Clean - Facility Design, Construction, & Maintenance

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Abstract: Successful pharmaceutical manufacturing plant projects incorporate practices that promote flow of the construction process toward completion on time and within budget. Engineering the clean room in accordance with recognized industry practice would produce construction documents that facilitate clear procurement and construction planning as well as a focused, efficient, construction effort. This article focuses on design, construction, and maintenance issues associated with clean-room construction projects.

Index Terms: Clean Room, Facility, Construction, Design, Maintenance, Procurement, Utilities

I. INTRODUCTION

While there are discrete steps in the design and construction of a pharmaceutical manufacturing plant project, those projects deemed successful incorporate certain practices that promote flow of the construction process toward completion on time and within budget. Proper front - end planning is not completed until it results in appropriate values for design parameters, "buy - in" at all levels of management, and clear direction for the design phase. Engineering the clean room in accordance with recognized industry practice would produce construction documents that facilitate clear procurement and construction planning as well as a focused, efficient, construction effort. A full return on the energy expended through the construction phase cannot be realized without a well - executed start - up and validation process that provides baseline data for effective ongoing operation and maintenance.

The steps in the clean - room construction project include:

- Needs assessment
- Front - end planning
- Preliminary design
- Construction document development
- Procurement
- Construction
- Start - up and validation

One of the truisms of the construction industry is that the greatest impact on the cost of a facility can be made at the earliest stages of the process. Careful work during the first three stages will ensure that the project begins on a well - directed course and moves to a successful conclusion. Sometimes the special nature of pharmaceutical manufacturing plant projects clouds the fact that building such a plant is in fact a construction project. The facility engineering team of a small to medium company may be tempted to turn away from such projects due to the projects' perceived uniqueness and leave the key decision making to others. In fact, it is the construction experience of that team that is most required to keep the project costs under control. The way to accomplish this is for the team to be involved in the process from its earliest stages.

II. PLANNING FOR PROJECT SUCCESS

- **Needs Assessment**

It is during this early stage that a requirement for a clean manufacturing facility is perceived. The need for the facility may be precipitated by a new product, an improved product, an improved manufacturing methodology, new or more stringent regulation requirements, or perhaps a change in marketing strategy. At this point a study should be undertaken to determine the benefits to be realized by the new facility as well as the costs to be incurred. Costs arise from not only construction but also ongoing operation and maintenance. These costs are affected by the plant location and the availability of a trained or trainable workforce. It is important that this study is complete and accurate in order to prevent any unrealistic expectations on the part of management and plant operations and to permit advanced planning for revised procedures once the facility is in use. The study should describe the goals of the project, its impact on present operations, budget restraints, tentative schedule, and path forward. It will serve as the basis for front - end planning and will provide the standard against which the success of the program is measured.

- **Front - End Planning**

While the needs assessment study may be conducted by a limited number of people, the front - end planning process should be open to all. Plant facilities people will be bearing the brunt of the responsibility for bringing the facility online, on schedule, and within budget. Process people are responsible for ensuring that the facility will adequately house the process equipment and that the facility incorporates sufficient space, utilities, process flow considerations, and provision for flow of people and material to support the goals of the building program. Human resources people have to staff the facility, either out of the present employee pool or from the general local labor market. They must know the requirements of potential employees as well as the conditions under which they will be working. Procurement people will be purchasing furnishings and process equipment for the plant as well as overseeing the contracts let to the design and construction professionals. Operations people should have input regarding design parameters such as temperature, humidity, lighting, vibration, cleanliness class, and energy needs. Materials handling people should participate in order to understand the requirements for storing and transporting raw materials as well as retrieving, storing, and shipping finished goods from the plant. An integral part of the front - end planning team should be the design professionals charged

with developing the plant design based on client input in such a way as to satisfy as many requirements developed in needs assessment as possible. This team may be assembled internally but frequently is drawn from specialty builders, architectural and engineering firms, and design/build firms active in the pharmaceutical industry. The team of design professionals should have pharmaceutical experience on facilities comparable in size and complexity to that being planned as well as extensive experience in construction projects of all types. The design team may offer design only, design/build, procurement, construction management, or combinations of these services. This design team should be considered a resource during the front - end planning phase. It is the wise client who takes advantage of the experience of the design team, permitting them a large role as facilitators of the planning sessions.

- **Preliminary Design**

Front - end planning typically utilizes the expertise of client process people to convey the requirements of the pharmaceutical facility to the design team. With this information in hand the design team begins the facility design incorporating process needs, code requirements, safety issues, material and personnel flow, work - in - process storage, utility needs, and so on, into a first - cut approach. Client representatives have an opportunity to review the effort and begin fine tuning the design to incorporate late - breaking process changes. The preliminary design is a target that helps both the design team and the client solidify design goals. Change is inexpensive, and therefore encouraged, at this stage and buy - in by all concerned is a major objective of this phase of the design effort. A budget based on the agreed - upon preliminary design should be developed to make sure that the overall project is on course. This will minimize surprises further along in the design/build process. Ideally the design will be "cast in stone" at the end of the preliminary phase. This permits the production work on the design documents to proceed unhindered. The more unknowns left at the end of the preliminary phase, the more difficult it will be to complete design documents in a timely fashion.

- **Procurement**

A detailed scope of work describing the materials and services required is a vital part of the procurement process. There is no purpose to keeping the project bidders in the dark regarding what is required of them. The role of the procurement function is to obtain maximum value, that is, the best quality and schedule at the lowest price. The clearer the scope of work and construction documents, the better will be the chance of this happening. A low price is not a good value if the schedule slips by several months as a result. A marginal plant that does not maintain design conditions or meet production goals is a poor value even if it was delivered within schedule. The procurement process should qualify potential bidders by ensuring that similar pharmaceutical projects have been delivered on time, within budget, and on schedule. References should be checked. It is expected that references offered by a potential bidder would have good things to say about that bidder, but this is not a certainty and pointed questioning about personnel, schedule, quality, change orders, follow - up, and so on, can help develop a warm feeling or an uncertain feeling about potential bidders. If bids are in fact quite close, it is the quality of references that might suggest a particular bidder be given preference. There are a number of ways in which the project can be procured. Use of in - house engineering and construction expertise may work in special situations or on smaller projects. Typically, problems arise when facilities departments, stretched to their limit with ongoing plant requirements, must lower the priority of the new facility to meet other commitments. Schedules may stretch out unacceptably. A number of specialty contractors have proven over the years to be adept at installing small turnkey facilities of limited complexity in a timely and economical fashion. If extensive engineering is required, if local code compliance becomes an issue, if complex process requirements must be met, or if the client requirements exceed the experience of the supplier there could be cause for concern. Design/build is a popular approach in that it suggests a single source of responsibility for all phases of the project. Frequently firms billing themselves as "design/ build" are strong in either design or build, but not both. The strong design firm can put the essentials on paper but the final price and schedule may suffer. The strong construction firm may lack the expertise to create an appropriate manufacturing environment, particularly where clean - room expertise is required. The project may be outstanding in all respects except performance. A good review of references is essential before selecting a design/build firm. Construction management has been increasingly used on larger projects. A good construction management firm will work closely with the client - selected design company to review constructability and adequacy of construction documents. It will assist to qualify bidders, maintain schedule, track costs, administer and oversee, and generally ensure that a team incorporating the strongest skills is assembled to complete the project.

- **Construction**

The construction process should proceed smoothly if the remarks presented above are followed. Cost can increase during this phase if changes must be implemented. While change is inevitable, a construction change procedure negotiated during the bidding phase and in place during construction will keep such change from getting out of control. The requirement for "building clean" has arisen in recent years as more stringent clean rooms have become more popular. Imposing a clean construction protocol on contractors can lengthen the schedule and increase cost. The protocol should be developed during the construction document phase and be an integral part of the bid documents. Once the decision is made to work clean, protocols developed should be followed by everyone on the jobsite associated with the clean areas. A poorly conceived and enforced protocol will be a costly and futile exercise. The tendency to build clean on every new or retrofit project should be carefully evaluated and a practical protocol should be developed consistent with the needs of the project. Client end users should be encouraged to observe construction as it progresses. They will be more intelligent about how their facility was built and therefore more attuned to maintaining the facility once it is completed and in operation. While suggestions should be welcomed as construction progresses, it is important that a chain of command be enforced. Any questions or suggestions or concerns should not be expressed to workers on the site but rather through project management channels. In this way good ideas can be implemented and bad ideas shelved without impacting the construction effort in a negative manner. Note the one exception to this practice is in regard to safety. Everyone on the site has safety responsibility. Any unsafe acts should be questioned and supervisors consulted immediately.

- **Start - Up and Validation**

Subcontractors on the jobsite should be responsible for start - up as well as installation of equipment. Equipment manufacturers typically have personnel available to ensure appropriate start - up procedures are followed. If several trades are involved in the installation of a particular piece of equipment, then one trade should be assigned, by contract, as having coordinating responsibility for that piece of equipment. This will minimize "finger pointing" when equipment does not start or operate properly. This can be a sensitive issue and a construction manager can set the tone for cooperation in this area. An independent contractor responsible to the construction manager or owner should do testing and balancing (TAB) of mechanical systems. All start - up should be complete and initial valve or damper settings made by the subcontractor before testing and balancing begins. The TAB contractor should not have to repair equipment or troubleshoot inoperative equipment but rather only adjust and verify performance of equipment. A separate contractor should certify clean - room areas. This might be the TAB contractor if that firm is suitably qualified. There should be no question of equipment being operative at this stage of the project since start - up and testing and balancing are complete. Certification is the verification of facility compliance with clean - room specifications. If the facility design is well conceived and the construction team has installed a quality project, any certification test failure will most likely be corrected through fairly minor adjustments. Failure of the clean room to pass certification tests might require redesign but more frequently requires some equipment adjustment or perhaps a filter repair and then a retest. It is important that a clear understanding of responsibility be communicated before problems are encountered. Failure to plan for potential problems could result in extending the schedule and incurring unforeseen costs at a crucial point in the project.

- **Summary**

Recognizing the step - by - step process involved in even the smallest pharmaceutical project can help focus attention in a manner that will result in a successful project. The formal schedule of a well - conceived project will include needs assessment, front - end planning, and preliminary design. It is important that project progress is measured against such a schedule and not just by the visual impact caused by bricks and mortar being installed.

III. DESIGN OPTIONS

- **Clean - Facility Scope**

The purpose of this section is to identify design and construction options for those parts of a pharmaceutical facility intended to house process equipment. These suggestions are intended to assure that the facilities, when used as designed, will meet the requirements of current good manufacturing practices (cGMP). Air cleanliness within the facility may range from International Organization for Standardization (ISO) 5 (Class 100) through ISO 8 (Class 100,000). In addition, areas may be considered clean or labeled as "controlled environment" without having a cleanliness class assigned to the space. A cleanliness classification in accordance with the latest revision of ISO 14644 is generally inadequate by itself to describe a facility used for pharmaceutical processes. The presence of viable particles (living organisms) within the particle count achieved by applying methods described in the standard may affect the product within the facility. A measure of both viable and nonviable particles is required to provide sufficient information upon which to base a decision regarding the suitability of the clean room for its intended purpose. The options presented herein are intended to provide facilities that will effectively restrict both viable and non-viable particles from entering the clean areas, minimize contamination introduced by the facility itself, and continuously remove contaminants generated during normal operations. Measurement of total particle count in the clean room is described in ISO 14644. This count may be composed of viable, non-viable, or non-viable host particles with a viable traveler. There is no generally accepted relationship between total particle count and viable particle count. While maintaining appropriate particle counts is important in clean - room design and operation, a protocol designed to identify viable particles should be inherent in the certification/validation testing of a pharmaceutical clean room. No facility design can compensate for excessive contamination generated within it. In addition to effective facility design, the user must also institute a routine maintenance program as well as maintain personnel and operational disciplines that limit particles both entering and being generated within the facility. While this section identifies options for contamination control in facility design, any such options must be implemented in accordance with all appropriate government and regulatory building and safety codes. The design guideline is non-specific as regards biological or chemical materials that may be used within the facility but generally addresses bulk pharmaceutical chemical plants (BPCs), secondary manufacturing chemical plants, bulk biopharmaceutical plants, and plants used for fill and finish operations. Good practice as well as any regulations governing biological and pharmaceutical processes conducted within the facility must be adhered to as required and could modify some of the suggestions contained herein.

- **Design Parameters**

The design of the facility is based upon specification of certain design parameters. These in turn are used to calculate building system equipment capacities and aid in the selection of the appropriate types of equipment that are required. Design parameters that may be critical are discussed below.

Cleanliness Classification

The classification of the clean areas is determined by the using organization consistent with the level of nonviable and viable particulate contamination acceptable to the process conducted within the facility. This may be governed by regulatory agencies, client organizations, or company protocols. Target goals are set for non-viable particle count in accordance with the ISO. Viable particle target goals should be stated in colony - forming units (CFU) per square centimeter. In accordance with ISO 14644, particle goals will typically be identified for "at rest" & "operational" modes. The room grades presented are from most critical (A) to least critical (E). The definition of criticality is left to the clean - room user organization.

Other Design Parameters

Facility design parameters that support the process within the clean room should be established by the user organization. Parameters such as temperature, humidity, lighting requirements, sound level, and/or vibration may be process driven or comfort driven and therefore are selected to accommodate specific process or comfort requirements as determined by the end user.

Local Control

Under some circumstances, cleanliness requirements can be achieved through the use of localized controls such as clean tents, glove boxes, mini-environments, or isolators. These provide unidirectional filtered airflow within a limited area. They may be located within a facility that provides the necessary temperature and humidity conditions or they may be provided with integral environmental control equipment designed to maintain necessary conditions.

Air Change Rate

The airflow pattern & air change rate in a clean room largely determines the class of cleanliness that can be maintained during a given operation. Non - unidirectional flow clean rooms rely on air dilution as well as a general ceiling - to - floor airflow pattern to continuously remove contaminants generated within the room. Unidirectional flow is more effective in continuously sweeping particles from the air due to the piston effect created by the uniform air velocity. The desired air change rate is determined based on the cleanliness class of the room & the density of operations expected in the room. An air change rate of 10 – 25 per hour is common for a large, low - density ISO 8 (Class 100,000) clean room. ISO 7 (Class 10,000) clean rooms typically require 40 – 60 air changes per hour. In unidirectional flow clean rooms, the air change rate is generally not used as the measure of airflow but rather the average clean - room air velocity is the specified criterion. The average velocity in a typical ISO 5 (Class 100) clean room will be 70 – 90 ft/min. A tolerance of plus or minus 20% of design airflow is usually acceptable in the clean room. The foregoing values have been found to be appropriate in many facilities. Generally, air change rate or air velocity is not a part of regulations. It is left to the user to demonstrate that the selected design parameter is appropriate for the products being manufactured. An exception to this may be in the case of filling operations where a unidirectional flow velocity of 90 ± 20 ft/min may be required.

Pressurization

A pressure differential should be maintained between adjacent areas, with the cleaner area having the higher pressure. This will minimize infiltration of external contamination through leaks and during the opening and closing of personnel doors. A minimum overpressure between clean areas of 5 Pa [0.02 in. of water column (in. WC)] is recommended. The pressure between a clean area and an adjacent unclean area should be 12 – 14 Pa (0.05 in. WC). Where several clean rooms of varying levels of cleanliness are joined as one complex, a positive - pressure hierarchy of cleanliness levels should be maintained, including air locks and gowning rooms. Note that for certain processes and products it may be desirable to have a negative pressure relative to the surrounding ambient in one or more rooms when containment is a major concern. A “room within a room” may have to be designed to achieve this negative pressure yet still meet the needs of clean operation.

Temperature Control

Where occupant comfort is the main concern, a temperature of 68 – 70 ° F ± 2 ° F will usually provide a comfortable environment for people wearing a typical lab coat. Where a full “bunny suit” or protective attire is to be worn, room temperature as low as 66 ° F may be required. If the temperature is to be controlled in response to process concerns, the value and tolerance should be specified early in the design phase to ensure that system selection is appropriate and that budgeting is accurate. Note that a tight tolerance (e.g., ± 1 ° F or less) will typically be more costly to maintain than a less stringent tolerance.

Humidity Control

The humidity requirement for comfort is in the range of 30 – 60% relative humidity (RH). If process concerns suggest another value, it should be specified as soon as possible in the design process. Biopharmaceutical materials sensitive to humidity variations or excessively high or low values may require stringent controls.

- **Architectural Design Issues**

Facility Layout

The facility layout should support the process contained within the clean room. While a rectangular shape is easiest to accommodate, other shapes may be incorporated into the facility as long as appropriate attention is paid to airflow patterns. The facility should be able to accommodate movement of equipment, material, and personnel in and out of the clean room. The layout of the clean suite should facilitate maintaining cleanliness class, pressure differentials, and temperature/humidity conditions by isolating critical spaces and by excluding non-clean operations. The potential for cross - contamination is addressed as both an architectural and a mechanical issue. Generally, in a facility where multiple products are to be processed, each product has a dedicated space, isolated physically from adjacent spaces, and each has its own air conditioning system, independent of adjacent systems.

Air Locks

This is a room between the clean room and an unrated or less clean area surrounding the clean room or between two rooms of differing cleanliness class. The purpose of the room is to maintain pressurization differentials between spaces of different cleanliness class while still permitting movement between the spaces. An air lock can serve as a gowning area. Certain air locks may be designated as an equipment or material air lock and provide a space to remove packaging material and/or to clean equipment or materials before they are introduced into the clean room. Interlocks are recommended for air lock door sets to prevent opening of both doors simultaneously. The air lock is intended to separate the clean from the unclean areas.

Prior to equipment or raw materials being introduced into the clean room, they should be prepared. This may mean removing an outer package wrap or perhaps surface cleaning of the object. Material handling equipment used within the clean room should be dedicated to the clean room. Physical barriers may be integrated into the material air lock design to prevent material handling equipment from leaving the clean room or outside equipment from passing into the clean room.

Windows

Windows are recommended in interior clean - room walls to facilitate supervision and for safety, unless prohibited by the facility protocol for visual security reasons. Windows in exterior building walls adjacent to a clean space are problematic. Windows can be a source of leakage and can result in contaminants entering the space. Windows should be placed to permit viewing of operations in order to minimize the need for non - clean - room personnel to enter the clean room. Windows should be impact -

resistant glass or acrylic, fully glazed, installed in a manner that eliminates or minimizes a ledge within the clean space. Double glazing is frequently used to provide a flush surface on both sides of the wall containing the window. Windows may be included if there is a public relations requirement for visitors to view the operations. Speaking diaphragms or flush, wall - mounted, intercom systems are recommended near all windows to facilitate communication with occupants of the clean room.

Pass – Through

A pass - through air lock should be provided for the transfer of product or materials from uncontrolled areas into the clean room or between areas of different cleanliness class. The pass - through may include a speaking diaphragm, intercom, or telephone for communication when items are transferred and interlocks to prevent both doors from being opened at the same time. A cart - size pass - through installed at floor level can be used to simplify the movement of carts between clean areas. Stainless steel is typically the material of choice.

Gowning Room

Gowning rooms should be designed to support the garment protocol established for the facility. A typical gowning room may have a wall - or floor - mounted coat rack for clean garment storage; a bench specifically designed for clean - room use; a full - length mirror installed near the door for gowning self - inspection; storage for new packaged garments; and bins for disposal of soiled garments. Personal lockers and coat racks for the storage of notebooks, coats, and personal items should be located outside the gowning room or in an anteroom separate from the clean gowning area. Restroom facilities may also be located outside the gowning room or in an anteroom adjacent to the clean gowning area. A common gowning room design has two areas divided by a bench. The “unclean” area is used to remove and store outer garments. Stepping over the bench as the clean - room footwear is being put on ensures that the “clean” side of the gowning room will remain that way. Final donning of the clean - room garb is then accomplished. Male and female gowning rooms may be required depending on the make - up of the work force and the type of garments being used.

Siting

A clean room that serves as an element of a larger process line should be integrated into the line to permit movement of personnel and materials in and out of the room. A free - standing clean room may be located in any convenient site; however, certain conditions adjacent to the facility may degrade its performance. Vibration sources inside or near a clean room will encourage particle release within the room and under severe conditions may cause leaks in filters and ductwork. Heavy equipment, including the heating, ventilation, and air conditioning (HVAC) system components, pumps, house and vacuum system, ought to be vibration isolated. Location of a clean room directly adjacent to heavy equipment or loading docks that see heavy truck traffic and other sources of vibration, shock, and noise may be problematic. The outdoor air intake for the clean - room makeup air must be carefully located to prevent overloading of filters or entrance of contaminating gases that the filter will not remove. Clean - room air intakes should not be located near loading docks, traffic lanes, or other areas where vehicles may drive through or idle. These intakes should not be located near the exhaust locations of other processing facilities. Use of gas - phase filtration may be required if the quality of make - up air is not acceptable.

- **Materials of Construction**

Walls

Generally, wall material selection should be based on the operations and material handling equipment to be used within the space. The walls should be strong enough to withstand repeated impact of carts or other equipment without deterioration. The materials should also be selected with the sanitizing protocol in mind. Chemicals, high - pressure wash, and steam can cause reduced wall life if proper materials are not selected. Seamless walls, to the extent possible, are desirable. Basic steel stud construction with gypsum board paneling can be used in biopharmaceutical clean rooms when appropriately coated with a non-shedding finish. Modular wall systems utilizing coated steel or aluminum panel construction are growing in popularity due to the ability to easily retrofit a lab or production space at a later date with minimal disruption and construction debris. Stainless steel may be appropriate but costly. Modular systems have been developed that address the concerns of the biopharmaceutical clean - room user relative to surface finish integrity and smooth surfaces. The joint between adjacent modular panels is commonly treated with a gunnable sealant to provide a smooth, cleanable joint that will not hold contaminants. Concrete masonry unit (CMU) construction is widely used. It can prevent buildup of contaminants when finished with an epoxy or other smooth, chemical - resistant coating. Where retrofit is not a regular practice, the strength of concrete block and its long life recommend it. Rounded, easy - to - clean corners and smooth transitions between architectural features such as windows and walls should be featured in all wall system designs, whether modular or “stick built”

Wall Finishes

Inexpensive latex wall paints will deteriorate over time and are unacceptable in clean rooms. Acceptable wall finishes include epoxy paint, polyurethane, or baked enamel of a semigloss or gloss type. These may be applied in the factory to metal wall system panels. Field application of epoxy to gypsum board or CMU should be done to ensure a smooth, non-porous, monolithic surface that will not provide a breeding site for organisms. Exposed outside corners in high traffic areas as well as on lower wall surfaces may have stainless steel facings or guards to prevent impact damage to the wall. This is particularly true when gypsum board construction is used. Corner and wall guards should extend from the floor to at least the 4 - ft height. Traditionally the clean room has been white throughout as an indication of the clean nature of the facility and to identify it as a special work space. Other colors may be used in the clean room to provide an interesting environment as long as the materials of construction do not contribute particles to the air stream and will withstand the sanitizing agents and procedures used in the facility.

Doors

Entry should be through air locks to maintain clean - room pressure differentials. Emergency exit doors should incorporate a panic - bar mechanism (or a similar emergency opening device) with alarms for exit only. Emergency exit doors must be secured in a manner that prevents entry from the outside yet permits exiting from within. All doors should include essentially air - tight

seals. Neoprene seals are generally acceptable. Brush - type door seals are not recommended. Foam rubber door seals are not recommended as these have been found to quickly deteriorate and shed particles. All personnel doors and swinging equipment doors should include self - closing mechanisms. Manual and automatic sliding doors may be useful when space is an issue or to facilitate movement between spaces of similar cleanliness class for personnel whose hands are otherwise engaged. As the mechanism of such doors can generate particles, a design specifically intended for clean - room application should be selected.

Ceilings

The ceiling finish should be similar to that used on the walls. The requirements for sanitizing typically address the ceiling as well as the walls and ceiling material and finish selection should reflect this. Suspended ceilings using an inverted - T grid and lay - in panels may have a place in that part of the clean - room suite not subjected to the rigors of frequent sanitizing and where the possibility of trapped spaces to support organism growth is not considered an issue. When suspended panel ceilings are used, the panels must be securely clipped or sealed in place to prevent movement due to air pressure changes. Modular wall systems designed for biopharmaceutical applications frequently have a “walk - on” ceiling designed using materials and finish similar to the wall. A rounded, easy - to - clean intersection between ceiling and walls should be a feature of the clean - room ceiling design, whether modular or stick built. Monolithic (seamless) ceilings can be installed using inverted - T grid supports and gypsum panels. This design permits incorporation of filtration and lighting into what is essentially a monolithic ceiling.

Floors

Commonly used floor finishes for biopharmaceutical clean rooms include sheet vinyl installed using heat - welded or chemically fused seams to provide a seamless surface. Troweled epoxy and epoxy paint have also found wide use. Compatibility of the floor material with solvents, chemicals, and cleaning agents to be used in the room must be considered. A minimum 4 - in. cove at the junction of floor and walls is recommended to facilitate cleaning. Some modular wall systems have a recess or offset that permits sheet vinyl to be installed in a manner that creates a seamless junction between floor and wall. When a stick - built approach is used, care should be taken to design cleanable intersections of walls and floors.

- **HVAC System**

Air Side

The clean - room HVAC system must be designed to maintain the required particulate cleanliness, temperature, humidity, and positive pressure at the expected outside environmental extremes and during the expected worst - case use operations. Rapid recovery from upset conditions such as door openings and contaminant - generating events is also a consideration. The high cost of conditioning outside air suggests that as much air as possible be recirculated. Recirculated air should be high - efficiency particulate air (HEPA) filtered in those spaces requiring a cleanliness classification in accordance with ISO 14644. Air that may be hazardous to health, even after HEPA filtration, should be exhausted after appropriate treatment. The required quantity of make - up air is calculated based on process exhaust plus air leakage from the clean room. A rate of two air changes per hour for clean room pressurization may be used in the absence of a more detailed calculation of air leakage. Make - up air should be drawn from the outdoors, conditioned, and filtered as necessary before being introduced into the clean - room recirculation air stream. Care should be taken to ensure that make - up air intakes are not drawing in contaminated air. The potential for cross - contamination is an issue that should be addressed. A flexible manufacturing facility is one in which a variety of products can be manufactured simultaneously. If the facility has a single air - handling system, the likelihood of materials from one space intruding into an adjacent space is high. For this reason, each filling or compounding operation, or operation where non-compatible product can be expected to be picked up by the air stream, should be served by its own air - handling system. Isolated systems will minimize the possibility of cross - contamination. This can be a costly option and should not be undertaken lightly. The current use of the plant and the anticipated future use should be assessed before a blanket decision that may lead to costly duplicated systems is made.

Filtration

The filtration system for a biopharmaceutical clean room typically consists of several stages of filters. Pre-filters are selected, sized, and installed to maximize the life of the final HEPA filters. With proper selection of pre-filters, the final HEPA filters should not require replacement within the life of the filter media and seal materials, a period of several years. Make - up air is commonly filtered by a low - efficiency prefilter followed by an intermediate or high - efficiency final filter. A screen should be included at the make - up air inlet to keep out pests and large debris. The make - up air is then directed to the recirculating air handler which also may have a low - efficiency prefilter, although prefiltration of recirculated clean - room air is often omitted because of its high cleanliness level even after having passed through the clean room. The air is then directed through HEPA filters into the clean room. HEPA filters must be a minimum of 99.97% efficient on 0.3 - μ m particles in accordance with military standard Mil - F - 51068 or the Institute of Environmental Science and Technology IEST - RP - CC001. Note that the filtration system for an unrated “controlled area” is the same, except that the HEPA filter stage may be omitted.

Filter Location

HEPA filters may be installed in a facility either within an air handler or at the inlet to a plenum above the clean room or in the clean room ceiling. High - velocity HEPA filters, that is, filters with a face velocity up to 500 ft/min, are frequently installed in air handlers serving Class 100,000 clean rooms and are also used in make - up air handlers. Where hazardous materials may be trapped by the filters a “bag - in – bag - out” filter arrangement, may be employed. During the design phase care should be taken to provide access to both the upstream and downstream face of these filters to permit periodic challenging and leak testing. To provide HEPA filtered air over a limited area within a larger controlled space, a ceiling - mounted pressure plenum may be used. This plenum has an air distribution means at its lower face that permits air to be introduced in a unidirectional manner over the critical process area. HEPA filters are installed at the upper face of the pressure plenum and the plenum is pressurized with filtered air. The ceiling - mounted HEPA filters have a face velocity up to 100 – 120 ft/min. This is somewhat higher than the HEPA filters serving the rest of the clean room. The filters are commonly supplied with air by a duct distribution network consisting of rectangular or

round trunk ducts and flexible or rigid round branch ducts. Full coverage, typical for ISO 5 (Class 100) clean rooms, or partial coverage, for higher class clean rooms, can be accomplished using 2 × 4 - ft lay – in.

- **Clean - Room Testing**

ISO 14644 describes methodology and instrumentation for particle counting in the clean room. The tests described there are the basis for assigning a cleanliness rating to the facility. IEST - RP - CC006 similarly provides a procedure for particle counting but goes beyond that to a full series of tests that can be conducted to determine the effectiveness of the clean - room design and operability. The determination of which tests should be run is up to the clean - room end user. As a minimum, particle counting, room pressurization, and filter leakage tests should be run. Other tests dealing with airflow patterns, temperature, humidity, lighting, and sound levels are available. The array of tests selected is determined by the owner based on the effect the various design parameters will have on the product. The data obtained in acceptance tests become baseline data against which future testing is compared to determine if clean - room performance is changing over time. Ongoing periodic monitoring of the facility will ensure that clean - room performance degradation is identified as it occurs. Pass – fail criteria are not part of the ISO standards but are to be developed on a case - by - case basis by the end user of the facility. These standards become part of the operational protocol of the facility. The clean - room testing described here is part of the commissioning or validation process wherein all equipment in the facility is run, tested, and observed to ensure it is working as designed.

- **Utilities**

Biopharmaceutical clean - rooms typically house process equipment requiring utilities such as pure water, electricity, vacuum, and clean compressed air. The source of these utilities is usually outside the clean room. During the design phase a utility matrix is developed, in conjunction with end users and equipment manufacturers, identifying all equipment and the utilities required. This is the basis for determining the capacity of the utility systems as well as the point - of - use location of specific utilities. When bringing the utilities to the point of use, care should be taken to ensure that the clean room is not compromised. A clean construction protocol should be implemented and wall, ceiling, and floor penetrations, if needed, should be flashed and sealed in such a manner as to prevent contaminants from entering the clean room. Such entry points should also be smoothly sealed to ensure that there are no crevices to harbor organisms. Drains should be avoided in the clean room wherever possible. When this is not possible, the drains should be covered when not in use with a means specifically designed for biopharmaceutical clean - room application. Such means are tight, smooth, cleanable, and corrosion resistant. In small facilities an individual pipeline may be run from outside the facility to the point of use. In large facilities a utility chase that enables major utility lines to be brought to the vicinity of process tools may be provided. Final hook - up between the chase and point of use then becomes a relatively simple, minimally intrusive procedure. The utility chase concept is also beneficial in facilities that undergo frequent retrofit or upgrade.

IV. CONSTRUCTION PHASE: CLEAN BUILD PROTOCOL

Ongoing experience has demonstrated that an aggressive clean construction protocol program is generally carries a cleanliness rating. Where cleanliness classifications less stringent than Class 10,000 are used, standard construction techniques followed by careful cleanup and wipe - down within the clean space have proven quite acceptable. Cleanliness levels of Class 1000 or Class 10,000 are achievable shortly after startup and maintainable thereafter. For cleanliness levels of Class 100 a somewhat more restrictive protocol is required. Once a facility is up and running, any intrusion into clean areas for retrofit work should be done in conjunction with some level of clean build protocol in place, dependent on the rating of the facility and the degree of disruption encountered during the retrofit project. The levels of clean construction described herein can provide a practical means of meeting operational cleanliness goals in a cost - effective fashion. Each project, whether new construction or retrofit of an existing process, should have as part of it an evaluation of the required elements of the build clean protocol to be employed. The information provided below is broad and can act as a template for the protocol put in place for a specific project. A key to successful clean construction is the appointment of an individual as a clean - room monitor who is well versed in the clean - room construction protocol. That person is charged with maintaining a clean environment and monitoring the activities of all personnel within the clean area during the construction phase and is concerned with maintaining budget and schedule goals. The clean - room monitor should have the confidence to make “real - world” decisions supporting the “spirit” of the protocol as well as the “letter.”

- **General**

All clean - facility construction, while employing standard construction techniques, should be accomplished in a manner that does not create excessive particulate contamination. A temporary lay - down area within the building adjacent to the clean area should be set aside for storage of clean construction components. All tools used for clean construction should be in an “as - new” condition and be cleaned and inspected prior to use. The pass – fail criteria for tool and material inspection is “no visible dirt.” Cleanup within the clean area at the end of each shift should consist of broom cleaning and vacuum cleaning the floor with a clean vacuum, that is, a vacuum with a HEPA filter (99.97% efficient on 0.3 - μ m particles). Clean - facility construction materials should be left in an outer shipping wrap until moved to the temporary lay - down area, where they should then be unwrapped and wiped down before being moved into the clean space. Adherence to these guidelines will make final clean - up faster and acceptable start - up and certification/validation more certain. While a goal of clean construction is rapid start - up and certification/validation, a long - range goal is the maintenance of the facility cleanliness without intrusion, over an extended period of time, of contaminants deposited during construction due to a poor protocol or improper implementation of the protocol.

- **Level I Clean Construction**

Level I clean construction is used for all areas with a cleanliness rating of Class 1000 (ISO 6) or higher (less stringent), including those spaces within which clean processes are conducted in mini-environments/isolators and those unrated areas identified as being “controlled environments.” Standard construction techniques are used until the clean - room envelope is completed, HEPA filters with protective film in place are installed and air handlers are ready to start. The clean envelope consists of clean - room walls, ceiling, and floor. Prior to starting the air handlers, a thorough clean - up of the space within the clean envelope is accomplished. Following clean - up and start - up of the clean - space air - handling system, particle counts should quickly drop to

well within operational requirements. Once the clean room is operational, as described above, additional construction related to process equipment installation and facility modification within the clean room can be done in compliance with the Guidelines.

- **Level II Clean Construction**

This is used for construction of those areas rated at Class 100 (ISO 5) employing a 100% HEPA filter ceiling. Generally standard construction techniques should be used. The clean - room envelope includes walls, ceiling, floor, return ductwork, supply fans, and supply ductwork. All ductwork sections should be cleaned and sealed with plastic wrap at the time of fabrication until just prior to installation or start - up to prevent contaminants from accumulating inside air - handling passageways. The sections of ductwork should be unsealed only as required for installation. Open ends of ducts and fans should remain sealed until connecting duct is about to be installed. A final isopropyl alcohol (IPA) wipe - down of all interior duct sections and fan surfaces should be done immediately prior to installation. When general construction of the clean room is completed. Following coarse cleaning the protective film can be removed from the HEPA filters and the air - handling system started. Successful completion of the cleaning process described above will indicate that installation of process equipment may begin. A black - and - white felt rub - down test is performed to demonstrate adequate cleanliness of the interior clean - envelope surfaces. This test consists of both black - and - white felt being wiped over any surface for 1 m linear distance with a firm hand pressure. No residue should be visible on the cloth. Each cloth should be 60 cm square black or white static - free natural fiber felt folded with cut edges inside to a 25 - cm square. The cut edges should be sealed with an approved latex sealant.

V. MAINTENANCE

To maximize the life and effectiveness of the facility, it must be maintainable. The facility should be designed to permit ongoing day - to - day preventive maintenance of the mechanical systems and, should a failure occur, permit needed repairs to be made in an expeditious manner. Perhaps of equal importance is the janitorial maintenance required to keep the facility suitable for pharmaceutical manufacturing. Proper janitorial maintenance begins with the design of the facility and evolves into an operational protocol, personnel training, and effective implementation. In the design phase it is important to provide sufficient access to mechanical and process equipment to enable preventive maintenance procedures to be carried out with minimum effort. Typically, manufacturer's installation instructions offer guidelines as to how much space should be left open around equipment to permit removal of critical components. One driver of construction cost is floor space. Making a space as small as possible to house an operation presumably will result in first - cost savings. If the space does not provide sufficient access for lubrication, filter changes, belt adjustments, and the like, there is a strong possibility that this preventive maintenance will be ignored. A predictable result is shortened equipment life and the disappearance of any first - cost savings that may have been realized. If there is a major equipment failure that requires replacement of an inaccessible component, the cost associated with knocking down a wall to gain equipment access will very likely negate first - cost savings. Storage of maintenance items should be identified early in the design process. Spare - parts storage, janitorial supply storage, janitors' sink closets, repair work shops, and storage space for consumable maintenance items (eg. air filters) will require floor space in the facility design. Frequently tools are dedicated to the clean facility or are required specifically for unique process equipment and must also have a storage area. Accommodation of these items is an important part of the planning process. A requirement of a clean facility is that the cleaning materials should be specifically intended for use in a "clean" operation, should be kept in good ("like new") repair, and should not be used in other, non-clean, areas of the facility. Using general cleaning materials manned by the "house" janitorial staff will invariably introduce more contamination into the clean portions of the facility than it removes. A central housekeeping vacuum is very useful in keeping contamination under control. While "wet - and - dry" versions of the central vacuum are available, the manner in which each is to be used should be carefully reviewed to ensure that it is in keeping with the sanitary requirements of the facility. A common housekeeping procedure addresses spills with local clean - up and uses a dry - type central vacuum for dry particulate contaminants.

VI. GUIDELINES FOR CONSTRUCTION PERSONNEL AND WORK TOOLS IN A CLEAN ROOM

- **General requirements**

A. Makeup will not be allowed inside the clean room.
B. Smoking will not be allowed in or around the clean room.
C. Tobacco chewing will not be allowed in the clean room.
D. Paper or paper by - products will not be allowed in the clean room except clean - room approved paper and pens.
E. Prints or papers will be allowed only if totally laminated in plastic and cleaned with isopropyl alcohol prior to entry.
F. Lead pencils will not be allowed in the clean room. Ball point pens only.
G. Clean - room garments, to include shoe covers, coveralls, and head cover, will be worn within the clean room.
H. Clean - room garments will not be unfastened or unzipped while inside the clean room.
I. No writing will be allowed on the clean - room garments.
J. Food and drink will not be allowed in the clean room.
K. Combing of hair will not be allowed in the clean room or gowning area.
L. Stepping on chairs, work benches, test equipment or process equipment is not allowed.
M. Damaged garments (rips, worn booties, torn gloves) will be replaced immediately. Do not wait for a convenient time. DO IT NOW!
N. Tool pouches are not allowed in a clean room.
O. All work areas and adjacent areas will be vacuumed after completion of work and prior to leaving the clean room.
P. ALWAYS wash hands before entering the clean room to remove residues from food, smoke, and/or other sources.

- **Personnel**

A. All personnel working inside a clean room will be required to follow all dress codes associated with the particular clean space.

B. Street clothes or company uniforms will be allowed as standard undergarments provided, they are well maintained and clean. No such garments will be allowed that are soiled with grease, dirt, or any detectable stains.
C. Any garments producing excessive fibers (such as fuzzy sweaters) will not be allowed as an undergarment.
D. Standard safety shoes (or another specified footwear) will be required. Shoe covers must be worn.
E. Bare feet, socks, and stockings are not allowed inside booties.
F. Coats, lunches, and private items will not be allowed inside the clean room.

- **Gowning procedure**

A. Each individual is responsible for knowing and using the correct method of gowning prior to entering the clean room.
B. Clean shoes prior to entering the gowning room.
C. The order of dress should be: a. Shoe covers, b. Hairnet/beard cover (required after final cleaning), c. Hood, d. Coveralls, e. Face cover (required after final cleaning), f. Gloves (required after final cleaning)
D. Ensure that hoods are tucked inside neck opening of coveralls and pants legs are tucked and snapped inside booties. Garments are to be snapped closed at the neck, wrist and ankle opening and sleeves tucked inside gloves.
E. All head hair must be covered at all times.
F. Do not allow garments to touch the floor while dressing or undressing.
G. Avoid leaning on walls, lockers, or other personnel at all times. DO NOT place feet on benches.
H. The order of undress should be as follows: a. Gloves b. Coveralls c. Face cover and hood d. Shoe covers
I. If you will be reentering the clean room, unsoiled garments may be hung for reuse; gloves are not to be reused.

- **Work tools, parts, and equipment**

A. All tools and equipment used in a clean room should be in like - new condition.
B. All parts will be removed from their shipping container prior to cleaning and introduction into the clean room. NO PAPER PRODUCTS will be allowed inside the clean room.
C. All tools, parts, and equipment will be properly cleaned prior to entering the clean room. Minimum cleaning should be a total wipe - down with isopropyl alcohol, using certified clean - room wipes, to assure that the last wipe does not leave visible residue on the wipe. Parts should be blown off outside the clean room using filtered nitrogen when available.
D. All parts and equipment should be sent through the equipment wipe - down area (material air lock) and not carried through the gowning area.

- **Working in a Clean Room**

A. A major concern when working in a clean room is the generation of particles of the size that cannot be seen and spreading these particles throughout the clean room. Every possible precaution must be taken to contain these contaminants and protect the clean - room environment. Everything that is done as a standard operation must be analyzed to determine if it will adversely affect the cleanroom. If you have any concerns, ask the clean - room monitor before you damage the environment and incur unnecessary clean - up cost.
B. All procedures must be reviewed with the clean - room monitor to ensure compliance with clean - room operation practices. All procedures that can generate particles should be done outside the clean - room whenever possible. In the listing below all prohibited procedures are subject to review by the clean - room monitor. The intent is to get the job done; however, some preplanning with the clean - room monitor can result in a positive result and a clean facility.

VII. BIBLIOGRAPHY

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