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LIFE SCIENCES

PHARMACEUTICALS AND MICROBIOLOGY **PART 2**

Project Planning and Basis of Design for cGMP Cleanrooms

There are two basic truths: "Form follows funding," and "All buildings grow."

It was Louis Sullivan, designer of so many of Chicago's famed high-rise buildings, who wrote, in 1960, "Form ever follows function." Years before, Winston Churchill had written, "We shape our buildings, and afterwards our buildings shape us."

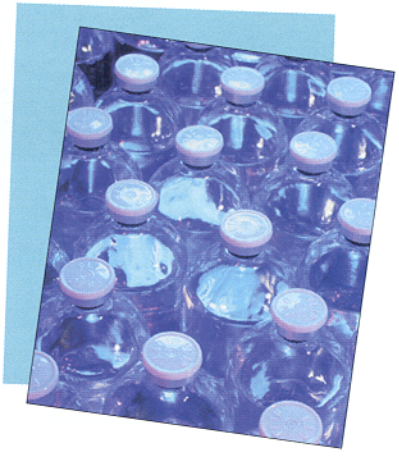
Both statements apply as readily to cleanrooms as they do to the other structures in which we work or dwell. Every facility must be designed around the process it will contain, with the superordinate goal a facility that "meets or exceeds the specification" for that process.

As we indicated in Part I of this article (May 1998, page 21), it is during the conceptual stage of a project in which the greatest impact on cost can be achieved. Fortunately, it is during this phase that we, as cleanroom builders, normally begin working with the owner and/or the owner's representative, to develop a facility that defines and adheres to the budget.

The most challenging issue in facility design and construction that we see in these preliminary planning stages is the lack of firm process knowledge. Many times the procedures are new, and will only be proven after the facility is in use. Consequently, all layouts are predictions—and, therefore, like most predictions, ultimately inaccurate!

When clients are asked to list their requirements they can seldom provide enough detailed information. Responses received usually fall into one of four general categories:

- **Stated requirements ("This is what I want or need!").**
- **Assumed requirements ("I thought you knew I needed that!").** These are the requirements that the client feels are obvious, and therefore does not bother to specify. They are frequently based on organization or industry culture, tradition, or common practice. The danger here is that the typically vague language associated with assumed requirements can lead the designer astray, unless time is spent up front converting assumed requirements into clear, precise stated requirements!



- **Witheld requirements ("I didn't know I could get that!").** Often, requirements remain unstated because the client assumes that these requirements are unobtainable. Again, it's important to have a structured dialogue so that withheld requirements, valid requirements that are known to the client, are revealed and incorporated into the BOD.
- **Unknown requirements ("I never thought of that!").** Unknown requirements are those that are beyond the client's current level of awareness. One of the most frequent examples of this that we see is the lack of awareness of the level of validation required, or of how and when the validation process is to be implemented. Identifying unknown requirements is the most difficult task to be faced in BOD

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Figure 1. Aseptic corridor for a fill-and-finish facility.

Figure 2. Self-contained, packaged, pre-engineered HVAC unit for aseptic processing.

preparation—and, probably, the most crucial item on the agenda.

Questions to Ask Before You Begin

The recently "released for review" International Society of Pharmaceutical Engineers (ISPE) *Baseline Guide for Sterile Manufacturing Facilities* asks the following questions in Appendix 3, Section 4. Asking (and answering) these questions before construction begins will reveal the information required for assessing the impact of process operations on environmental control systems and developing the optimal process facility.

Product flows:

- **At what point does the product become sterile?**
- **How does it enter the "aseptic" manufacturing area?**
- **At what point is the product exposed to the environment?**
- **How is the product placed into its final enclosure?**
- **Does the product have to be transferred in its final enclosure before it is sealed?**
- **How is the product protected until it is sealed?**
- **At what point is the product considered sealed into its final enclosure?**
- **How does the product leave the "aseptic" manufacturing area?**

Component flows:

- **Do the components need washing?**
- **Do the components need sterilization?**
- **How do the components enter the "aseptic" manufacturing area?**
- **Do the components need cooling in the "aseptic" area?**
- **How are the components fed into the filling machine?**
- **How is the sterile stopper bowl protected; where is it located?**
- **How are the components handled after filling and sealing?**

Operator intrusions:

- **At what points in the process do the operators intervene with the product?**
- **At what points in the process do the operators intervene with the product's contact components?**
- **How are the components and product transferred and handled within the "aseptic" manufacturing area?**
- **How many operators are required in the preparation area?**
- **How many operators are required in the "aseptic" manufacturing area?**
- **Where will operators stand in the "aseptic" area under normal operation?**

Equipment:

- **What type of washing equipment is used before sterilization of components?**
- **What type of sterilization equipment is used to transfer components into the "aseptic" area?**
- **Is any accumulation of the sterilized product's final enclosure required?**
- **Do any parts of the equipment produce large amounts of particulate loads? (Will this be considered "background?" What are the particulates? Are there any OSHA regulations that must be considered?)**
- **Do the equipment items which have exposed sterilized components or product require regular operator intervention?**
- **Is the equipment maintained from within the "aseptic" area or from outside the area?**

General:

- **What other items need to enter the "aseptic" manufacturing area?**
- **How do other items enter the "aseptic" area?**
- **Must product contact parts (machine parts, filters, etc.) be stored within the "aseptic" area?**
- **What is the cleaning/sterilization regime?**
- **What are required hours of operation of the facility?**

Establishing the BOD

If the following minimum facility conceptual design elements have not been established by the time we are asked to design a project, we must establish the list that forms the "Basis of Design Document" (BOD). Such a list consists of the following:

- Process description and process flow diagrams
- cGMP floor plan and general equipment arrangement
- Sized major process equipment list, with utilities requirements/consumption
- Sized process support services utilities list (e.g. water for injection [WFI], etc.)
- Functionality flow diagrams (process, people, product, material, components, air, waste)
- HVAC zoning and room classifications, including microbial limits
- Budget quality (± 20%) cost screening estimate, w/preliminary "scope of work" description, i.e. who is responsible for for design, specficiation, forecasting, inspection, T/B/C, guarantees

After completion of a BOD—assuming that we don't have to go back and do significant "value engineering" (although at least now we have a rational, analytical basis for it!)—we can proceed into generation of the elements of modular systems detail design.

Additional HVAC Considerations

The need for flexibility, prevention of cross-contamination, and the requirement for individual room pressure, temperature, and humidity control often results in a more costly HVAC system for a biotechnology facility than for the typical pharmaceutical facility, where a classic large-volume system would ordinarily be installed. Most biotechnology facilities consist of several suites of small rooms (**Figure 1**).

Generally the closer the HVAC equipment can be located to the processing areas, and the smaller the volume of 100% once-thru air, the lower the installed cost will be. Pre-engineered, pre-fabricated, pre-tested, packaged double-wall HVAC equipment—with a relatively small footprint—will often provide an advantage in these applications. Most packaged HVAC units today utilize direct drive variable frequency control plug fans, lending flexibility to the initial placement and orientation, making post-installation balancing faster and easier (**Figure 2**).

Also, 100% once-thru outside air containment facility applications require more extensive MUA pretreatment than that needed for recirculating type systems. Outside air intakes should be located on the side of the building exposed to the prevailing winds and all ductwork should be leak tested in situ. Individual room pressure control is typically provided by variable frequency, direct drive-controlled exhaust fans, with all of the room exhaust receiving HEPA filtration prior to discharge into the atmosphere.

When multiple small HVAC units are used and controlled from a central station, a PC-based operator interface for control and monitoring must be provided. This interface should provide:

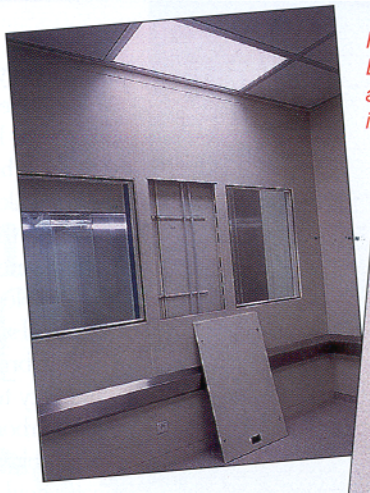

Figure 3A. (left) Built-in technical access panel allows ample room for utility installation and service.

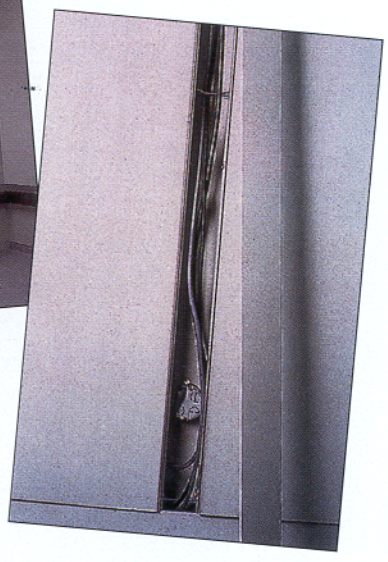

Figure 3B. Postcap utility chase runs between prefabricated steel panels to provide ready access for modifications or repair.

- Full, user-friendly graphic display of information, including system start/stop and status information
- Access to individual zone devices and environmental condition monitoring of individual zones as well as the system as a whole
- PID settings for all control loops and mechanical devices
- The ability to change setpoints, force (and view) outputs for OQ protocol challenge tests
- Alarm management
- Networking; data trending, storage, and transfer
- Report generation
- Remote monitoring capability

Architectural Issues

Prefabricated cGMP steel wall panels are far more appropriate for cGMP facilities than conventional gypsum board style construction. Gypsum board is clearly not impermeable to moisture; nailed to stud walls, it inevitably shifts on the studs and, over time, cracks. With daily cleaning, solutions will permeate the gypsum board and create a non-validatable condition.

Unlike gypsum board or concrete masonry unit (CMU) construction, prefabricated cGMP steel wall panels allow ready access for process support services. Small-diameter piping and process/convenience cabling (for electricity or data) can be chased throughout the entire cleanroom envelope—both walls and ceilings—with entry (and exit) at each postcap junction. Because no exposed piping or conduit is permitted in a cGMP facility, this built-in chase system (**Figure 3A,B**) will save time and money both during installation and in the future, when it becomes necessary to add additional process support services. Using prefabricated steel or stainless steel panels with integral utility chases eliminates the frustration and delay that inevitably accompanies trying to locate services that were "buried" in gypsum board or CMU construction by the contractor during ☛

Glossary

For readers who may have missed Part 1 of this article (May 1988), definitions of terminology used therein are included here. For copies of back issues, phone 603-672-9997; fax 603-672-3028; or contact info@a2c2.com

Basis of Design (BOD)—The document that serves to define the conceptual engineering effort. The Basis of Design becomes an integral part of the conceptual engineering work product. The BOD documents will minimally develop the purpose and function of the facility, along with:

- a description of the cGMP and non-cGMP areas and
- a description of the process and process flow requirements

The BOD will also provide an outline of major equipment and utility requirements. It also provides a reference point for future alterations or renovations.

cGMP (current Good Manufacturing Practice)—Generally accepted to be defined by Title 21, Parts 210 & 211 of the Code of Federal Regulations. May also include "Guidelines" as published from time to time by agencies such as the FDA. Found in the regulations are the minimum practices and methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that the drug meets requirements for safety, efficacy, quality, purity, and identity as purported by the manufacturer.

Containment—A cleanroom designed to ensure that the element of interest remains within the cleanroom. Containment may be primary (e.g. within a sealed vessel) or secondary (the facility itself). Containment applies with equal validity to biological agents as well as to toxic or potent compounds. Containment design will vary for biologicals or potent compounds in accordance with the risk of airborne contagion or dispersion, virulence, toxicity, carcinogenicity, etc. Containment is achieved through the proper design and implementation of effective engineering controls to protect people, product, and the environment.

DOP Integrity Testing—Traditionally known as the DOP (dioctyl phtalate) test. In this test, a thermally-generated DOP aerosol with a uniform, controlled size of approximately 0.3 microns is utilized as the challenge aerosol. The upstream and downstream concentration of the aerosol is measured by an aerosol photometer, and the ratio of the two indicates the rate of penetration of the filter. This test is performed in the filter manufacturer's facility.

Integrity testing alone is insufficient to adequately describe filter performance, as the filter can pass penetration testing requirements even though minute defects may be present. Integrity testing is normally combined with "leak testing" or "scan testing," utilizing polydispersed cold DOP to fully characterize the filter and determine the location and magnitude of specific defects. Scan testing is typically performed in the factory and again in the field after filter installation for HEPAs destined for use in critical aseptic fill areas (Figures 3A,B).

Validation—support utilities and HVAC systems are typically not specifically challenged, but they are determined to be operating within acceptable criteria. In contrast, terminal HEPA filters are in situ cold DOP challenged—after installation. In general, we can say that those systems that directly affect the product are *challenged*, while those that support the operation are *qualified*. The entire documentation and testing effort is generally referred to as "validation."

Validation Master Plan—Serves to define and crystallize all the project validation requirements. Typically the MVP will list the facility equipment and utilities to be validated, identify all required protocols and Standard Operating Procedures, assign responsibilities for the aforementioned to the various organizational entities and resources, and provide a schedule for validation activities.

initial facility construction.

Fully cleanable double-wall return chases and technical access panels for areas with high densities of process support services are standard features that don't have to be redesigned from scratch each time. When utilized in a design/build facility delivery package, these prefabricated envelope systems eliminate the "finger pointing" that sometimes occurs between the architectural/engineering firm that prepared the design and the general contractor responsible for execution, a common point of contention in such so-called "plan and spec" projects.

Prefabricated steel panels have been subjected to rigorous strength and durability testing, including smoke and fire testing, immersion in various hydrocarbon solvents, body fluids, and typical cleaning, disinfecting and sterilizing solutions, including cationic surfactants, hydrogen peroxide, peroxyacetic acid, sodium hypochlorite, and sporocidin, all without noticeable effect.

Recently we have seen some manufacturers offering plastic coated panels. We don't recommend them, since, according to Factory Mutual, Fire retardant plastic panels should not be used in construction of cleanrooms. Plastic increases the fuel available to fire within the room.

Conclusion

During the Silicon Valley's early stages of development we began putting up tilt-up metal buildings and populating them with modular vertical tunnel-type laminar flow cleanrooms. Today the same basic techniques—updated and improved, of course—can be applied worldwide to build cost effective cGMP facilities. You don't need to wait three to four years and raise hundreds of millions of dollars to build the Taj Mahal to get a product safely to market. Today, we can say: *Form follows funding*.

Consider a 4000 sq. ft. cGMP facility in $50/sq. ft. metal building. Contingent space may be available for mirror-image expansion. A project such as this can be ready for occupancy and validation protocol execution in as little as 20 weeks from design initiation (given an adequate BOD!).

Modular systems technology encourages the use of rational optimization (benefit cost analysis) in facilities design. The manufacturing process should be designed first, independent of the facility; development of the process flow and facility layout can then proceed.

Modular systems construction is the favored route for fast-track projects with tight deadlines. It will be cost-comparable with conventional construction if—and only if—the designer takes advantage of the features and benefits this approach provides early in the design process. Panelized construction will meet "build-clean" protocols with little extra effort.

Facilities are always expected to provide greater throughput and be used longer than their designers anticipated. It's becoming increasingly difficult to predict whether or not today's plant will meet tomorrow's requirements. Consequently the design goal today should be to provide the owner with future-planned engineered contingency.

There's a universal rule: *All Buildings Grow*. Today, it's likely that more money is being spent on changing existing facilities than on building new ones. With careful planning, the facility you build today will meet tomorrow's needs.

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