure rates of similar equipment.
    - Potential consequence of failing to complete PM.
    - Identified failure modes.
    - Cost to maintain equipment and equipment life cycle.
    - If required, PM frequencies may be adjusted based on the PM history. The justification for changing the PM frequency must be documented and approved by concerned persons.

- The equipment owner and the site quality authority shall be notified if PM is not performed within the scheduled frequency.

- All PM work performed on direct impact equipment shall be documented. The documentation shall include, but is not limited to :

    - Maintenance performed, including reference to the SOP used.

    - Identification and location of direct impact equipment, building, or utility on which maintenance was performed.

    - Identification of any parts replaced during maintenance.

    - Materials used (e.g., spares and consumables).

    - Identification of any change control requests implemented.

    - Measurements or observations made.

    - Signature and date of the person performing maintenance.

    - Signature and date of the person approving the maintenance.

10 Failure Mode And Effect Analysis (FMEA)

FMEA is a detailed analysis of a piece of equipment (or process that equipment performs) to identify failure modes and their impact. The FMEA identifies existing controls that prevent and detect the failure modes, as well as highlighting those that require additional controls, design changes, procedural changes, training, etc.

FMEA captures failure modes, existing controls, and identifies improvement opportunities. Identifying failure modes helps determine maintenance and production activities to mitigate, prevent, and detect those failures.

The FMEA. once created, is updated whenever an actual failure occurs in equipment. This continuous updating assures that the ways in which the equipment can fail are known, and that appropriate action is being taken.

Annexure – I

Basic Format for the Maintenance Master Plan

1.0 Executive Summary

a. Purpose.
b. Scope.
c. Roles and responsibilities.
d. Team and structure.
e. Proposals.
f. Cost elements.
g. Business benefits.

2.0 Objectives

a. Maintenance vision and mission.
b. Maintenance charter.
c. Governing principals.
d. Priorities.
e. Baselines and targets.

3.0 Strategies

a. Lubrication.
b. PM optimization.
c. Assets criticality ranking.
d. Maintenance strategy.
e. Spare parts strategy.
f. Planning and scheduling optimization.
g. Leadership.
h. Colleague development.

4.0 Assessments and Plans to improve

a. Maintenance practices.
b. Prioritize the improvement areas.
c. Define the right tools.
d. Training colleagues on the tools.

5.0 Master Plant Implementation

a. Master plan action strategy.
b. Tactics and metrics.
c. Timelines for implementation.

6.0 Deliverables

a. Benchmark figures and core metrics.
b. KPIs and reports.
c. Tracking mechanism.
d. Compliance to benchmark figures.
e. Cost improvements.

7.0 Review Mechanism

Annexure – II

Basic Format for the Annual Maintenance Plan

1.0 Executive Summary

a. Purpose.
b. Scope.
c. Roles and responsibilities.
d. Team and structure.
e. Proposals.
f. Cost elements.
g. Business benefits.

2.0 Objectives of the Year

a. Production volumes.
b. Plant utilization summary.
c. Priorities.
d. Baselines and targets.

3.0 Strategies

a. PM optimization.
b. Assets replacement.
c. Spare parts strategy.
d. Planning and scheduling optimization.
e. Turnaround plans and schedules.
f. New projects.
g. Training to colleagues.
h. Human resource requirements.

4.0 Budget Planning and Control

a. R&M budget proposal.
b. Capital budget proposal.

5.0 Contingency Planning

a. Contingencies for unscheduled activities.
b. Compliance issues.
c. Unresolved Issues.

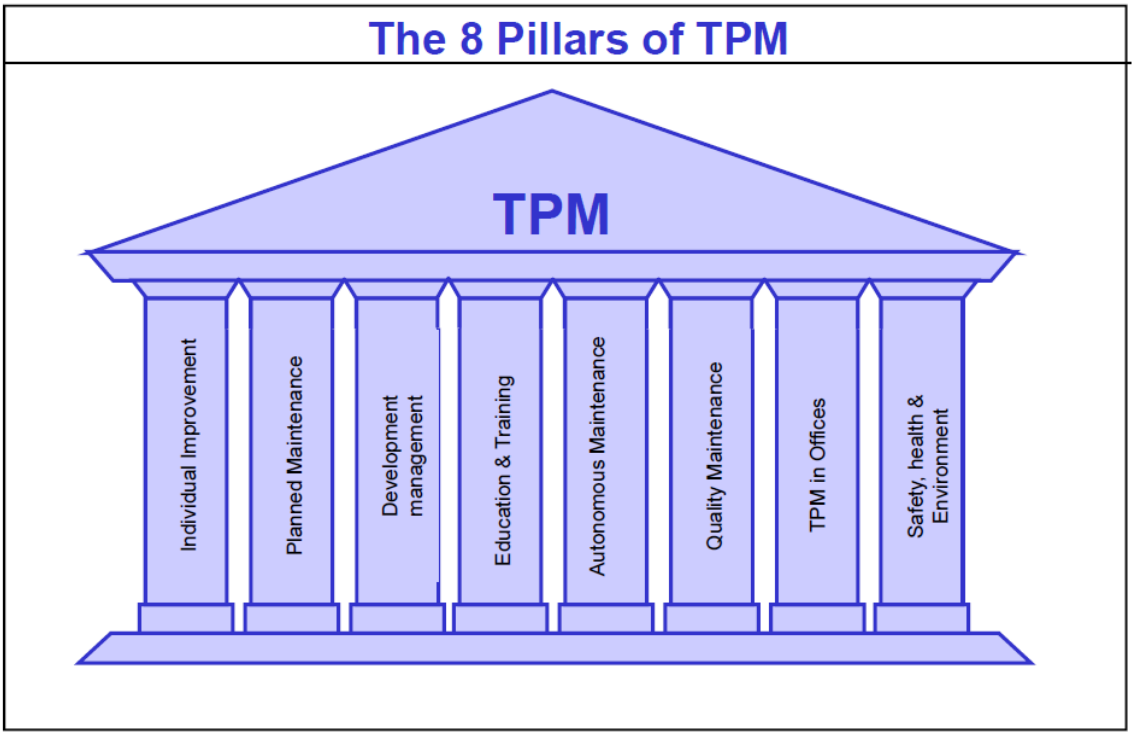
6.0 Deliverables

a. Compliance to benchmark figures.
b. Cost improvements.

7.0 Review Mechanism

Annexure – III

Introduction to TPM



Relationship between "Input" and "Output" in Production Activities

Output \ Input	Man	Machine	Material	Technique
	Money			
Production				Production Control
Quality				Quality Control
Cost				Cost Control
Delivery				Delivery Control
Safety				Safety & Pollution
Morale				Human Relation
Output / Method	Manpower Management	Plant Eng. & Maintenance	Inventory Control	Output / Input = Productivity — Ultimate Goal of Plant Operations

What TPM Aims at

To restructure the corporate culture through improvement of human resources and plant equipment

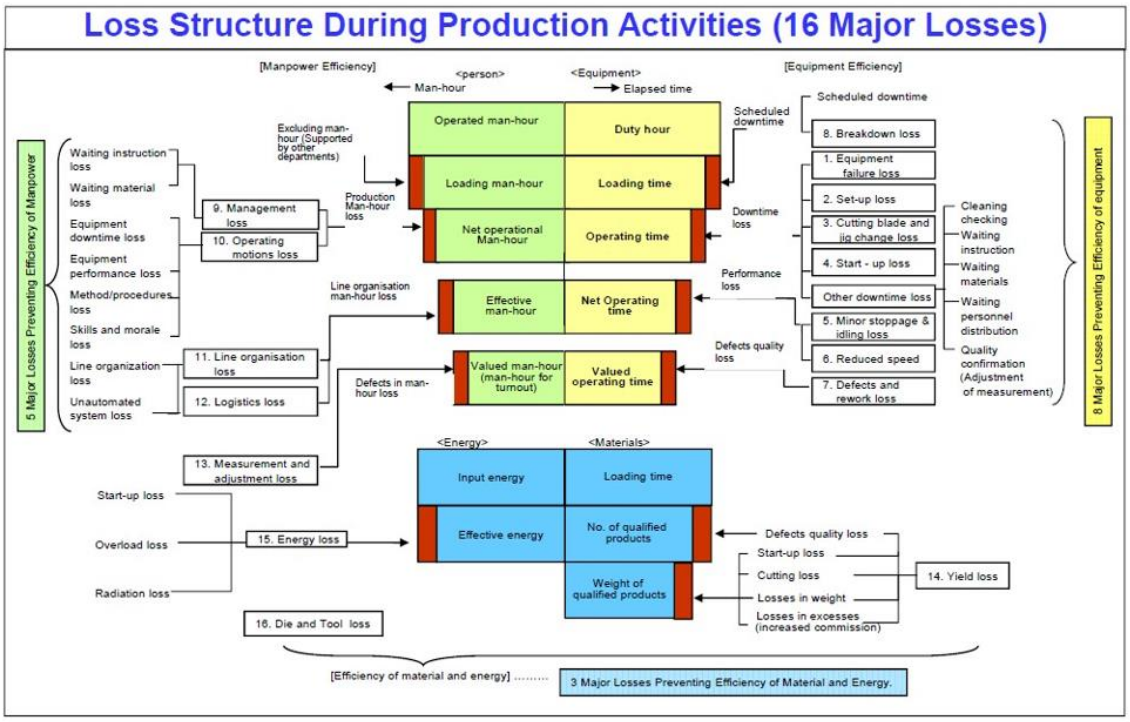
Improving human resources	- Educate and foster employees so that they can respond to the needs of FA – (1) Operator : Ability to perform 'Jishu Hozen' (2) Maintenance man : Ability to perform high-quality Maintenance (3) Production engineer : Ability to execute maintenance-Free equipment plan
Improving Plant equipment	(1) Attain efficiency through revamping of the existing equipment (2) LCC – considered design of new equipment and minimizing their run-up time

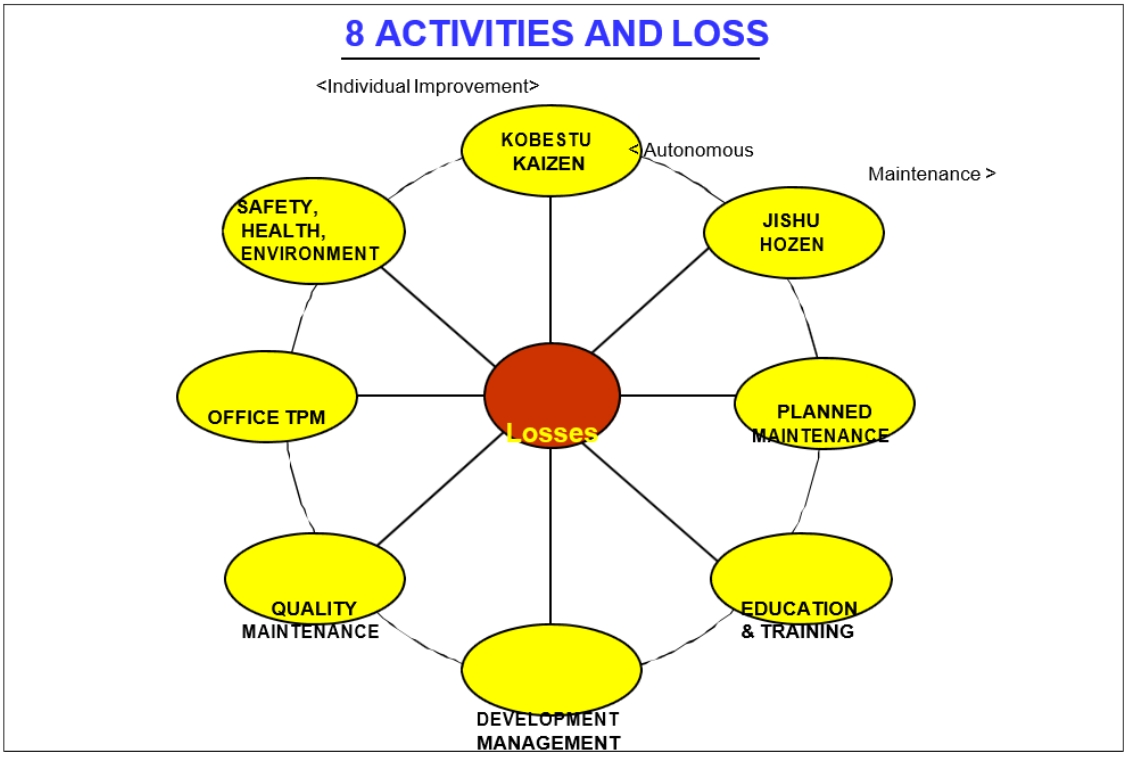
Improving the corporate culture

Definition of TPM

What is TPM?

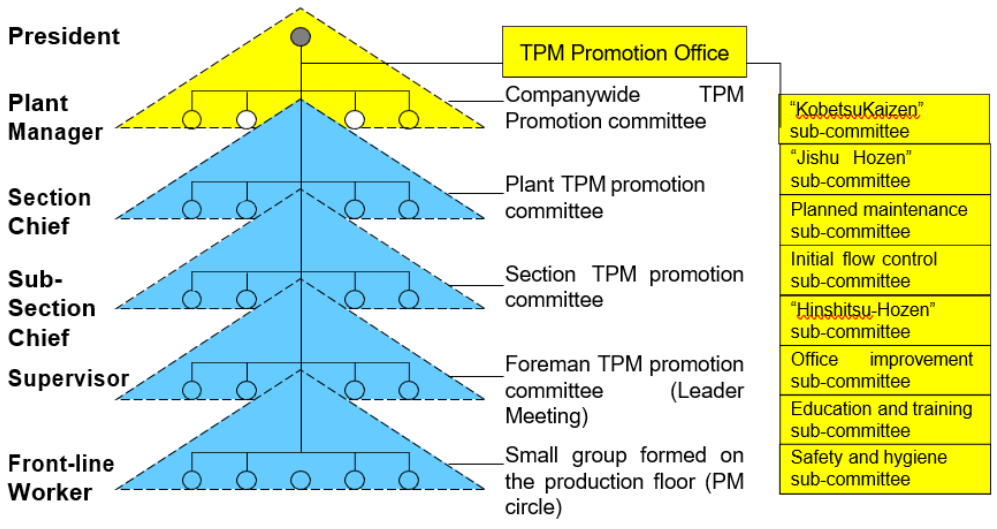
1. To maximize equipment efficiency (overall efficiency).
2. To establish total system for productive maintenance for the entire life of equipment.
3. Through participation by all departments
4. Involving all personnel, including top personnel to first-line operators.
5. Promotion of autonomous small-group activities.


Loss Structure During Production Activities (16 Major Losses)
[Manpower Efficiency]
<person>
Man-hour
<Equipment>
Elapsed time
[Equipment Efficiency]
Operated man-hour
Duty hour
Loading man-hour
Loading time
Net operational Man-hour
Operating time
Effective man-hour
Net Operating time
Valued man-hour (man-hour for turnout)
Valued operating time
Excluding man-hour (Supported by other departments)
Production Man-hour loss
Line organisation man-hour loss
Defects in man-hour loss
Scheduled downtime
Downtime loss
Performance loss
Defects quality loss
5 Major Losses Preventing Efficiency of Manpower
Waiting instruction loss
Waiting material loss
Equipment downtime loss
Equipment performance loss
Method/procedures loss
Skills and morale loss
Line organization loss
Unautomated system loss
9. Management loss
10. Operating motions loss
11. Line organisation loss
12. Logistics loss
13. Measurement and adjustment loss
Scheduled downtime
8. Breakdown loss
1. Equipment failure loss
2. Set-up loss
3. Cutting blade and jig change loss
4. Start - up loss
Other downtime loss
5. Minor stoppage & idling loss
6. Reduced speed
7. Defects and rework loss
Cleaning checking
Waiting instruction
Waiting materials
Waiting personnel distribution
Quality confirmation (Adjustment of measurement)
8 Major Losses Preventing Efficiency of equipment
<Energy>
<Materials>
Input energy
Loading time
Effective energy
No. of qualified products
Weight of qualified products
Start-up loss
Overload loss
Radiation loss
15. Energy loss
Defects quality loss
Start-up loss
Cutting loss
Losses in weight
Losses in excesses (increased commission)
14. Yield loss
16. Die and Tool loss
[Efficiency of material and energy] .....
3 Major Losses Preventing Efficiency of Material and Energy.


8 ACTIVITIES AND LOSS
<Individual Improvement>
KOBESTU KAIZEN
<Autonomous Maintenance >
SAFETY, HEALTH, ENVIRONMENT
JISHU HOZEN
OFFICE TPM
Losses
PLANNED MAINTENANCE
QUALITY MAINTENANCE
EDUCATION & TRAINING
DEVELOPMENT MANAGEMENT

12 Steps for TPM Development Programs

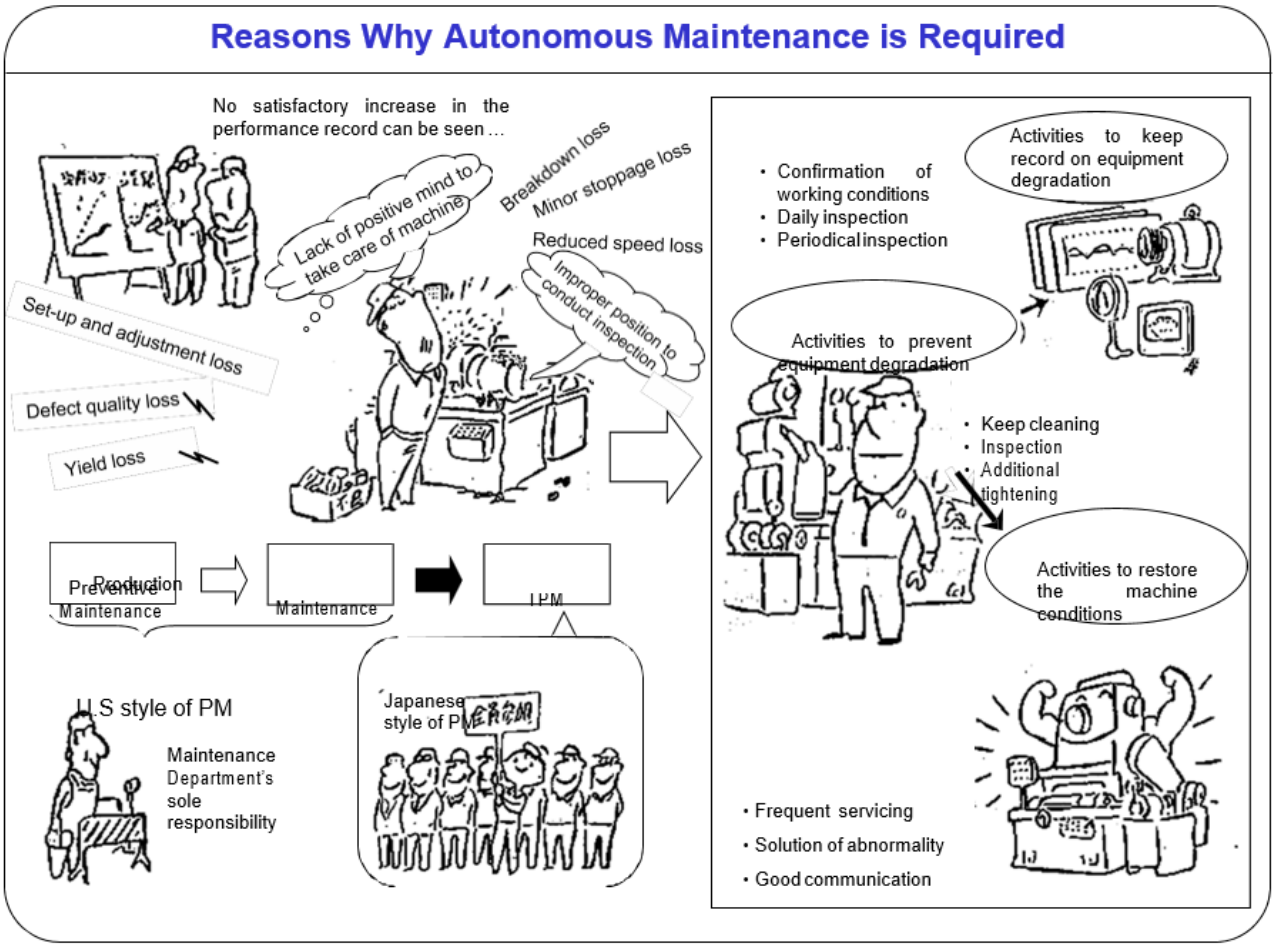
Stage	Step		Essential
Preparations for introduction	1. Declaration by top management to introduce TPM		Declared in TPM in-house seminar Carried in company magazine
	2. Introductory education and campaign for TPM		Managers : Trained in seminar camp at each level General employees : Seminar meeting using slides
	3. Establishing TPM promotion organization		Committee and subcommittees Secretary
	4. Setting basic principles and target for TPM		Bench-mark and target Prediction of effects
	5. Creation of master plan for establishing TPM		From preparations for introduction to examination
Beginning of introduction	**6. Kick-off of TPM**		Suppliers Related companies } are invited Affiliated companies
Actual introduction	7. Establishing systems for improving production efficiency		Pursuing maximum efficiency of production
		7.1 Individual improvement	Project team activities and small group activities in the workshop
		7.2 Autonomous maintenance	Step system, diagnosis and qualification certification
		7.3 Planned maintenance	Improvement maintenance, periodic maintenance, predictive maintenance
		7.4 Operation and maintenance skills upgrading training	Group education of leaders and training members
	8.	Establishing initial control systems for new products and equipment	Development of easy-to-manufacture products and easy-to-operate equipment
	9.	Establishing quality maintenance organization	Setting conditions without defectives, and its maintenance and control
	10.	Establishing systems to improve efficiency of administration and other indirect departments	Support for production, increasing efficiency in the department and of equipment
	11.	Establishing systems to control safety, sanitation and working environments	Establishing zero accidents and zero pollution systems
Steady application	12.	Total application of TPM and raising its level	Application of PM award Challenge of a higher target



Autonomous Maintenance Activities

Objectives of autonomous maintenance

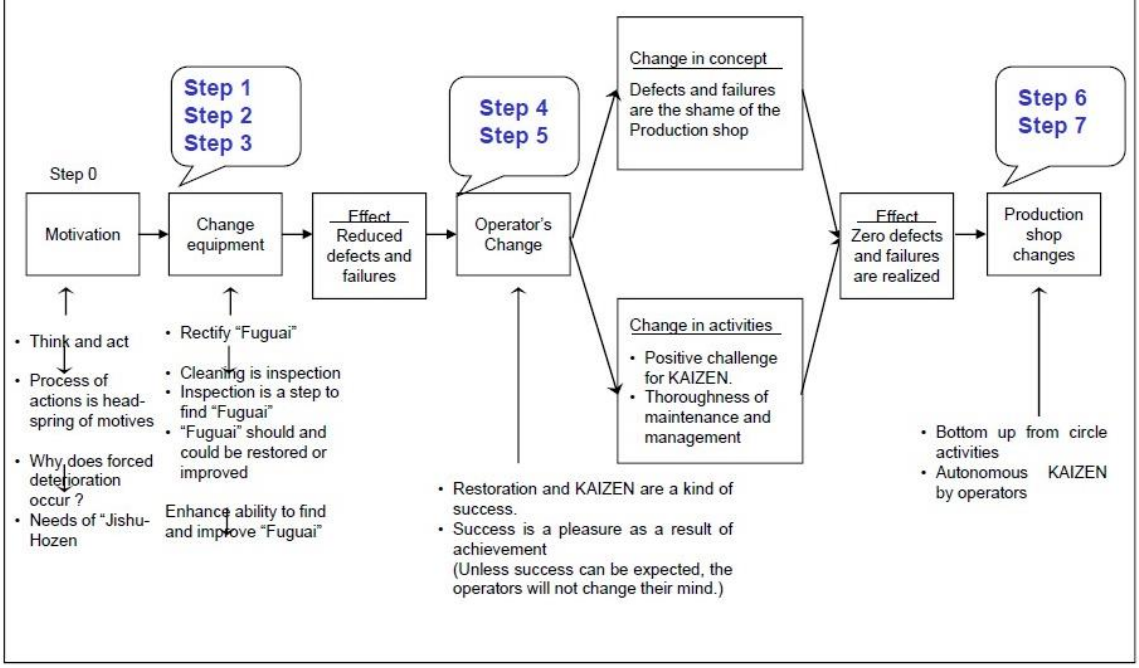
Autonomous maintenance ensures that routine preventive maintenance tasks such as cleaning, lubricating, and oiling are consistently performed on equipment that need them. These simple but crucial tasks help prolong the optimal performance of equipment and company assets.



Steps for Evolving Autonomous Maintenance

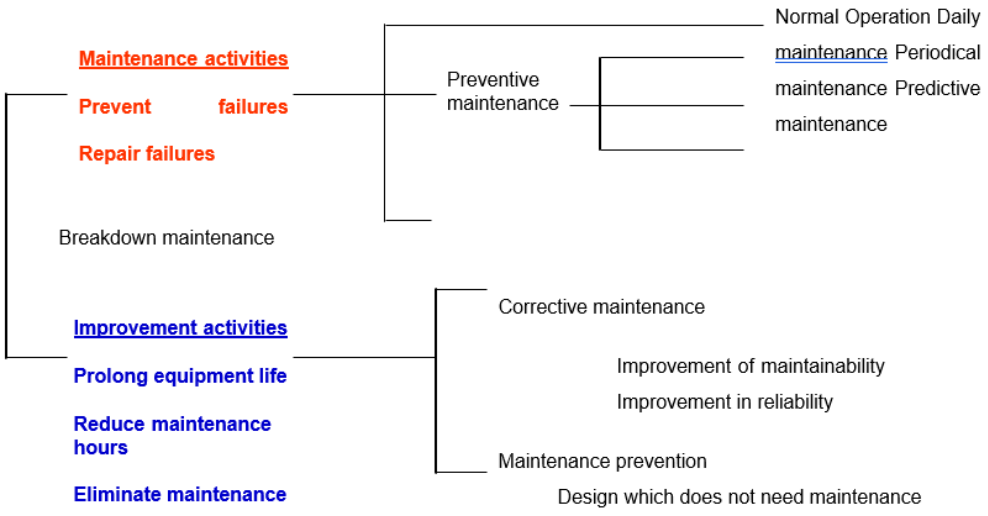
Step	Name	
1	Initial clean-up	All-around clean-up of dust and dirt, centering on equipment proper, and implementation of lubrication, and machine parts adjustment; discovery and repair of malfunctions in equipment
2	Measures against Sources	Prevent causes of dust and dirt and scattering, improve places which are difficult to clean, and lubricate and reduce the time required for clean-up and lubrication.
3	Formulation of clean-up and lubrication standards	Formulate behavioral standards so that it is possible to steadily sustain clean-up, lubrication, and machine parts adjustment in a short period. Necessary to indicate a time frame-work that can be used daily or with some periodicity.
4	Overall inspection	Training in check-up skills through check-up manuals; exposure and restoration of minor equipment defects through overall check-ups.
5	Autonomous check-up	Formulation and implementation of autonomous check-up sheets.
6	Orderliness and tidiness	Standardize various types of on-the job management items and devise complete systematization of up-keep management. • Standards for clean-up, check-ups and lubrication. • Standards for physical distribution in the workplace • Standardization of data records. • Standardization of die management, jigs, and tools.
7	All-out autonomous management	Development of corporate policies and goals, and making improvement activities routine: steadily record MTBF analysis, analyze these, and carry out equipment improvements.

Concept of "Jishu-Hozen"

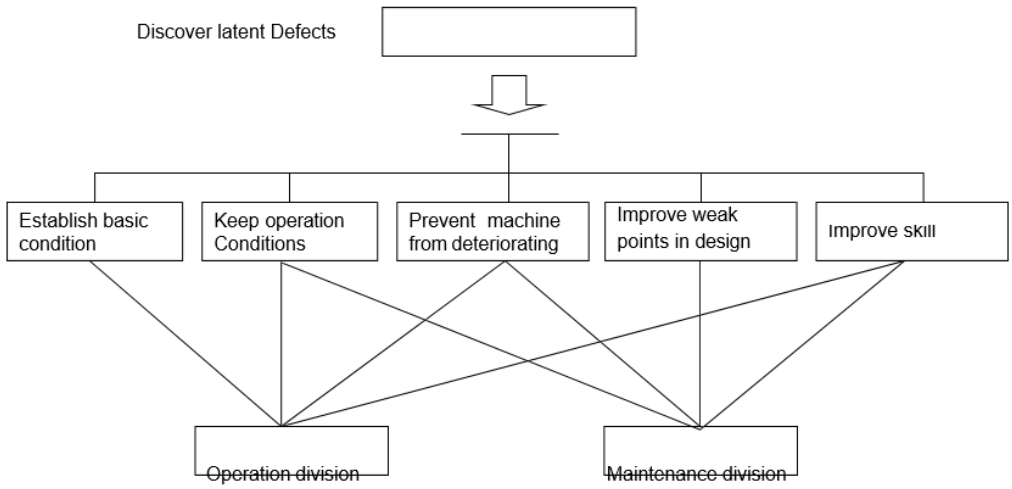


PLANNED MAINTENANCE ACTIVITIES

Classification of Maintenance Activities



Role of Operation and Maintenance Division



EDUCATION AND TRAINING ACTIVITIES

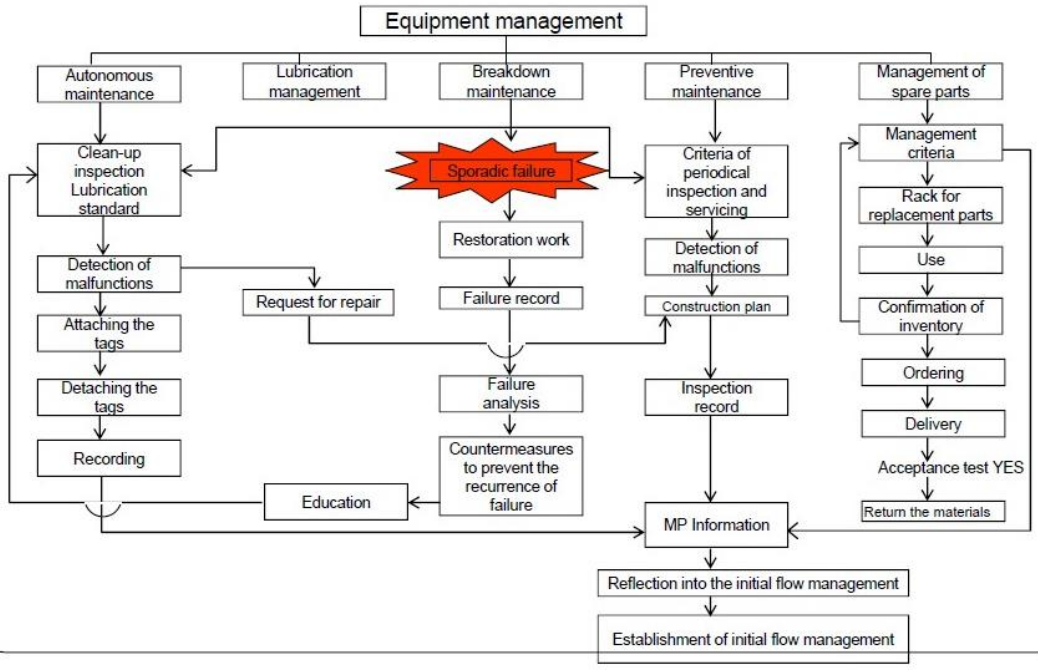
Objectives:

to develop employees by providing formal education and training.

Five Steps for Skill

(1)	Not familiarized (Not educated)	→	Lack of knowledge
(2)	Have a basic knowledge	→	Lack of training
(3)	Can perform by oneself to the certain extent		
(1)	Have a confidence in performing appropriate maintenance	→	Skills have been well acquired like habit
(2)	Can impart the knowledge to the trainees	→	Knowledge has been completely mastered

Equipment Management flow



Annexure – IV

Equipment Maintenance History Card

Document No.		Version	1.0
Effective Date		Department	Engineering

Equipment Maintenance History

Duration : From To :
Equipment Description :
Equipment Number :
Equipment Make :
Equipment Model :
Maintenance Plant :
Functional Location :
Technical ID Number :
Asset Number :

Maintenance type	Maintenance order number	Maintenance Start Date time	Maintenance Finish Date & time	Operations (long text)	Material Used	Qty with UOM	Cost in Rs.	Attended By

Annexure – V

ANNUAL MAINTENANCE REVIEW CARD

Equipment Name		Equipment ID	
Review Date :		From Date :	To Date :

1.	2.	3.

Prepared By :
(Engineering)

Reviewed By :
(Engineering Section Head)

Approved By :
(Engineering Head)

Annexure – VI

PREVENTIVE MAINTENANCE SCHEDULE

Sr. No.	Equipment Name	Equip. Id	Weekly (W) / Fortnightly (Ft)	Monthly (M) / Bi Monthly (Bm)	Quarterly (Q) / Four Monthly (Fm)	Half Yearly (Hy) / Eight Monthly (Em) / Ten Monthly (Tm)	Yearly (Y) / Bi Yearly (By) / Tri Yearly (Ty)

Legend		Weekly (W) / Fortnightly (Ft)	Monthly (M) / Bi Monthly (Bm)	Quarterly (Q) / Four Monthly (Fm)	Half Yearly (Hy) / Eight Monthly (Em) / Ten Monthly (Tm)	Yearly (Y) / Bi Yearly (By) / Tri Yearly (Ty)

Prepared By :

Reviewed By :

Annexure – VII

Equivalency evaluation of critical components & Instruments

Equipment Name		Equipment Make	
Equipment ID No.		Equipment Model No.	

Sr. No.	Existing component & instrument specification	Proposed component & instruments specification	Equivalency status (Yes/No)	Remarks If Any

	PREPARED BY (ENGINEERING)	REVIEWED BY (USER)	APPROVED BY
Sign & Date			

Sr. No.	Existing component & instrument specification	Proposed component & instruments specification	Equivalency status (Yes/No)	Remarks If Any

Remarks & Replacement approval by Engineering Head or designee :

_____

_____

(Sign/Date)

	PREPARED BY (ENGINEERING)	REVIEWED BY (USER)	APPROVED BY
Sign & Date			

Annexure – VIII

Assessment for Equipment Categorization for Maintenance

Sr. No.	Equipment Name	Area/Location	Equipment Tag No.	Description of Equipment	Evaluation of equipment category				Equipment Category Critical/Non Citical	Remarks
					Equipment has direct contact with the product (Yes / No)	Operation of equipment has direct impact on quality of product (Yes / No)	Failure or alarm of equipment has direct impact on product quality (Yes / No)	Equipment is provided with process control systems that may affect product quality (Yes / No)		

If any of the check point evaluation applicability result is Yes, then consider the equipment category as Critical else it shall be non-critical.

Prepared By	Reviewed By	Reviewed By	Approved By
Engineering	Engineering (HOD/Designee)	User (HOD/Designee)	QA Department (HOD/Designee)

Modern GEMBA Walkthrough for Pharmaceutical Industries

CONTENTS

1 An Introduction to GEMBA

GEMBA is a Japanese term meaning "the actual place". In business, GEMBA refers to the place where value is created; in manufacturing, GEMBA is the factory floor. In pharmaceutical plant, it can be any place where the value is added to the product, for example, process/production areas, warehouses, service/technical floors, water systems, QC labs, sampling areas, and so on.

GEMBA Walks denote the action of going to see the actual process, understand the work, ask questions, and learn. It is also known as one of the fundamental parts of lean management philosophy.
The GEMBA Walk is an opportunity for staff to stand back from their day-to-day tasks to walk the floor of their workplace to identify wasteful and improvement activities. The objective of a GEMBA Walk is to understand the value stream and its problems rather than review results.
The GEMBA Walk adopted in pharmaceutical industry gives deep insights to the management and senior leaders on the following aspects:

1. How effective and robust are their validation and qualification systems in line with regulatory requirements.

2. How effective and robust are their facility maintenance and machine maintenance programs in line with regulatory requirements and global industrial engineering standards.

3. How effective are their CAPAs and change management systems in line with regulatory requirements.

4. How effective are their training systems in line with regulatory requirements.

5. How effective are their safety systems in line with global industrial safety standards.

Based on the effectiveness, the firm can take calls to improve the systems and stride towards continuous and incremental improvement. This in turn gives long term and sustaining success to the organization.

2 Definitions

GEMBA : GEMBA is a Japanese term meaning "the real place." In business however, GEMBA refers to the place where value is created. In pharmaceutical industry GEMBA could be any process area like production area, water systems, service/technical floors, quality labs, ware houses and storage areas and utility areas.

Walk through : the act of going slowly through the steps of a process, job, etc., in order to learn how exactly the process is.

Critical thinking : critical thinking is the analysis of facts to form a judgment.

Non-conformity : a non-conformity is a deviation from a specification, a standard, or an expectation. This includes, but is not limited to sample failures, deviations, equipment failures, OOSs, OOTs, OOCs, or any process that fails to meet regulatory requirements.

Immediate action : an action taken immediately to save the situation and to prevent the non-conformity from spreading further. Immediate action may involve some remedial actions.

Remedial action : an action taken to correct a non-conformance, and return the process, product, or materials to an acceptable state or validated state.

Corrective action : an action taken to eliminate the cause of a detected non-conformity or other undesirable situation. Corrective action is taken to prevent recurrence of the problem.

Preventive action : an action taken to eliminate the cause of a potential non-conformity or other undesirable potential situation. Preventive action is taken to prevent occurrence of the problem.

Observation : An 'observation' is a statement of fact made during an audit and substantiated by objective evidence. Observations can indicate conformity or non-conformity, and provide opportunities for improvement.

Deficiency : 1. the quality or state of being defective or of lacking in some necessary quality or element; 2. the quality or state of being deficient: e.g., inadequacy suffers from a deficiency of critical thinking; and, 3. an amount that is lacking or inadequate.

Critical observation : any non-conforming observation that has the potential to impact the integrity of the company. An observation that has produced, or may result in a significant risk of producing, e.g., an API that, when used in a finished product, is harmful to the user, a deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or patient, or a product which could result in a harmful residue in a food producing animal.
An observation describing a situation that is likely to result in a NC product or a situation that may result in an immediate or latent health risk is a critical observation; so is any observation that involves fraud, distortion or falsification of products or data.

Major observation/deficiency: any non-conforming observation that has the potential to affect the safety, quality, identity, purity, or strength of an affected item, i.e., product or input material, is a major observation.
A non-critical observation that: 1) has produced or may produce a product which does not comply with its prequalification application (including variations); 2) and/or indicates a major deviation from the GMP guide; 3) and/or indicates a failure to carry out satisfactory procedures for release of batches; 4)and/or indicates a failure of the person responsible for QA/QC to fulfill his/her duties; 5) and/or consists of several other deficiencies, none of which on its own may be major, but which may together represent a major deficiency, and should be explained and reported as such.
An observation that has produced or may produce a product, which does not comply with its marketing authorization; or which indicates a major deviation from EU Good Manufacturing Practice; or which (within EU) indicates a major deviation from the terms of the manufacturing authorization; or which indicates a failure to carry out satisfactory procedures for release of batches; or (within EU) a failure of the qualified person to fulfil his legal duties; or a combination of several other deficiencies, none of which on their own may be major, but which may together represent a major deficiency, and should be explained and reported as such.

Minor observation/deficiency: any non-conforming observation that does not have the potential to impact the safety, quality, identity, purity, or strength of an affected item, i.e., product or input material, is considered to be a minor observation. A deficiency which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice is a minor deficiency. A deficiency m ay be classified as “other” either because i t i s assessed to be a mi nor one, or because there i s i nsuff i ci ent i nform ation to classify it as major or critical. Several related major or other deficiencies may be taken together to constitute a critical or major deficiency, respectively, and will be reported as such. All critical and major deficiencies found will be reported even if remedial action has been taken before the end of the inspection.

Root cause : root cause is an initiating cause of either a non-conformity or a causal chain that leads

3 Overall Objective

The overall objective of this document is to define a robust framework for progressive periodic compliance of facility maintenance, procedures in line with training, and health safety compliance.

- This framework shall ensure the facility in the state of compliance to meet global quality standards, and to identify continuous improvement opportunities.
- The objective of the walkthrough is to evaluate effectiveness of cleaning of area, equipment, and its ancillary units.
- As per visual observation, interaction and feedbacks from the walkthrough, adequacy in defined process versus actual observation shall be evaluated.
- An objective is to continuously enhance the skill sets of the operating staff with respect to process, product, cleaning, and machine minding.
- Another is to identify the shortfall and deficiencies in the current process, and have a corrective approach to mitigate the shortcomings in order to strengthen the process within Industry.
- Further, the intention is to create a database of observations and shortfalls and in turn to evaluate the risk.
- Based on the observations and risk, the scope of system upgradation and replacement shall be evaluated.
- Quality compliance would be the direct objective, and productivity enhancement would be the secondary objective.
- The walkthrough shall identify gaps in terms of safety of process and machine.

4 Scope

This document lays down a framework applicable for GEMBA walkthrough at sites within formulation and API facilities. This framework shall define guidelines for effective GEMBA walkthroughs to be carried out for process areas, quality areas, warehouse areas and engineering areas within sites.

- This document will define the guidelines for GEMBA walkthrough model in detail and end-to-end implementation of the model.

- This document will define dynamic checklists to be used for GEMBA walkthroughs in different areas. These dynamic checklists focus on 4 major entities in the area where the GEMBA walkthroughs are made as per applicability. These are facility, machine, training, and safety. For example, if the GEMBA walkthrough is planned in a process area, for example the compression room, there shall be 4 different checklists carried by the inspector, viz. facility checklist, machine checklist, training checklist, and safety checklist.

    - Facility checklist would contain all the necessary and minimum checkpoints to look for in terms of facility maintenance.

    - Machine checklist would contain all necessary and minimum checkpoints to look for in terms of machine maintenance and machine conditions.

    - Training checklist would contain all necessary and minimum checkpoints to look for in terms of competency/capability of the operator in KYMs and KYPs, and also checkpoints to look for awareness of previous 483s and observations and corresponding CAPAs to the operator.

    - Safety checklist would contain all necessary and minimum checkpoints to look for in terms of operator safety while working in the facility and with the respective machine.

5 GEMBA Walkthrough Framework

There are three phases of implementation of modern GEMBA Walkthrough model, viz.:

1. Establishment phase
2. Improvement phase
3. Sustenance phase

Phase	Phase I (Establishment phase)	Phase II (Improvement phase)	Phase III (Sustenance phase)
Tenure	Initially 3 months	Minimum 1 year	Review based*
Area Covered	Process areas,warehouse, quality, engineering	Process areas,warehouse, quality, engineering	Process areas,warehouse, quality, engineering
Eligibility	Default gret zone	Orange zone	Green zone
Review Frequency	Monthly	Yearly/Half-yearly	Yearly/Half-yearly

The classification of area shall be done into three stages,

Primary area : The primary classification shall be by department; e.g.\, production, quality, and engineering.

Secondary area : Within each department, the relevant sections are identified at the secondary level. For example,, secondary areas could be compression, granulation and coating within production. and testing, stability, raw material, packing in process.

Tertiary area : Within secondary areas, section and sub section areas shall be classified. For example, within compression areas compression-I, compression-II can be tertiary classifications.

The classification of area will be done by the user department designee as per Annexure-I.

Rules for Classification of Areas for GEMBA Walkthrough Planner

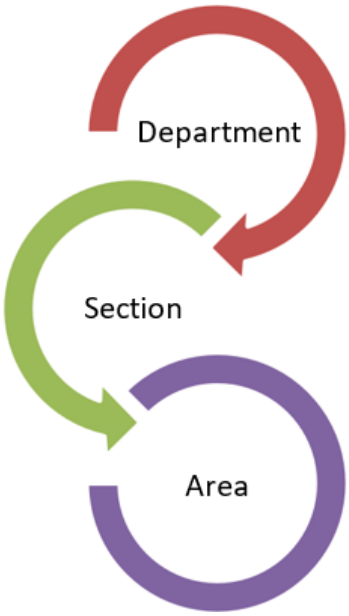
1.The areas will be classified for GEMBA walkthrough planner on department wise, if the Sections are 3 and less within the department.

2.The areas for the GEMBA walkthrough planner will be classified under section wise under following circumstances a. If there are more than 4 section within department b. If there are more than 6 tertiary areas within each section.

Frequency of GEMBA Walkthrough :

The planner will be prepared and maintained by section observer and the frequency of GEMBA walkthrough will be monthly ± 15 days as per Annexure II. However, the frequency can be changed based on nature of observations and size of the facility.

Classification of areas is a onetime activity which is done before start of the GEMBA walkthrough program; However, it will undergo changes if there are addiction or deletion of areas in each facility.



5.1.2 Roles and Responsibilities

For conducting GEMBA , there are three (3) ain roles: Inspector, Auditee and Observer.

1. GEMBA Inspector : Responsibilities

- GEMBA inspector is a senior leader from Quality Assurance, e.g., HOD of the department or QA SME, or a cross-functional leader.
- GEMBA inspector shall lead and conduct the GEMBA walk along with observer.
- The inspector shall prepare for the walkthrough on the basis of market complaints, CAPA, previous 483, other regulatory observations and operational SOP of the particular area.
- The inspector shall refer to the checklist for walkthrough as per the area to be audited.
- GEMBA inspector shall observe and identify the gaps between the procedures/systems, which are established, versus procedures/systems being followed in practice. He/she shall identify shortfalls in the defined process adequacies in terms of 6Ms: Material, Machine, Manpower, Mother Nature, Method and Measurement, with scientific justification based on rationale .
- The inspector has the sole right to question the ground/operating staff during walkthrough.
- GEMBA inspector shall assess the competencies of the operating/ground staff, and shall identify training needs in terms of KYMs and KYPs
- GEMBA inspector shall also observe and identify the gaps in safety requirements.
- Based on the findings, the inspector should coach/train the ground staff on what could be the best way to answer the asked questions through interactive sessions, and ‘dos and don’ts’ in closure sessions of GEMBA walkthroughs.
- Its sole responsibility of GEMBA inspector to complete the walkthrough in a time bound manner.
- The Inspectors need to maintain the time, place of the walkthrough confidential, and can inform others only 3 hours before the start of the walkthrough.

2. GEMBA Auditee : Responsibilities

- It is responsibility of the HOD to nominate the auditee for the respective area based on the criteria for the auditee.
- An auditee can voluntarily give observations during closing session of GEMBA without impeding the GEMBA walkthrough.
- GEMBA auditee shall be aware of the systems and procedures established.
- GEMBA auditee is responsible for providing compliance for the observations given during the GEMBA walk in consultation with his/her functional head in timebound manner.
- GEMBA auditee is responsible for deriving suitable action plans using the lean tools to comply with the observations raised by the GEMBA auditor.
- HeHe or she is also responsible for training the ground/operating staff and keeping them trained at all times.
- Auditee should be available during closure meeting of GEMBA walkthrough and should acknowledge the observations identified by the inspector.

3. Observer : Responsibilities

- An observer is a neutral person who need not be SME but shall be a keen observer, good listener, and shall have in-depth knowledge of GEMBA walkthrough framework procedures.
- Observer shall maintain the GEMBA schedule for respective areas.
- Observer can voluntarily give observations in walkthrough closer session.
- It is the responsibility of the observer to classify the facility based on criticality; all auditable areas are to be considered under the classification areas.
- An observer shall observe the auditor and auditees' conversations during the walk, and shall note down the observations with respect to regulatory requirements, training needs, SOPs, procedures, cGMP, safety, etc.
- Observer plays a vital role. He/she is not part of the interview process, but responsible for maintaining the details of observations and questions asked during walkthrough in the walkthrough templates.

- An observer shall communicate the gaps observed with auditor, auditee, and ground staff, during the closure meeting of the GEMBA walkthrough.

- Observer is responsible for classifying the observations of the GEMBA walkthrough into critical, major, minor and continuous improvement, based on observation classification matrix. (Refer Annexure).

- Based on the observations noted down, the observer will provide the observations report within 3 working days to HOD of user department.

- Observer is responsible for defining the quality score of the individual area and department on a quarterly basis.

- If any observation is repetitive beyond the target date, then it's the responsibility of the observer to escalate the matter in the site quality forum.

5.1.3 Selection Criteria of Roles

Eligibility Criteria for GEMBA Inspector

- He/she needs to HOD of the Department to be inspected, OR CFT member, OR QA Personnel with relevant experience.

- Ideally, he/she should have minimum 7 years of total experience.

- He/she should have minimum 4 years' experience in answering/handling audits.

- He/she needs to be a good observer-cum-listener. and needs to be well-versed in regulatory guidelines.

- He/she can be dynamic and not a fixed individual person depending on area.

Eligibility Criteria for GEMBA Auditee

- Auditee has to be from within the audited department. He or she may be designated area section leader, or team leader, or manager, or designee.
- He/he should have relevant experience in audits and regulatory compliance.
- He/she should have knowledge and experience in the area to be audited.
- He/she can be dynamic and not a fixed (?? – JS) individual person depending on area.

Eligibility criteria for GEMBA Observer

- He/she must be from Quality Assurance department
- He/she needs to be good observer-cum-listener, and needs to be proficient with regulatory guidelines.
- He/she should have minimum 4 years' experience in answering/handling audits.
- Observer should be a dynamic person but specific to the department; he or she is the backbone for the GEMBA walkthrough process.

5.1.4 Dos and Don'ts of GEMBA

Dos

- Inspector shall come prepared about line of observation and subject to be focused on.
- Inspector shall always have a short briefing on the purpose of the visit.
- Inspector shall try to understand the thought process and level of understanding of ground staff during the interview stage.
- Inspector shall ask for their learning and improvement actions.
- Inspector shall encourage and coach ground staff on improvement opportunities, and shall congratulate them at the closure meeting.

- Inspector shall ask ground staff regarding their process difficulties and hurdles that they face during execution of the process, and always try to respect their opinion and feedback.

- Ensure inspector is trained has subject knowledge expertise to perform GEMBA walk

Don'ts

- The Speed Walker: flying into the GEMBA, and speeding things along should be avoided. However, there should be no need to spend more than 45 minutes in a single area.

- The Mind Fully Preoccupied: it can be hard for a person who has a million things to do to complete his or her own tasks; but while he or she is at the GEMBA, he or she must pay full attention, and park everything else on the wayside.

- The Know It All: showing staff how to do things while you are at a GEMBA should be avoided.

- Do not ask what is right as per procedures.

- When you are asking questions to ground staff, be polite and do not try to enforce your understanding and knowledge of the subject onto the staff.

- Always try to understand the ground staff's perspective on the particular subject.

- Auditee should not try to be intermediator during the question and interview session of GEMBA.

- GEMBA walks should focus on process and not on people; do not use this exercise as a tool to evaluate the performance of the employee.

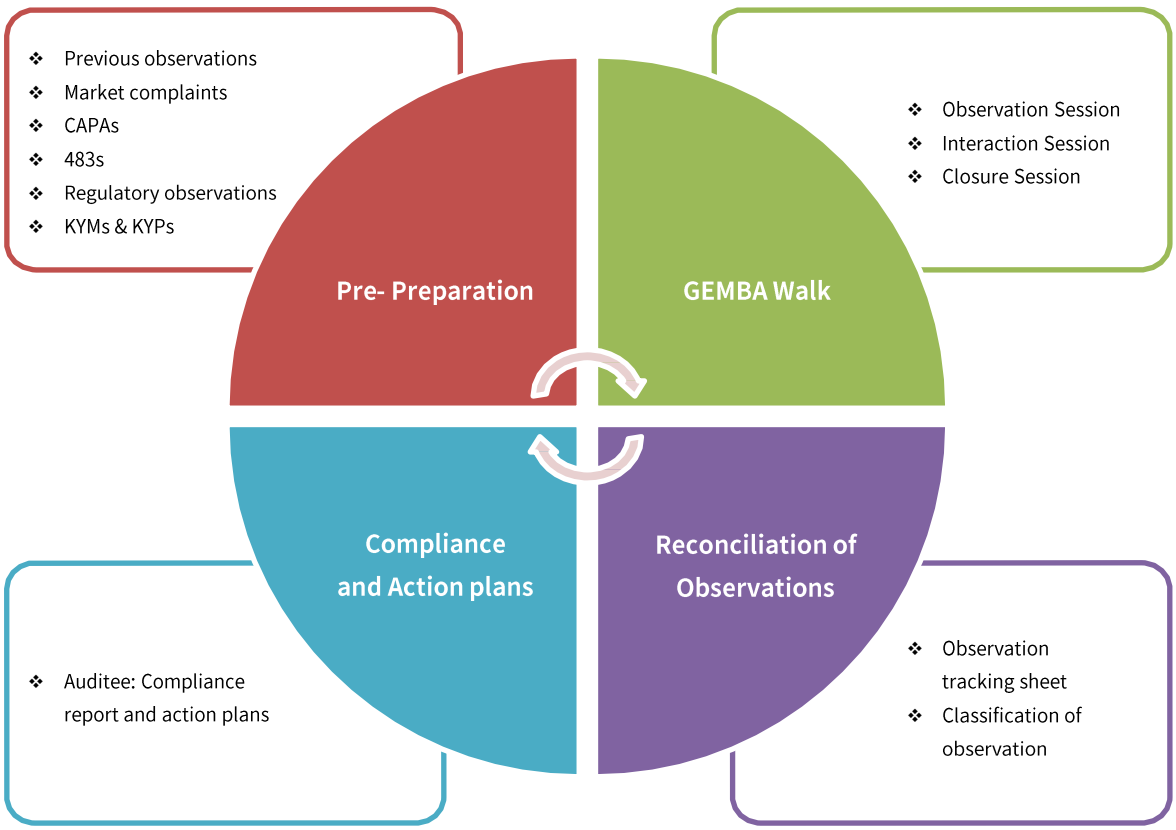
- Do not speak or interact with other cross-functional staff and activities during walkthroughs.

- Use of cell phone should be prohibited.

- If any deficiencies are observed pertaining to process, the same cannot be shared with ground staff.
- Do not enforce to perform any activity that is not part of the daily routine.
- Do not shout/yell/scold the ground staff for any observed shortfalls.

5.1.5 Dos and Don'ts of GEMBA

Typical Flow Chart



A typical GEMBA walkthrough works in a cyclical manner wherein there is improvement at the end of each cycle. There are four major stages of GEMBA walkthrough:

1. Pre-preparation,
2. GEMBA walkthrough.
3. Reconciliation of observations.
4. Compliance and action plans.

Pre-preparation :

- Observer shall decide on the area which is going to be inspected and shall facilitate inspector with all the relevant data, like previous observations, market complaints, CAPAs, SOPs, previous 483s and regulatory observations.
- Inspector shall go through previous GEMBA walkthrough observations and compliance of the area to be inspected.
- Inspector shall go through all the market complaints and CAPAs taken in the areas be inspected. (as per organization).
- Inspector shall refer to all 483s, audit observations, SOPs, KYMs, KYPs pertaining to areas to be inspected. He shall also be updated on statutory requirements and safety requirements.
- Inspector shall refer to the pre-defined checklists as per Annexure-III, and shall prepare his own checklist as per his study.
- Based on the preparation, Inspector should intimate auditee and observer on walk through schedule.

GEMBA walkthrough

- Inspector shall initiate the GEMBA walkthrough along with checklists which he prepared.
- Observer shall join the walkthrough along with inspector.
- In a GEMBA walkthrough, there are three sessions:

OBSERVATION SESSION

INTERACTION SESSION

CLOSURE SESSION

- During the observation phase, the Inspector shall observe the process without interacting with ground staff.
- In this phase, the Inspector shall use the checklists with respect to facility, machine, training, and safety as per Annexure-III. These checklists are derived as per general and common requirements in a pharma plant; however, these checklists are intended to be exhaustive. Each organization can derive their own checklists as per their requirements.
- In observation phase, the inspector shall evaluate all the checklist points that he prepared with respect to CAPAs, previous 483s, audit observations, and shall inform observer on gaps, if he has found any.
- In interaction phase, the inspector shall interact with ground staff, and try to understand the processes and procedures followed.
- Inspector shall assess the awareness of the rationale behind the practices and procedures followed by the ground staff.
- Upon evaluation, inspector shall inform observer regarding the gaps found, if any.
- During closure phase, observer shall update the auditee on all the observations found during the walkthrough.
- In closure phase, inspector shall give feed back to the ground staff on scope of improvement.

Reconciliation of Observations:

- After GEMBA walkthrough, observer shall gather all the observations in the observation tracking sheet (Annexure-V).
- Observation will be classified based on the approach below given:
    - Every observation at site need to be evaluated as per Annexure–IV Observation Classification Matrix. Based on the criteria for evaluation, the observer shall identify the observation as
        - Critical observation/deficiency
        - Major observation/deficiency
        - Continuous improvement
    - The detailed approach for classification of identified observation/deficiency is given in (Annexure-IV).
    - Based on the categorization, the Observer will update the Observation Tracking Sheet (Annexure-V).
- Observer shall classify the observations based on the observation classification matrix, and shall share the observations with auditee and his HOD within 3 working days.

Compliance and Action Plans

- Upon receiving the observations from observer, the auditee shall prepare a compliance report and action plans in discussion with HOD.
- Based on criticality of observations, he/she shall refer suitable tools to derive action plans. Refer Annexure-VIII (Hand book for Lean Tools) for tools and their applications.
- Auditee is responsible for timebound compliance with the observations.

5.1.6 RACI Matrix

Step	Responsible	Accountable	Consulting	Information
Pre-preparation	GEMBA Inspector/auditor	GEMBA Inspector/auditor	SME	QA Head
GEMBA Walk	GEMBA Inspector/auditor and Observer	QA	SME	QA Head/SH
Reconciliation of observations	Observer	QA	SME	QA Head/SH
Compliance for the observations	Concerned Function	Function Head	SME	QA Head/SH
Focus area projections	QA/Observer	QA	QA Head	SH

5.2 Phase II (Improvement Phase)

After establishing the walkthrough model, the organization starts realizing the improvements in the systems and procedures as and when it starts acting on the observations and deficiencies found during the GEMBA walkthroughs. The improvement phase shall run for at least a year.

5.2.2 Half-yearly Review

The organization shall establish a review committee. Members of review committee shall be from QA, Engineering and User departments, who are involved in the GEMBA walkthrough program. The review committee shall conduct half-yearly reviews of GEMBA walkthrough observations as per
Annexure-VI.

The committee shall review the observations in terms of criticality and repeatability of the observations. Based on the review, the User department HOD/Designee shall propose recommendations on improvement plans.

5.2.3 Yearly Review

The review committee shall conduct yearly review of GEMBA walkthrough observations as per Annexure-VII. The committee shall review the observations in terms of criticality and repeatability of the observations.

Based on the review, HOD/Designee shall propose the recommendations on improvement plans and future GEMBA walk approaches. Focus area projections shall be done based on yearly review. Based on the review, HOD/designee of the area shall prepare TNI of the ground staff.

Also based on the review, HOD of the user department shall provide recommendations on short term and long term plans to the management, in terms of refurbishment/upgradation/replacement of machine and area.

5.3 Phase III (Sustenance Phase)

Once the GEMBA walkthrough model is established and the site is in improvement phase, the review committee shall decide on qualifying the area into sustenance phase, based on yearly review of quality of observations.

To qualify an area into sustenance phase, the area should be in improvement phase for at least one year, and the quality of observations should be focused towards continuous improvements, rather than critical and major observations. In other words, there should be nil critical observations, and major observations should be analyzed for risk reduction factor (refer Annexure-III).

Once an ample amount of areas are qualified for sustenance phase, auditees from each area can be evaluated for the best performer in terms of compliance, and shall be rewarded as “GEMBA GURU” on a half yearly basis.

Based on the ground staff performance during the interaction phase of GEMBA walkthrough, the best team can be awarded as “GEMBA Gladiators.”

6 Abbreviations

1. QC: Quality Control.
2. QA: Quality Assurance.
3. KYM: Know Your machine.
4. KYP: Know your Procedures.
5. SOP: Standard Operating Procedures.
6. CAPA: Corrective Action and Preventive Action.
7. SME: Subject Matter Expert.
8. SH: Site Head.
9. TNI: Training Need Identification.
10. OOS: Out of Specification.
11. OOT: Out of Trend.
12. OOC: Out of Calibration.
13. HOD: Head of the Department.
14. API: Active Pharmaceutical Ingredient.
15. NC: Non-conformity.
16. cGMP: current Good Manufacturing Practices.

7 Annexures

1. Annexure – I : Area Classification.
2. Annexure – II : GEMBA Planner.
3. Annexure – III : GEMBA Templates.
4. Annexure – IV : Observation Classification Matrix.
5. Annexure – V : Observation Tracking Sheet.
6. Annexure – VI : Six-monthly Review Sheet.
7. Annexure – VII : Annual Review Sheet.
8. Annexure – VIII : Handbook for Lean Tools.

Annexure – I

GEMBA
Area Classification

Primary Department	HOD of the Department

Sr. No.	Secondary Section Name	Section Designee Name	No. of Tertiary Areas

Prepared by

Date

Annexure – I

GEMBA
Walkthrough Planner

Department

Section	January Actual Date	February Actual Date	March Actual Date	April Actual Date	May Actual Date	June Actual Date

Section	July Actual Date	August Actual Date	September Actual Date	October Actual Date	November Actual Date	December Actual Date

Annexure – III A

Facility Checklist Template

Date			Area Name	
Sr no	**Test particulars**	**OK √ /Need attention X**	**Observation**	**Exact location**
1	Check for operation of safety guards of machine.			
2	Check for calibration of Magnehelic gauge.			
	Doors and Accessories			
1	Check for alignment of door and door-closer.			
2	Check for any abnormal sound of doors while in operation; there should be no bulging screws.			
3	Check for door handles looseness; the door handles need to be firm.			
4	Check for functioning of door gap and drop seals.			
5	Check for interlocking of doors if applicable.			
6	Check for door view glass for any damage and fitting.			
	Floor and Epoxy			
1	Cracks on floor and level floor surfaces.			
2	Check for epoxy of flooring for cracks, abnormal stains and marks, scratches.			
3	Check for area coving for any observation.			
4	Check for polyvinyl flooring and their intactness.			
5	Check and inspect the drain of the area for rusting.			
	Walls and paint			
1	Check the walls for any crack or discoloration.			
2	Check the walls for any paint peel off.			
3	Check for coving paint in the area.			
	Utility Pendants			
1	Check for utility pendants for names and coding.			
2	Check for calibration of pressure gauge on pendant.			
3	Check for rusting and buffing of utility pendants.			
4	Check for mounting coving of pendants.			
5	Check for functioning of lights and cleanliness of light fitting.			
	Miss			
1	Check for switch board for proper edges.			
2	Check for proper sealing of return risers.			
3	Check for coding of supply and return grills.			
4	Check for proper fixing of signages in area.			
	Rate the area aesthetically on 0-10 scale.			

Annexure – III B

Machine Checklist Template

Date			Area Name	
Sr no	**Test particulars**	**OK √ /Need attention X**	**Observation**	**Exact location**
1	Is the machine's major spare/change parts and critical parts identified and marked?			
2	Are machine as built drawings available?			
3	Are machine as built drawings matching with actual machine?			
4	Are machine physical conditions fine with respect to surfaces and cleanliness?			
5	Is the machine mounting and placement fine? Is there adequate place available to do preventive maintenance?			
6	Is machine included in the preventive maintenance schedule?			
7	Is preventive maintenance done for the machine and maintenance tag available on the machine?			
8	Is the preventive maintenance tag capturing all the minimum and necessary details like PM done date, PM due date, PM done by, signature?			
9	Are all the utility requirements provided for the machine?			
10	Is the preventive maintenance done to the machine within the due date in the past as per frequency defined in the SOP?			
11	Are all the major check points added in the preventive maintenance checklist?			
12	Are all the replacement policies of major components according to the vendor recommendations?			
13	Are all the contact surfaces of certified MOCs and are the COAs available?			
14	Are the lubricants/oils used for the machine maintenance of recommended/suitable grade?			
15	Are instruments on the machine identified and tagged accordingly?			
16	Is there any periodic calibration program?			
18	Are instruments on the machine calibrated?			
19	Are calibration tags available at each instrument?			
20	Is the calibration tag capturing minimum necessary details like calibration done date, calibration due date, calibration done by, and signature?			
21	Are there certificates of calibration available and traceable for the standards?			
22	Are the calibration certificates capturing all the minimum necessary details?			
23	Are the acceptance criteria defined for the calibration of instruments?			
24	Are the calibration certificates checked by appropriate personnel.?			
25	Is the machine provided with HMI/IPC? If 'Yes,' then check below points:			
26	Does the system have access levels for user login?			
27	Is control panel dressing proper?			

Annexure – III C

Training Checklist Template

Date			Area Name	
Sr no	**Test particulars**	**OK √ /Need attention X**	**Observation**	**Exact location**
1	Are all employees following the entry and exit procedure as per SOP?			
2	Is the department neat and orderly with sufficient space for equipment and operations?			
3	Are all work areas and equipment clearly labelled with status label, the name, and the batch number of the product being processed?			
4	Are doors closed at all times except during man and material movements?			
5	Is personnel clothing clean, unstained, and dust free, including footware?			
6	Is pressure differential maintained in working areas at all times during work?			
	Is the person performing the activity as per operating procedure?			
1	Ask about the name of SOP for operation and number.			
2	Ask more details about cleaning of the equipment.			
3	Inspect the machine for proper cleaning			
4	Examine the following records: Machine Log (Operation and Cleaning). Verify the online record/audit trail of any equipment/instruments in use (if applicable) equipment/instrument ID: Entry no./date: Batch no.: Audit trail (satisfactory/not satisfactory): Status board:			

Annexure – III D

Safety Checklist Template

Date			Area Name	
Sr no	**Test particulars**	**OK √ /Need attention X**	**Observation**	**Exact location**
1	Are the electric power points provided flameproof as per requirement?			
2	Is earthing done properly for all the machines?			
3	Are the jumper wires connected to the flange joints of FBEs and coaters ducts to reduce the static charge?			
4	Is emergency switch on the machine identified and tagged?			
5	If there are sliding doors and rolling doors, are there sensors to control the opening and closing of door as per man and material movement			
6	Is the machine provided with door/guard limit switches, and is it interlocked with machine operation?			
7	Does the machine have fire/smoke detection system? Are they interlocked with the operation of the machine?			
8	Does the machine have explosion flaps and fire dampers? Is it they interlocked with the operation of the machine			
9	Is the operator trained on all the safety interlocks available in the machine?			
10	Is PSSR done before commissioning of the machine?			
11	Are all the points complying with respect to PSSR during operation of the machine?			
12	Are all the doors provided comply with required safety standards?			
13	Is machine is having any sharp/pointy edges which may cause cuts on operator while routine operation?			
14	Are PPEs mapped against the operations? Are the PPEs mapped used during routine operations? Is this mapping and usage of PPEs captured in SOPs?			
15	Is the area in-charge trained on First Aid?			
16	Is fire extinguisher available in the area or near the area?			
17	Are fire fighters identified and trained on using firefighting systems?			
18	Is there any hazardous material handling during routine operations? If yes then, is the operator trained on safe handling of the hazardous material, and is operator facilitated with necessary PPEs?			
19	Is the area adequately lit to carry out the routine operations?			
20	Is the area provided with evacuation plan?			
21	Are there signboards in place to show the emergency exit directions during evacuation?			

Annexure – III E

HVAC Checklist Template

Date			Area Name	
Sr no	**Test particulars**	**OK √ /Need attention X**	**Observation**	**Exact location**
1	Check for display drawings available on the AHU and verify the Specifications as actual Given specification			
2	Check for Readings on Magnehlic gauges across Pre and fine filters ,the observed reading need to be within acceptance criteria .			
3	Verify dates of preventive maintenance and HVAC validation on the status board of the AHU.			
4	Check for operation of chilled and hot water/steam actuator valves.			
5	Check for any air leakages from door and blower edges.			
6	Check for insulation; there should not be any insulation peel off and condensation observed on the HVAC system.			
7	Check for functioning of Limit/Micro switch for operation for blower section.			
8	Check that all door handles are intact;they must be fastened properly.			
9	Check for operation of inspection light of the AHUs.			
10	Check for calibration of magnehelic gauge and pressure gauge. and DPTs if applicable			
11	Check for cleanliness of the AHUs externally.			
12	Check for footings of the AHUs and coving.			
13	Check and inspect the drain line for any condensation and inspect the bottom section of the AHUs.			
14	Check for position of fresh air damper; it should partially open to circulate fresh air in the area ...			
15	Check for profiles of AHUs autodoor body for paint peel off or puncture in the insulation.			
16	Check for alarms of the AHUS in BMS and DAS system for any observation.			
17	Check for any abnormal vibration on the AHU.			
18	Check for operation of relief air damper; it needs to be partially open.			
19	Check for filter coding.			
20	Check for cable dressing for sensors and actuators.			
21	Check for period PM check list of AHU.			
22	Check for terminal HEPA reading of corresponding AHU.			
23	If any AHU is not in operation and under maintenance, inspect the inner section of filter, blower and coil section for any observation of rusting.			
24	Ask orally for alert limits and action limits of pre and post filters of AHU.			
25	Ask orally for alert limit and action limits of DP across HEPA terminal and plenum.			
26	Ask about validation procedure of HVAC system.			
27	Ask for filter replacement approach of the AHU filters.			
28	Ask for MOC of AHUS and filter media and its corresponding micron rating.			

Annexure – III E

Water System Checklist Template

Date			Area Name	
Sr no	**Test particulars**	**OK √ /Need attention X**	**Observation**	**Exact location**
1	Are all the sensors identified and labelled?			
2	Are all the sensors taken under periodic calibration schedule?			
3	Do all the sensors have calibration tags?			
4	Are instruments on the machine calibrated?			
5	Are calibration tags available at each instrument?			
6	Is the calibration tag capturing minimum necessary details like calibration done date, calibration due date, calibration done by, and signature?			
7	Are there certificates of calibration available and traceable for the standards?			
8	Are the calibration certificates capturing all the minimum necessary details?			
9	Are the acceptance criteria defined for the calibration of instruments?			
10	Are the calibration certificates checked by appropriate personnel?			
11	Are all the TC clamps and welded joints identified and labelled?			
12	Is the area is having display drawing (P& ID)?			
13	Is the display drawing (P& ID) updated as per the latest change control?			
14	Is the display drawing (P&ID) is matching with the physical water system?			
15	Are SOPs available for operation of the system?			
16	Is SOP available for preventive maintenance of the system?			
17	Is SOP covering all the operational parameters specifications and limits?			
18	Are all the operational parameters, specifications, and limits in line with respective guidelines?			
19	Does the system have access levels for user login?			
20	Is the privilege matrix defined?			
21	Is the audit trial captured in the HMI?			
22	Is the audit trial captured having minimum necessary details.?			
23	Is the audit trial editable.?			
24	Is the alarm handling matrix defined?			
25	Are all the controls and interlocks mentioned in the SOP?			
26	Is the area clean and free from dust?			
27	Are all the filters are identified and tagged?			
28	Are all the filters having filter replacement/cleaning status labels.?			
29	Has the system been identified and tagged?			
30	Is the preventive maintenance status tag available in the system?			

Annexure – IV

Observation Classification Matrix

DEFINITIONS

1. Critical observation/deficiency (see Appendix 3 for examples of Critical Deficiencies).

This is an observation which has produced, or leads to a significant risk of producing, either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

A 'Critical' observation also occurs when it is observed that the manufacturer has engaged in fraud, misrepresentation, or falsification of products or data.

A 'Critical' observation may consist of several related deficiencies, none of which on its own may be 'Critical', but which may together represent a 'Critical' observation, or systems failure where a risk of harm was identified and should be explained and reported as such.

2.1 Major observation/deficiency (see Appendix 3 for examples of Major Observations)

An observation that is not a 'Critical' observation, but which:

- Has produced or may produce a product which does not comply with its marketing authorization, clinical trial authorization, product specification, pharmacopoeia requirements or dossier;
- Does not ensure effective implementation of the required GMP control measures;
- Indicates a major deviation from the terms of the manufacturing authorization;
- Indicates a failure to carry out satisfactory procedures for release of batches or (within PIC/S) failure of the authorized person to fulfil his/her duties;
- Consists of several 'Other' related deficiencies, none of which on its own may be 'Major', but which may together represent a 'Major' observation or systems failure and should be explained and reported as such.

Annexure – IV

Observation Classification Matrix

3. Other observation/system improvement

These are observations that are not classified as either 'Critical' or 'Major', but indicate a departure from Good Manufacturing Practice (GMP).

Such observations may be pertaining due to ineffectiveness or inadequacy of the defined system and procedures.

Observation may be judged as 'Other' because there is insufficient information to classify it as 'Critical' or 'Major'.

4. Management tool to support consistent and objective categorisation of gmp observation in accordance with risk management principles

4.1 When classifying an observation as 'Critical', inspectors should determine if there is clear evidence by considering risk of harm as in the definition. An example is provided in the flow chart in Appendix 1, Figure 1.

4.2 When a 'Critical' observation is not clearly evident, the observation may be rated as 'Critical', 'Major' or 'Other'. A determination on the classification should be made for which the guidance provided below may be followed:

4.2.1 Perform a detailed evaluation of the observation to determine an initial classification, as per Appendix 1, Figures 2-5; then

4.2.2 Perform an evaluation of factors that would either increase or reduce the risk regardless of the initial classification, as described in Appendix 2; then

4.2.3 Make a decision as to whether the initial risk classification may be as described in Appendix 1, Figure 1:

- Upgraded, due to effects that increase the risk, i.e., risk increasing effects,
- Maintained, or
- Downgraded, due to effects that reduce the risk, i.e., risk reducing effects.

4.3 Examples of observation classification (a non-exhaustive list) are provided in Appendix 3 which can be used to assist in the classification determination if required.

4.4 The format of how deficiencies/observations are written and grouped can also be a factor affecting the classification of the observation.

5. Actions to be taken by inspectorates in response to the reporting of critical and major deficiencies

5.1 Compliance and enforcement measures are dependent upon a number of factors, including significance of violations such as a 'Critical' observation, and a large number of 'Major' deficiencies, history of the site, potential risks to products, and assessment of the manufacturer's proposed corrective actions. Where appropriate, this may include assessment of interim risk mitigating actions while long term remediation continues.

5.2 The clinical impact of the deficiencies on specific 'at risk' groups (e.g., children or immunocompromised patients) as a result of the observed quality or regulatory failures should be considered separately, and used to inform quality defect decisions and market actions such as recall. When assessing the clinical impact of observed deficiencies, expert advice such as medical and toxicological input should be sought.

5.3 If the findings are linked to patient safety, immediate action needs to be taken.

5.4 Additional factors that should be considered include :

a. The risk to health and safety

b. Compliance history of the manufacturer

c. Whether the manufacturer acted with indifference or premeditation

d. The degree of co-operation offered

e. The likelihood that the same problem will reoccur

f. The likelihood of the enforcement action being effective

5.5 Typically, the first steps could include a letter of warning/cautionary letter or a re-inspection or reassessment inspection, for which failure to address risk with repeat deficiencies may result in a non-compliance or similar rating.

5.6 Depending upon the severity of the observation, the inspectorate will determine if appropriate inspectional or regulatory actions are needed.

5.7 The actions that can be taken may include:

a. Compliance related communications which alert the manufacturer to the inspectorate's concern, and possibility for future regulatory action if remedial action is not effective;

b. Regulatory action against the site authorization or GMP approval (refusal, suspension, or amendment of an establishment license);

c. Market actions such as recall (voluntary, or mandated by the regulatory authority);

d. Prohibition of supply/importation;

e. Prosecution;

f. Communications to the public using public warning/public advisory or information updates;

g. Suspension or cancellation of Marketing Authorization/Product License;

h. Health product label or packaging changes.

6. Enhancing communication, information sharing and scientific exchange to promote increased consistency and predictability in regulatory assessments and decisions and the rapid exchange of safety and quality information regarding manufacturers

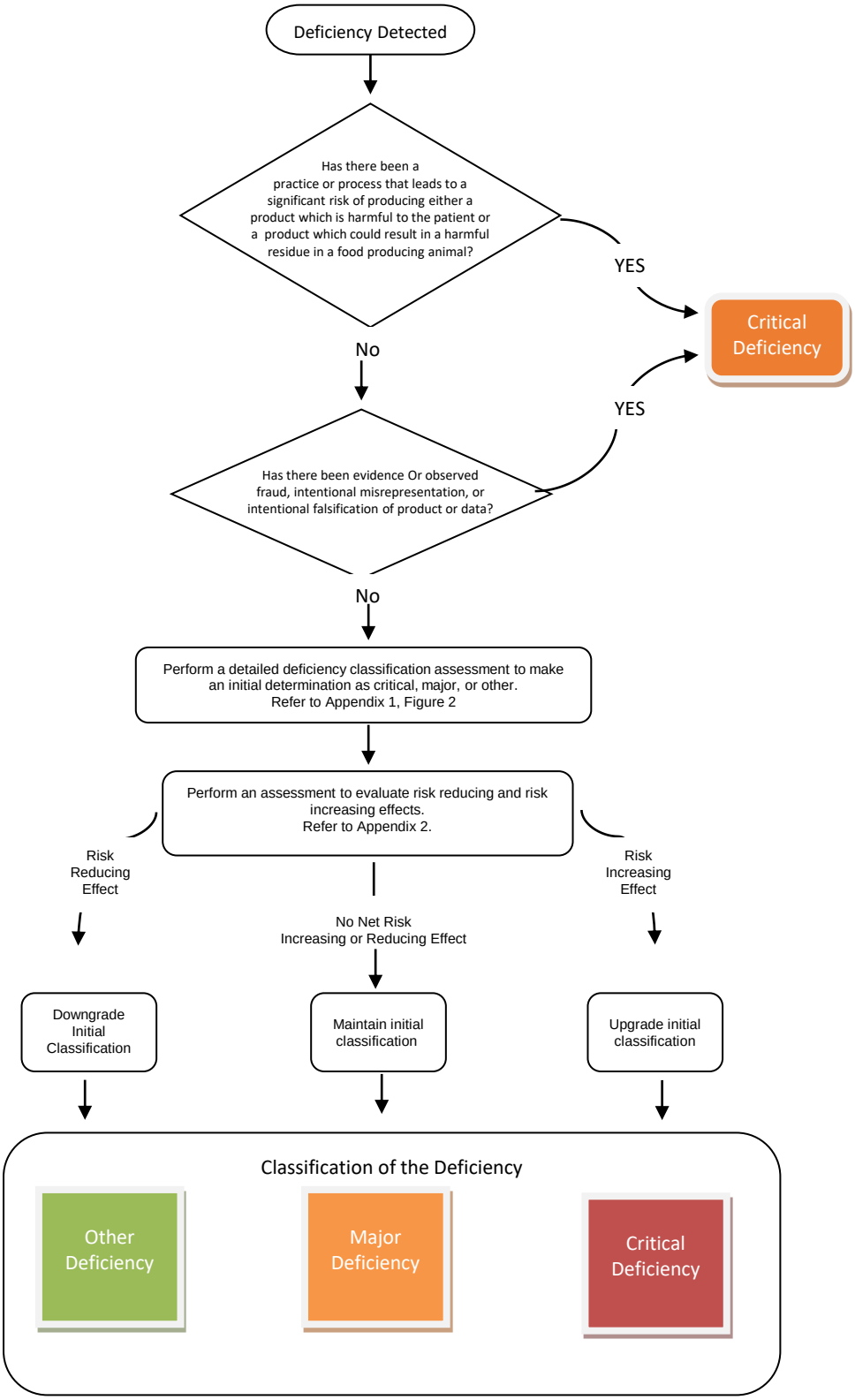
6.1 In the global pharmaceutical supply chain, GMP non-compliance of a manufacturer can impact many different markets. Although the inspecting authority's primary focus is ensuring the quality of medicines for their population, the impact of possible regulatory actions on supply to other markets should also be considered.

6.2 The sharing of non-compliant inspection findings between trusted partners, particularly when regulatory action may follow, may help authorities in other territories to prepare risk mitigating market actions.

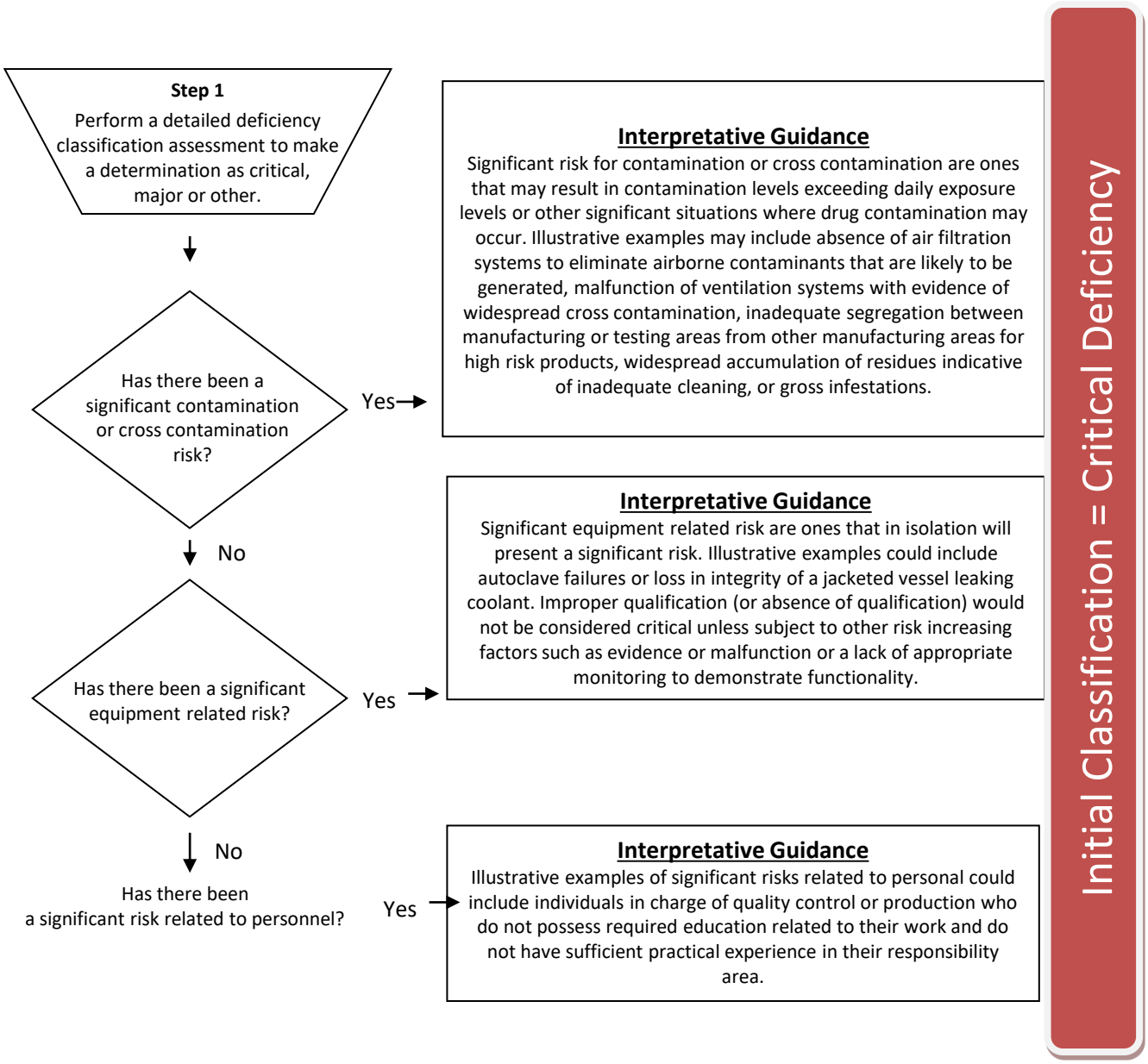
6.3 Maintaining close communication between affected inspectorates facilitates coordinated supply chain actions to avoid shortage of essential medicines. This also ensures that external notifications to healthcare professionals and patients are consistent and published at a time which is compatible with the actions in other territories.

APPENDIX 1 : Management tool to support consistent and objective categorisation of gmp deficiencies in accordance with risk management principles

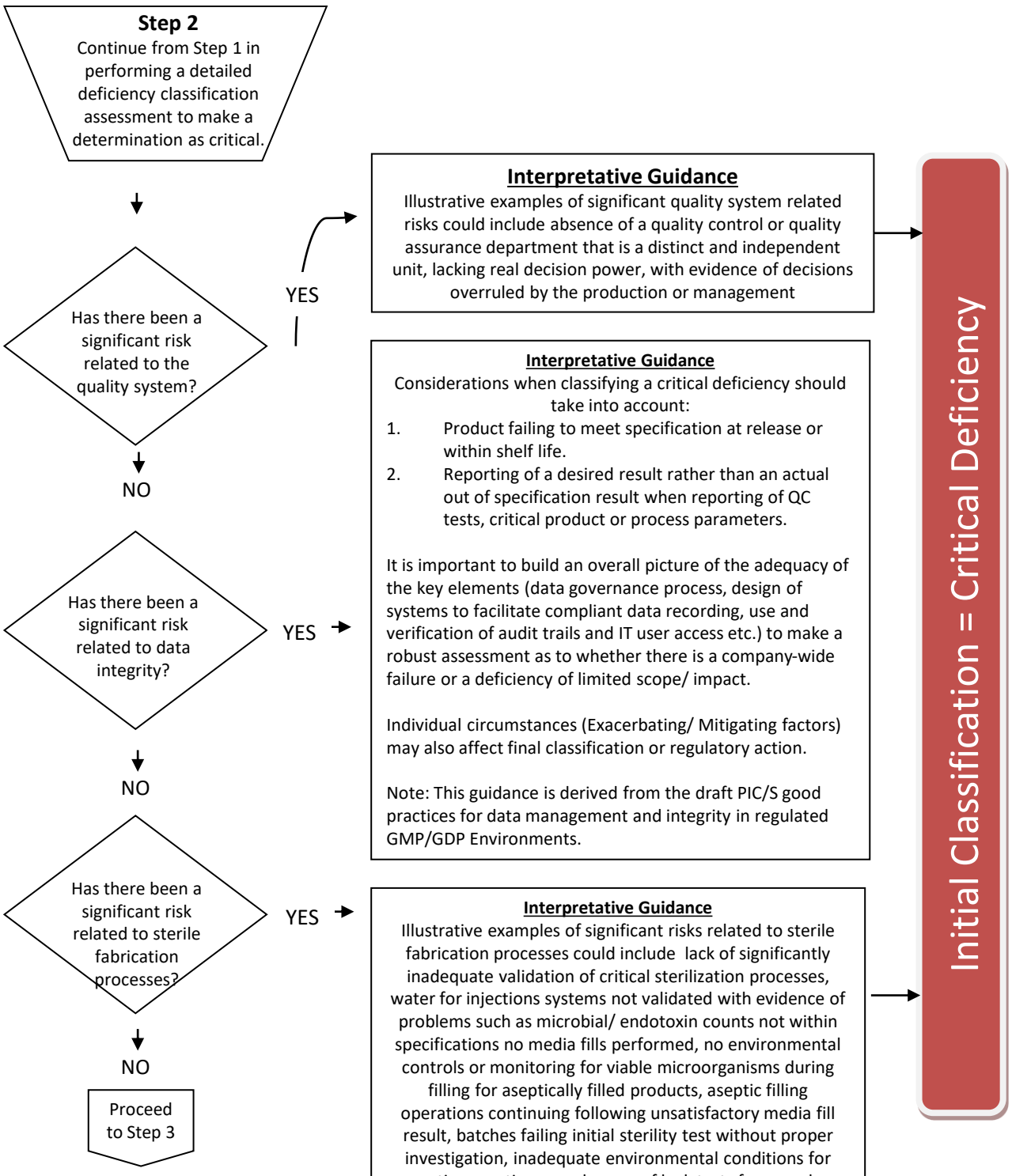
Appendix 1 Figure 1 – Classification Process – Overview



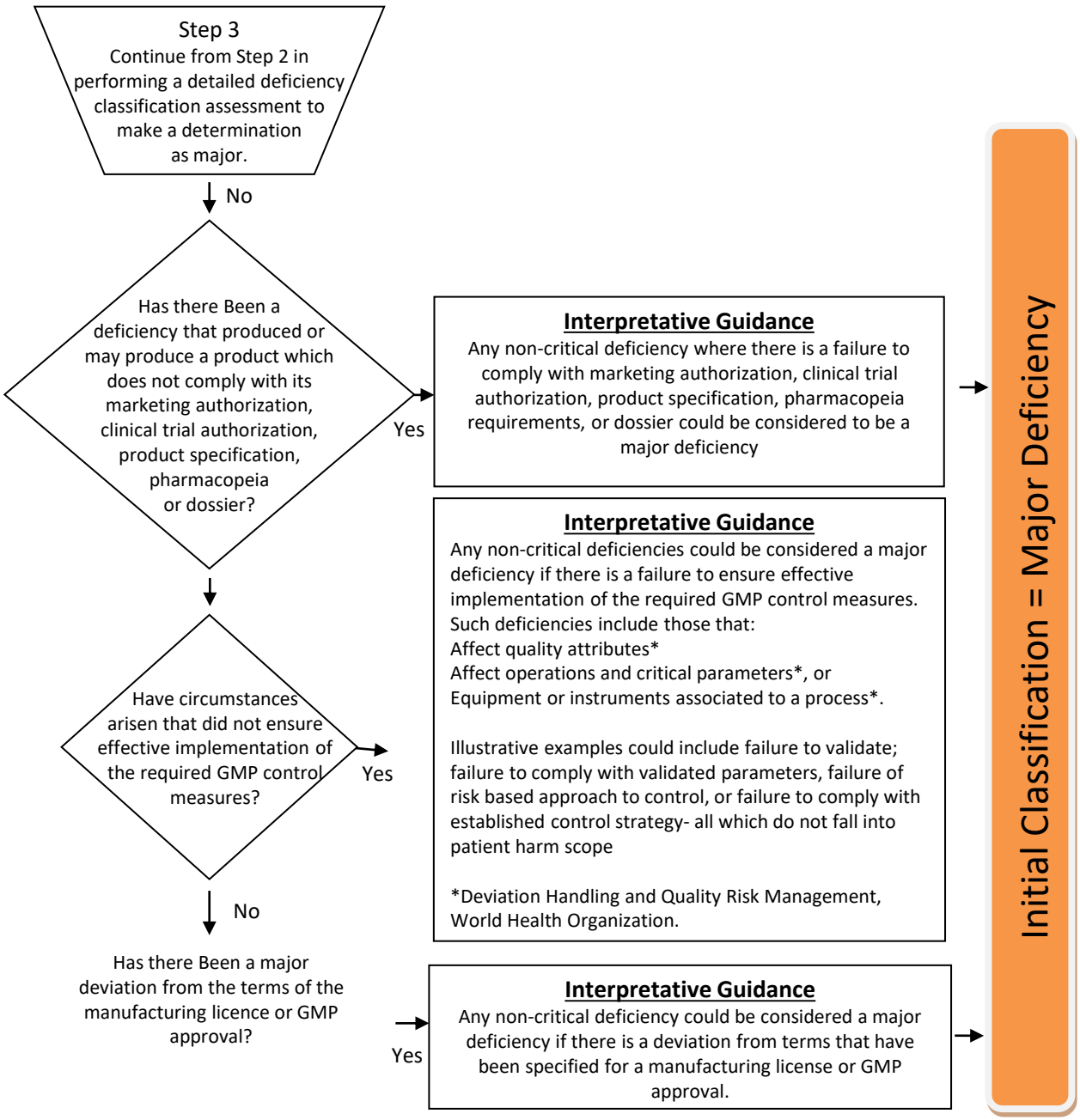
Appendix 1 Figure 2 – Classification Process – Detailed Assessment Step 1



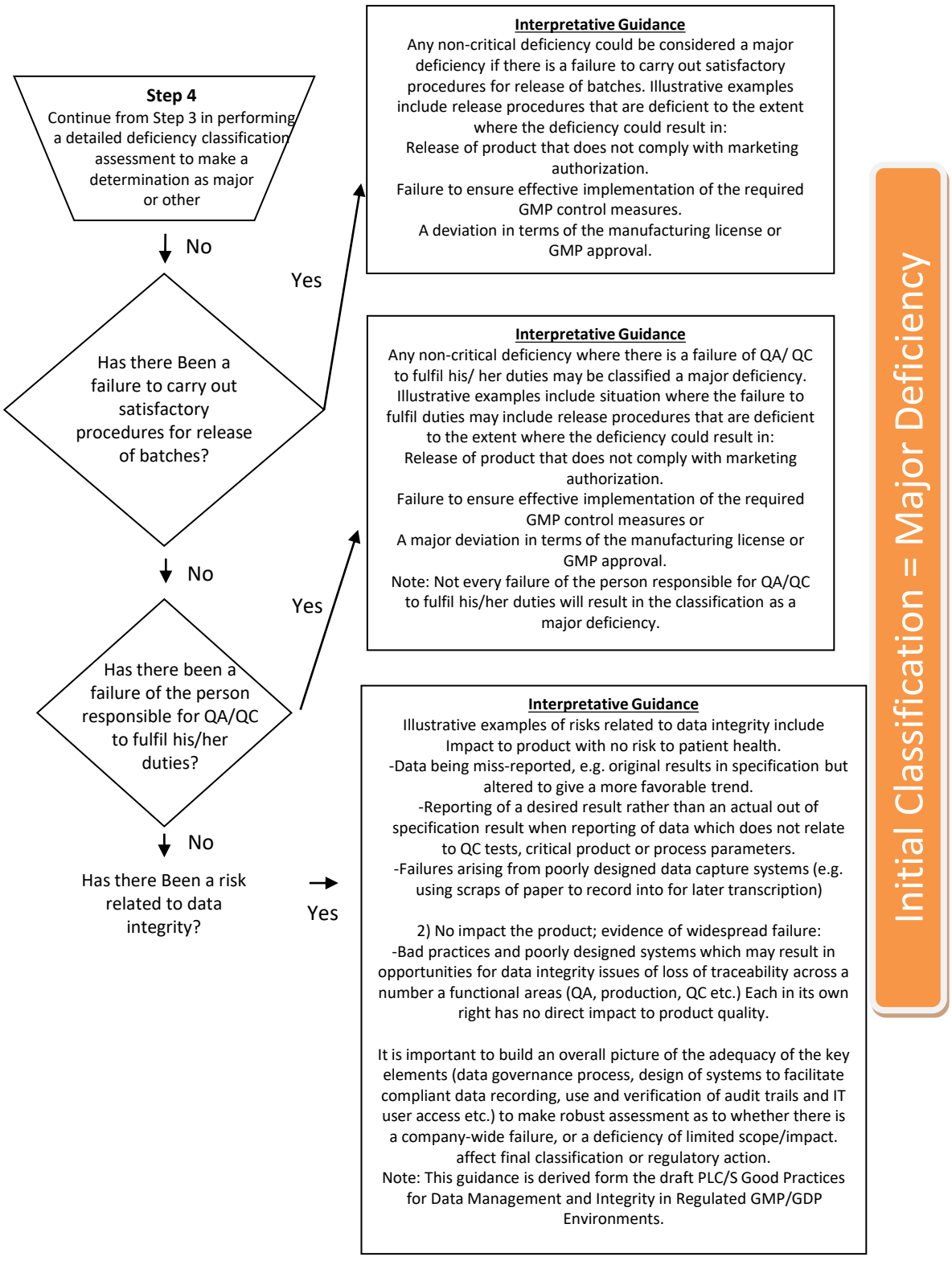
Appendix 1 Figure 3 – Classification Process – Detailed Assessment Step 2



Appendix 1 Figure 4 – Classification Process – Detailed Assessment Step 3



Appendix 1 Figure 5 – Classification Process – Detailed Assessment Step 4



Note: For data integrity issues an other classification may be considered when there is no impact to product or limited evidence of failure such as: 1) Bad practice or poor designed system which result in opportunities for data integrity issues or loss of traceability in a discrete area or 2) Limited failure in an otherwise acceptable system

APPENDIX 2 : Interpretative guidance on risk increasing or reducing factors

1. Risk Increasing Factors – Upgrading Initial Classification

A 'Major' and 'Other' observation may be upgraded by one level to either a 'Critical' or 'Major' observation respectively, when conditions may exist to satisfy the intent of the definition for the upgraded risk classification. This is considered to be achieved when defined risk increasing factors are present.

Risk increasing factors include:

- Repeat or recurring deficiencies (Appendix 2 Step 3).
- Grouping or combination of deficiencies (Appendix 2 Step 4).
- Product risk (Appendix 2 Step 5).
- Failure of a manufacturer's management to identify and take prudent measures to reduce the patient risk to an acceptable level for a product distributed, and future production from a deficient practice or process.

2. Risk Reducing Factors – Downgrading Initial Classification

A 'Critical' or 'Major' observation may be downgraded by one level to either a 'Major' or 'Other' observation respectively, when conditions may exist to satisfy the intent of the definition for the downgraded risk classification. This is considered to be achieved when defined risk reducing factors are present.
When considering risk reducing factors, it is important to ensure that these factors are both consistent and effective.

Risk reducing factors include:

- Minimizing product risk (Appendix 2 Step). 5) Minimizing risk of patient harm.
- Other risk reducing factors (Appendix 2 Step 6).
- Actions taken by the manufacturer, e.g., CAPA plan to reduce the risk of the observation.
- The impact of product already distributed to market should be considered when downgrading a critical observation.

3. Repeat or Recurring Deficiencies – Upgrading Initial Classification

Repeat or recurring deficiencies are deficiencies that were also identified at a previous inspection where appropriate corrections or corrective actions have not been implemented

In certain cases, recurring deficiencies may be considered to be subject to a risk enhancing effect to permit upgrading the initial risk classification, particularly if it is apparent that there is wilful or unsatisfactory effort to resolve the observation. A risk increasing effect should only be considered when:

- There is a serious failure in the Quality System that fails to satisfactorily identify the potential root causes for the observation, or fails to adequately address these causes without other risk reducing factors being present; or

- There are other factors for consideration such that the definition of the upgraded risk classification is achieved, for example, unreasonably protracted implementation of corrective actions.

Note: it is expected that the upgrading of risk for a recurring observation will require understanding of potential factors that may have led to the reoccurrence.

4. Grouping or Combining of Deficiencies- Upgrading Initial Classification

Different issues identified during an inspection may be grouped or combined into one observation, if each issue supports or relates to the core observation that is stated.

A risk increasing effect can be applied to upgrade an initial risk classification by one level when the definition of the upgraded risk classification has been achieved.

Examples of several 'Other' deficiencies, none of which on its own may be "Major" but which may together represent a 'Major' observation should be explained and reported as such.

5. Product Risk – Upgrading or Downgrading Initial Classification

Some manufacturing sites have products and processes that involve much higher risks than others.

Product risk classification definitions:

- High risk: products that are highly susceptible to contamination through the manufacturing process, including shelf life, e.g., microbial, or chemical.

- Low risk: products that have a lower chance of contamination through the manufacturing process including, shelf life.

Both risk increasing and risk reducing factors may be applied after considering product risks as follows:

- High risk products may have certain 'Major' observation or 'Other' observation classifications, respectively, upgraded to a 'Critical' observation or a 'Major' observation. This can be applied when circumstances of an observation under consideration meets the interpretation of the definition for a 'Critical' observation.

- Low risk products may have certain 'Critical' observation or 'Major' observation classifications downgraded to a 'Major' Observation or 'Other' observation respectively. For low risk products, a 'Critical' observation may be downgraded to a 'Major' observation unless the definition of 'Critical' observation is achieved.

6. Other Risk Reducing Factors

When other risk reducing factors are evident to mitigate the risk associated with an observation, then the risk rating may be downgraded.

Other risk reducing factors can typically be considered only when a secondary system has been established that can mitigate risks associated with an observation. For example, a validated packaging vision system, that provides 100% verification of every packaged product may be considered as a risk reducing factor for an observation associated with printed (primarily) packaging materials stored in a disordered manner that could cause a mix-up.
If there are a number of risk increasing and risk reducing factors, all risk factors should be considered at the same time, and subsequently an overall risk assessment should be taken to upgrade or downgrade the initial risk.

APPENDIX 3 : Classification Examples

Note: the list is illustrative, in order to help position the tool, and is not exhaustive and binding.

Examples are provided of deficiencies that are classified as “Critical,” “Major,” and “Other”. In some examples, classification is also based on the type of manufacturer or product risk. These examples also assist the user in providing a quick reference for the classification of the Observation or to verify the classification that has been determined using the management tool.

The classification may be in the context of the physical inspection performed, information provided at the time, and its associated risk.

For complex deficiencies, refer to Appendix 1 for more information on classification.

1. Examples of Critical Observation

Examples of deficiencies rated as ’Critical‘ (in the absence of risk reducing factors) include the following where it can be reasonably expected that the definition in this Guidance will be met. A ’Critical’ Observation is a serious situation that could result in regulatory action being considered.

- Lack of sterilization validation (relevant to all sterile products).
- Lack of adequate control measures resulting in an actual, or significant risk of, cross contamination above the level of the health-based exposure limit in subsequent products.
- Evidence of gross pest infestation (relevant to all manufacturers).
- Falsification or misrepresentation of analytical results or records (relevant to all manufacturers).
- Failure to ensure the quality and/or identity of starting materials (relevant to all manufacturers).
- No master batch documents (relevant to all manufacturers).
- Absence, falsification, or misrepresentation of manufacturing and packaging records (relevant to all manufacturers).
- Water system for sterile products not validated (for manufacturers of sterile products).
- HVAC system for sterile products not validated (for manufacturers of sterile products).
- Grossly unsuitable premises so that there is a high or likely risk of contamination (relevant to all manufacturers).
- No evidence that mandated recall processes have been complied with (relevant to all manufacturers).

2. Examples of Critical Observation

Examples of deficiencies rated as 'Major' (in the absence of risk reducing factors) include the following:

- Lack of validation of critical processes (applicable to all medicines, but could be 'Critical' for low dose/high potency products, particularly sterilization processes for sterile products).
- No or grossly inadequate air filtration to minimize airborne contaminants (applicable to all medicines manufacturers; could be 'Critical' if possible contaminants are a safety concern, and 'Critical' for sterile medicines).
- Missing or ineffective control measures to provide adequate confidence that cross contamination will be controlled within the health-based exposure limit in subsequent products. (This would be 'Critical' if resulting cross contamination has or is likely to exceed the health-based exposure limit).
- Damage (holes, cracks, peeling paint) to walls/ceilings in manufacturing areas where product is exposed in non-sterile areas.
- Design of manufacturing area that does not permit effective cleaning.
- Insufficient manufacturing space that could lead to mix-ups.
- No raw material sampling area for medicine manufacturers (could be classed as 'Other' if adequate precautions are taken).
- Sanitary fittings not used on liquid/cream manufacturing equipment.
- Stored equipment not protected from contamination.
- Individuals in charge of QC/production not qualified by education, competency training, and experience
- Inadequate initial and ongoing training and/or no training records. Cleaning procedures not documented and/or no cleaning records
- Production equipment cleaning procedures not validated
- Reduced QC testing of raw materials without data to certify suppliers
- Incomplete testing of raw materials

- Test methods not validated
- Complex production processes for non-critical products not validated
- Unapproved/undocumented changes to master batch or equivalent document
- Deviations from instructions not approved
- No or inadequate internal inspection program
- No proper release for supply procedure
- Product reworked without proper approval
- No system/procedures for handling complaints or returned goods
- Inadequate testing of packaging materials
- No ongoing stability program, and/or stability data for all products not available.
- Insufficient lighting in production or inspection areas.
- Containers from which samples have been taken not identified.
- The temperature of critical temperature-controlled storage areas not monitored and alarmed.
- Inadequate change control system.
- Inadequate deviation system.
- No investigation into alarms and temperature excursions for deviations from storage or transport requirements.

Annexure – V

Observation Sheet

Annexure – V

OBSERVATION SHEET

A unique # is assigned to each UID. Any owner / user shall not change this field for their observations	This is the date when the WT was conducted	This field captured function / dept for review with management	This is the section to which the area belongs to	Whole of Site shall be defined into areas and shall be followed as a standard to locate	This field captures WT Lead who will lead the WT	Owner is assigned to have single point of accountability for giving compliance to the observation given by WT lead	Specific location of the observation	Mandatory Column: Capture the complete observation accurately. Observations shall be captured by "OBSERVER" with specific details such as location, room#, equipment#, shelf#, document#	Observation severity categorization (Critical/major/minor/ continous improvement)	Personnel / Process / Deviation / Integrity / Validation / SOP/ Engineering / Facility design / System / Housekeeping /Warehouse / QC Lab facility / IT / Cleaning / Documentation / Sample management	Mandatory Column (Action Plan Developed/ In Progress/ Closed/ Not Started)	Action Plan developed
Obs UID	WT Date	Department	Section	Area	WT Lead	Area Owner/Auditee	Location of observation	Observation	Category of Observation	Theme	Status	Action plan

Annexure – VI

Half-yearly GEMBA Walk-through Review Format

	ANNEXURE - VII	
Department	YEARLY GEMBA WALKTHROUGH REVIEW FORMAT	Date

Observation/deficiency	Number	Percentage	Repeatability
Observation	A	P = A/T	
Deficiency	B	Q = B/T	
Total	A+B = T	100%	

Type of observations	Number of observations	Percentage of observations	Repeatability
Critical	X	E = X/N	
Major	Y	F = Y/N	
Continuous improvement	Z	G = Z/N	
Total	X+Y+Z = N	100%	

Theme of observations	Number of observations	Percentage of observations	Repeatability
Training	A	A/N	
Facility	B	B/N	
Procedural non compliance	C	C/N	
SOP Inadequacy	D	D/N	
CAPA ineffectiveness	E	E/N	
Total	A+B+C+D+E=N	100%	

Auditee Remarks/Comments

Signature :

Date :

Annexure – VII

Yearly GEMBA Walk-through Review Format

	ANNEXURE - VII	
Department	YEARLY GEMBA WALKTHROUGH REVIEW FORMAT	Date

Observation/deficiency	Number	Percentage	Repeatability
Observation	A	P = A/T	
Deficiency	B	Q = B/T	
Total	A+B = T	100%	

Type of observations	Number of observations	Percentage of observations	Repeatability
Critical	X	E = X/N	
Major	Y	F = Y/N	
Continuous improvement	Z	G = Z/N	
Total	X+Y+Z = N	100%	

Theme of observations	Number of observations	Percentage of observations	Repeatability
Training	A	A/N	
Facility	B	B/N	
Procedural non compliance	C	C/N	
SOP Inadequacy	D	D/N	
CAPA ineffectiveness	E	E/N	
Total	A+B+C+D+E=N	100%	

Auditee Remarks/Comments

HOD Remarks/Comments:
1. Change in frequency of walkthrough: YES/NO 2. Replacement of machine: 3. Change in procedures or practices: 4. Recommendations:

Auditee Signature :

Date :

Definitions/ Abbreviations/ References

1 Definitions

TERM	DEFINITION
Action level	An established microbial or airborne particle level that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.
Airlock	A small room with interlocked doors, constructed to maintain air pressure control between adjoining rooms (generally with different air cleanliness standards). The intent of an aseptic processing airlock is to preclude ingress of particulate matter and microorganism contamination from a lesser controlled area.
Alert level	An established microbial or airborne particle level giving early warning of potential drift from normal operating conditions, and triggers appropriate scrutiny and follow-up to address the potential problem. Alert levels are always lower than action levels.
Asepsis	A state of control attained by using an aseptic work area and performing activities in a manner that precludes microbiological contamination of the exposed sterile product.
Aseptic manufacturing area	The classified part of a facility that includes the aseptic processing room and ancillary cleanrooms. For purposes of this document, this term is synonymous with “aseptic processing facility” as used in the segregated segment context.
Aseptic processing facility	A building, or segregated segment of it, containing cleanrooms in which air supply, materials, and equipment are regulated to control microbial and particle contamination.
Aseptic processing room	A room in which one or more aseptic activities or processes is performed.
At rest	The “at-rest” state is the condition where the production equipment is installed but with no operating personnel present.
Barrier	A physical partition that affords aseptic processing area (ISO 5) protection by partially separating it from the surrounding area.

TERM	DEFINITION
Bio-burden	The total number of microorganisms associated with a specific item prior to sterilization.
Biological Indicator (BI)	A population of microorganisms inoculated onto a suitable medium (e.g., solution, container, or closure) and placed within appropriate sterilizer load locations in order to determine the sterilization cycle efficacy of a physical or chemical process. The challenge microorganism is selected based upon its resistance to the given process. Incoming lot D-value and microbiological count define the quality of the BI.
Clean area	An area with defined particle and microbiological cleanliness standards.
Cleanroom	A room designed, maintained, and controlled to prevent particle and microbiological contamination of drug products. Such a room is assigned and reproducibly meets an appropriate air cleanliness classification.
Closed isolator	Closed isolator systems exclude external contamination from the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations.
Closed process systems	The product is processed within closed or sealed process equipment, including closed sterilized pipe-work transporting product or material.
Colony Forming Unit (CFU)	A microbiological term that describes the formation of a single macroscopic colony after the introduction of one or more microorganisms to microbiological growth media. One colony forming unit is expressed as 1 CFU.
Component	Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in the final drug product.
Controlled Not Classified (CNC)	An area without airborne particle limits, but with filtered ventilation.

TERM	DEFINITION
Critical Area	An area designed to maintain sterility of sterile materials. Sterilized product, containers, closures, and equipment may be exposed in critical areas.
Critical surfaces	Surfaces that may come into contact with or directly affect a sterilized product or its containers or closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation, and sterility is maintained throughout processing.
Decontamination	A process that eliminates viable bio-burden via use of sporicidal chemical agents.
Depyrogenation	A process used to destroy or remove pyrogens (e.g., endotoxin).
Disinfection	Process by which surface bio-burden is reduced to a safe level or eliminated. Some disinfecting agents are effective only against vegetative microbes, while others possess additional capability to effectively kill bacterial and fungal spores.
Dynamic	Conditions relating to clean area classification under conditions of normal production.
Endotoxin	A pyrogenic product (e.g., lipopolysaccharide) present in the bacterial cell wall. Endotoxin can lead to reactions in patients receiving injections ranging from fever to death.
In operation	The “in operation” state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.
Intervention	An aseptic manipulation or activity that occurs at the critical area.
Isolator	A decontaminated unit, supplied with Class 100 (ISO 5) or higher air quality, which provides uncompromised, continuous isolation of its interior from the external environment (e.g., surrounding cleanroom air and personnel). There are two major types of isolators – closed and open.

TERM	DEFINITION
Isolator setup	The surrounding room environment does not come in contact with the product and its immediate process environment at any period during processing, and it is, therefore, not part of the product protection equation, although control of the surrounding room is still a regulatory requirement.
Laminar flow	An airflow moving in a single direction and in parallel layers at constant velocity from the beginning to the end of a straight-line vector.
Open isolator	Open isolator systems are designed to allow for the continuous or semi-continuous ingress and/or egress of materials during operations through one or more openings. Openings are engineered (e.g., using continuous overpressure) to exclude the entry of external contamination into the isolator.
RABS setup	Either all or the majority of interactions with the surrounding environment occur through integral glove-ports. However, as infrequent cabinet door openings may occur, the surrounding environment classification and finishes must meet the Grade B standards.
RABS, Active	RABS using an integral HEPA-filtered air supply to the critical area and manual high-level disinfection, usually with sporicidal agents. Gloves and transfer ports are used for manipulation and commodity addition.
RABS, Passive	RABS wherein the airflow to the critical area is provided by ceiling-mounted HEPA filters extending laterally outside the enclosure and the bottom of the enclosure is open to provide for air flow through the system. Gloves and transfer ports are used for manipulation and commodity addition.
Restricted Access Barrier System (RABS)	An aseptic processing system that provides an enclosed, but not closed, environment meeting Grade A conditions utilizing a rigid-wall enclosure and air overspill to separate its interior from the surrounding environment.
ULPA filter	Ultra-low penetration air filter with minimum 0.3 µm particle retaining efficiency of 99.999 percent.

TERM	DEFINITION
Unidirectional flow	An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area.
Worst case	A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure (when compared to ideal conditions). Such conditions do not necessarily induce product or process failure.
Qualification/validation	Qualification/validation can be defined as ‘establishing documented evidence which provides a high degree of assurance that specific equipment procured will consistently produce its predetermined specification and quality attributes’

2 Abbreviations

TERM	DEFINITION
ACPH	Air Changes Per Hour.
ADP	Apparatus Dew Point.
AHU	Air Handling Unit.
ASHRAE	American Society of Heating, Refrigeration, and Air Conditioning Engineering.
ASTM	American Society for Testing and Materials.
BMS	Building Management System.
CAV	Constant Air Volume.
CFM	Cubic Feet Per Minute.
cGMP	Current Good Manufacturing Practice.
CMH	Cubic Meter per Hour.
CNC	Computer Numerically Controlled.
CPP	Critical Process Parameter.
CQA	Critical Quality Attribute.
DBT	Dry Bulb Temperature.
DDC	Direct Digital Controller.
DEX	Dust Extraction System.
DOP	Dioctyl Phthalate.
DP	Differential Pressure.
DQ	Design Qualification.
EDB	Entering Dry Bulb Temperature.
EWB	Entering Wet Bulb Temperature.

TERM	DEFINITION
FDA	Food & Drugs Administration, U.S.A.
FLP	Flame Proof.
FPM	Feet per Minute.
GI	Galvanized Iron.
HEPA	High Efficiency Particulate Air.
HVAC	Heating Ventilation Air Conditioning.
IQ	Installation Qualification.
ISHRAE	Indian Society of Refrigeration & Air Conditioning Engineers.
ISO	International Organization for Standardization.
LDB	Leaving Dry Bulb Temperature.
LWB	Leaving Wet Bulb Temperature.
MCC	Motor Control Center.
MS	Mild Steel.
N.A.	Not Applicable.
OQ	Operation Qualification.
OSHA	Occupational Safety and Health Administration.
PAO	Poly Alpha Olefin.
PQ	Performance Qualification.
RA	Return Air.
RAT	Return Air Temperature.
RH	Relative Humidity.

TERM	DEFINITION
RTV	Room Temperature Vulcanization
SA	Supply Air.
SMACNA	Sheet Metal and Air Conditioning Contractors' National Association.
SS	Stainless Steel.
TFA	Treated Fresh Air Unit.
TR	Tonnage.
UAF	Unidirectional Air Flow.
UFH	Unidirectional Flow Hoods.
UPS	Uninterrupted Power Supply.
VFD	Variable Frequency Drive.
WBT	Wet Bulb Temperature.
ΔP	Pressure Difference.
ΔT	Temperature Difference.
QC	Quality Control.
QA	Quality Assurance.
KYM	Know Your Machine.
KYP	Know Your Procedures.
SOP	Standard Operating Procedures.
CAPA	Corrective Action and Preventive Action.
SME	Subject Matter Expert.
SH	Site Head.

TERM	DEFINITION
TNI	Training Need Identification.
OOS	Out of Specification.
OOT	Out of Trend.
OOC	Out of Calibration.
HOD	Head of the Department.
API	Active Pharmaceutical Ingredient.
NC	Non Conformity.

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