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.
- **Withheld 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...
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, products, material, components, air, waste)
- HVAC zoning and room classifications, including microbial limits
- Budget quality (±20%) cost screening estimate, with preliminary "scope of work" description, i.e., who is responsible for design, specification, 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-through air, the lower the installed cost will be. Pre-engineered, prefabricated, pre-tested, packaged double-wall HVAC equipment—often 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-through 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:

- 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...
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, peroxycetic 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 $500/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 a adequate BODI).

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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