



A Modular Approach to Engineering Guidelines for Pharmaceutical Cleanroom Construction, Rick Dobson, April 2004

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The requirement to manufacture drug products is at an all time high. With the forecast for increased demand, pharmaceutical and bio-tech companies continue to set goals for finding ways to increase product yield and to reduce overall construction schedules. The implementation of pre-engineered modular architectural systems for cleanrooms and critical environments within new and existing facilities has allowed owners and engineers to achieve these goals while maintaining or exceeding the design standards established in current engineering guidelines. The materials selected for construction of cleanroom areas are ultimately the responsibility and the decision of the owner and the project team. Together they must take into consideration a number of factors such as flexibility, relocatability, cleanability, particle emission, microbial resistance, fungal resistance, corrosion resistance, cost, and schedule. Pre-engineered modular architectural systems provide a construction alternative to traditional stick-built construction and offer designers a variety of construction alternatives and finishes.

Engineering Design Guides

Engineering Design Guides provide an excellent source for construction material guidance. They assist owners, architects, and engineers, in the design and the planning process of cleanrooms and controlled environment areas. These sources include FDA guidance documents, United States Pharmacopeia (USP), European regulations, and industry guidance documents (ISPE Baseline Guides®, and IEST guidelines). Pre-engineered modular architectural systems have incorporated the principles outlined in current engineering guidelines and applied them to a technology that takes cleanroom construction to a new level. Modular architectural systems have incorporated design criteria for system performance following good engineering practices, taking into account GMP, cGMP, safety, health, regulatory requirements, and industry guidelines.

Modular Approach

The modular approach incorporates construction with standardized units and dimensions. This allows for flexibility and variety. The principle by which pre-engineered architectural systems are designed and manufactured provides the ability to meet strict engineering guidelines while incorporating flexibility in design, construction, and process integration. The use of modular architectural systems in Level II, Level III, and Sterile Aseptic Processing areas has now become a design standard for numerous pharmaceutical, bio-tech, and life science companies worldwide. Typical modular construction applications include the following:

- * Bulk Pharmaceutical Chemicals (BPC) facilities for the manufacture of penicillins, cephalosporins, cytotoxic drugs, radioisotopes, and steroidal hormones.
- * Oral Solid Dosage (OSD) facilities for the manufacture of tablets, capsules, and powders.
- * Sterile Manufacturing (SM) facilities for the manufacture of topicals, oral solid dosage, oral liquids, sterile injectables, and active pharmaceutical ingredients (API).
- * Classified Areas: Design criteria meeting the requirements of ISO14644 and EU GGMP design to include:
 - * ISO 5, 6, 7, and 8 (international cleanroom classifications)
 - * Grade A (filling zones, open ampoules, open vials, aseptic connections, etc.)

* Grade B (background environment for Grade A areas)

* Grade C (clean areas for manufacture of drug products)

* Grade D (PAL, MAL, and other clean areas for manufacture of drug products)

Design Criteria

Whether the process is weighing and dispensing, compounding and mixing, milling and granulation, or aseptic processing, cleanrooms need to meet design criteria applicable to the level of protection required for that application and product exposure; in effect, the ability to remove viable and non-viable sources of extrinsic contamination. Research indicates that architectural finishes contribute approximately 5% of the overall source of cleanroom contamination. The source of particulate can be minimized with the use of non-shedding materials and by using materials that minimize particulate emission at point of impact. Architectural finishes should be selected to minimize room structure particulate within the cleanroom area. Contaminant sources are, by percent: room structures 5%; ventilation 15%; and personnel 80% (source: Encyclopedia of Cleanrooms).

Good Engineering Practice

The design of classified spaces requires that architectural finishes be designed to be smooth, easy to clean, have minimal ledges and joints, and be installed with radius corners for ease of cleaning. The surfaces provided should be non-shedding, non-porous, and resistant to sustaining microbial and fungal growth. The architectural finishes should also be able to withstand repeated cleaning and sanitization with various chemical solutions. Due diligence should be paid to the review of cleaning protocols, SOPs, and cleaning processes to ensure that the architectural finishes specified are compatible with the cleaning solutions used and in the concentrations specified.

Value

An architectural system's value should not be identified solely by initial cost. Rather, one should consider the cumulative value, taking into account life cycle costs, payback period, and operational and functional advantages. There needs to be an engineering review for maintenance, certification, performance, flexibility, longevity, and scheduling. Also to be considered are the versatility of present and future facility layouts, and the integration of process equipment and services. "Modular wall and ceiling systems, when appropriate, reduce construction time and may provide flexibility to expand, rearrange, or relocate in the future," (ISPE Baseline Guides). Consideration should also be given to financial advantages available with modular construction. These advantages may include lease options, tax incentives, tax exemption, and accelerated depreciation. A careful review of local, state, and federal tax laws should be undertaken to find available incentives and ensure any eligibility requirements are met in the construction process.

Architectural Finishes

In compliance with good engineering practices, there are design guidelines for architectural finishes used in cleanrooms and controlled environments. Those guidelines can vary according to room classification, room usage, and product manufacturing; therefore finishes should be carefully evaluated for specific compliance. Architectural finishes are required to meet building regulatory requirements and should be accompanied by written documentation and certified test data verifying compliance. Applicable testing may include: ASTM E84 Flame Spread and Smoke Development Values; UL-723, ANSI No. 2.5, NFPA No. 255; and UBC 42-1. As part of the overall design, architectural systems and finishes should meet project specific health and safety requirements, state and/or local building codes and local seismic codes. Architectural systems should also have the ability to integrate process equipment and process utilities via utility chases or stainless steel utility panels.

Pre-engineered Modular Systems

* Floors: Pre-engineered architectural systems incorporate the installation of vinyl, epoxy, epoxy terrazzo, and other applied flooring systems with a smooth transition between the flooring material and the surface of the wall panel. The flooring materials should be provided with a radius cove detail from floor to wall and from wall to wall, maintaining the radius detail for ease of cleaning and maintenance. The type of flooring material used within the cleanroom areas is typically owner specified and is based

on experience from use of that or similar flooring materials installed within the owners facility. Owners and engineers are faced with difficult decisions providing flooring materials that will withstand repeated cleaning and sanitization with various chemical solutions, and allowing for installation into typically aggressive construction schedules.



* **Walls:** Walls should be manufactured to be smooth, easy to clean, have minimal ledges, joints, and installed with radius corners for ease of cleaning. The surfaces provided should be non-shedding, non-porous, and resistant to sustaining microbial and fungal growth. The architectural finishes should be designed to withstand repeated cleaning and sanitization with various chemicals. Modular cleanroom wall systems are designed for flexible room heights allowing for unlimited process applications. U.L. rated raceways should be incorporated to allow for installation of electrical wiring and devices. Architectural systems should be suitable for wet and wash down applications. In the architectural design review, materials should be evaluated for their use in specific applications. Areas that will be repeatedly washed down or are prone to wet processes should be constructed of materials that are non-hygroscopic and corrosion resistant. Areas utilizing cart traffic should include wall protection in the form of corner guards or bumper rail systems. The protective systems need to be cleanable and maintain cleanroom design standards.

* **Walkable Cleanroom Ceilings:** Walkable cleanroom ceilings can offer owners the ability to utilize the area above the cleanroom for mechanical services or maintenance access when applicable. The use of walkable ceilings for access can minimize the need for catwalks above the cleanroom areas, reducing steel costs and installation time. The use of catwalks can then be limited to areas where equipment access is needed for maintenance or replacement of larger pieces of equipment (AHU motors, cooling coils, heat exchangers, etc.). Cleanroom ceilings should be designed and installed in compliance with local seismic zone requirements. Panelized ceiling systems can be utilized in GMP non-classified spaces, as well as, ISO 6, ISO 7, ISO 8, and Grade C and Grade D areas. Areas requiring a more stringent classification may be designed to incorporate grid or plenum ceiling systems due to the HEPA filters quantities.



* **Doors:** Doors should be manufactured to be smooth, easy to clean, have minimal ledges, joints, and the surfaces provided should be non-shedding, non-porous, and resistant to sustaining microbial growth. The door finishes should be designed to withstand repeated cleaning and sanitization with various chemicals. Doors should have the option to be provided with vision windows when applicable. Door heights and widths should be flexible to allow for specific owner personnel and process requirements. Door hardware should be stainless steel. Doors should be designed to incorporate manual or automatic door operators. Doors should also be designed to incorporate door interlock systems, card key access, and owner specified security system requirements. Door operators should be designed to overcome room differential pressures. Door air leakage rates should be provided for assistance in HVAC design requirements. Example: pre-engineered architectural door air leakage for a 3' x 7' single door - three sided gasket system - total door gap $\text{mm}^2 = (4575 \text{ mm}^2)$, differential pressure "wg = (0.05" wg), approximate leakage rate = (0.025 m^3/s) or (+/-55 CFM), a potential reduction in leakage of 15 to 40 CFM per door. Door leakage rates vary from manufacturer to manufacturer and should be reviewed by the design team.

* **Windows:** Vision panels should be available for installation into the architectural system minimizing ledges and joints. Window units should be hermetically sealed and desiccant filled to eliminate condensation. Glazing materials should be of a tempered or laminate construction for safety compliance. Details should be available to incorporate cleanroom windows into a single wall application or a double wall application such as return air walls. Windows are an important architectural detail in the construction of cleanroom areas. Windows offer owners the ability to monitor manufacturing processes while limiting personnel traffic within the cleanroom areas. Windows can also be used as a safety tool to allow full visibility and assist with communication within and between cleanroom areas or be utilized as a sales tool to increase visibility in facilities where potential customers can be brought into the clean corridor area to view manufacturing process without having to enter the actual cleanroom work space.



* **Utility Integration:** Process service panels should be stainless steel and designed to fit within the

architectural system minimizing ledges and joints. Service panels should be designed for maintenance access and allow for future piping expansion capability. The architectural system selected should incorporate the requirements of the utility process design. Modular panel systems allow owners and contractors the ability to make field modifications during the process installation offering additional installation flexibility and potential design cost savings.

* **Process Integration:** Piping penetrations and enclosures, when integrated into the clean space, should be smooth, easy to clean, have minimal ledges, joints, and the surfaces provided should be non-shedding, non-porous and allow for future piping expansion capability. Piping chases and enclosures can be manufactured utilizing the pre-engineered modular architectural systems incorporating radius cove details and cleanable surfaces.



Conclusion

Project scope, design requirements, manufacturing processes, and construction schedule are all factors in the consideration and selection of materials of construction for cleanroom environments. The material selection review process will ensure that the materials selected meet the design requirement for the specific manufacturing process and that these materials comply with accepted design and regulatory guidelines. Flexibility remains the key design option available in the use of modular architectural systems. The ability to incorporate only those materials that best suite the project scope and design requirements. Pre-engineered modular architectural systems for cleanrooms and critical environments can offer owners, architects, and engineers, construction alternatives and flexibility while maintaining the design criteria and regulatory guidelines required for specialty cleanroom environments.

Note: The author wishes to acknowledge the use in this article of ISPE and IEST guideline materials as a basis for technical reference.

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