

A publication of
The Williamsburg BioProcessing Foundation

Fall 2006

BioProcessingTM JOURNAL

The Most Trusted Source of BioProcess TechnologyTM



Vol. 5 No. 3

www.bioprocessingjournal.com

Conquering Design Challenges in the Construction of Immunomedics' Multiproduct Cell Culture Bioreactor Facility

By JENG-DAR YANG*, CARL SHARO, GRANT MERRILL, and CYNTHIA SULLIVAN

In the last few years, we have seen many biotech products approved by FDA. These products have gained public awareness because of their ability to treat several debilitating diseases with very minimal side effects, and thereby impact the quality of life for many people. As a result, the biotech industry is constantly in the news for its successes and programs to develop new therapeutics for many unmet medical needs.

Immunomedics, Inc., a New Jersey biotechnology company, recently completed an expansion project that included new bioreactor manufacturing suites and support laboratories. Building on the company's existing headquarters site and fully integrating the new capacity into the existing operational facility, the project spanned two years and was completed in 2003.

The new suites are currently in use for the clinical manufacturing of Epratuzumab, which is an anti-CD22 humanized monoclonal antibody currently being tested in two worldwide Phase III trials in patients with systemic lupus erythematosus (SLE). This article describes several challenges that the design team encountered during the course of the expansion project, and particularly during the design phase. It also discusses the approaches that were

taken to overcome these obstacles while demonstrating the dynamic, and often iterative, process involved in designing a biotech facility.

Birth of the Project

Founded in 1982, and with its current headquarters in Morris Plains, New Jersey, Immunomedics, Inc. is a biopharmaceutical company focused on the development of monoclonal antibody-based products for the treatment of cancer, as well as autoimmune and other serious diseases. In the late 1990s, as the company gradually shifted its

focus from the area of immunodiagnostics to immunotherapeutics, it evolved from an R&D based organization to one which manufactures products for late-stage clinical trials. Then in 2000, encouraging clinical results and the prospects for additional trials made the organization realize it did not have sufficient manufacturing capacity to meet its future needs for clinical production and licensed products. As a part of an overall strategy to secure capacity, Immunomedics decided to expand its manufacturing facility at the current site and construct a new 3,400 sq. ft. facility with upgraded utility capacity.

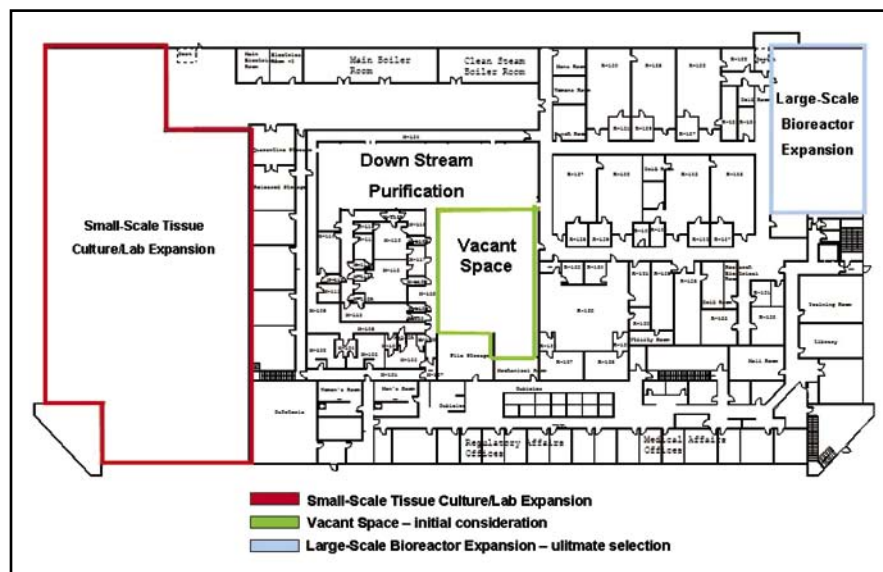


Figure 1. Immunomedics Facility Layout: The vacant space (green) next to the Down Stream Purification facility was the site of the initial consideration for the project. However, several concerns prohibited this choice. Eventually the site at the northeast corner of the building (blue) was selected.

Jeng-Dar Yang, Ph.D. (jyang@immunomedics.com, ph: 973-605-8200 x205, fax: 973-605-3112), Senior Director of Cell Culture Production; **Carl Sharo**, Facility Manager; and **Cynthia Sullivan**, President and CEO; Immunomedics Inc., Morris Plains, NJ; and **Grant Merrill**, Systems Sales Engineer at AES Clean Technology, Inc., Montgomeryville, PA. This article is based on a presentation given at Williamsburg BioProcessing Foundation's eighth annual Facilities for Mammalian Cell Products conference, October 24-26, 2005, Philadelphia, PA. *To whom all correspondence should be addressed.

Executive Guidance and Project Scope

Table 1 shows the guidance given to the project leader for the facility expansion, and reflects the thinking of executive management. After several reviews and refinements, the above guidance was translated into the Project Scope (Table 2), which served as the foundation for the project design criteria. After considering Scope No. 1 (speed to market) together with the company product pipeline and technology platform, it was concluded that the facility would be used solely for manufacturing monoclonal antibody-based products via mammalian cell culture technology. In the scope, the “speed to market” requirement became significant because the lead product candidate had completed Phase II trials, and it was anticipated that the future phase III trial would take about two years to complete. Furthermore, when a fast track approval process was granted to the drug, we knew the required FDA review period would be significantly reduced to six months following the Biologic License Application (BLA) submission. These events created a significant amount of pressure on the project timeline, and required strong leadership from the project team to resolve the good-fast-less expensive conflict, which typically impacts many biotechnology construction projects.¹

As a mid-sized company, financial constraints are very real. Therefore, when it came to the decision of whether to build a development or commercial

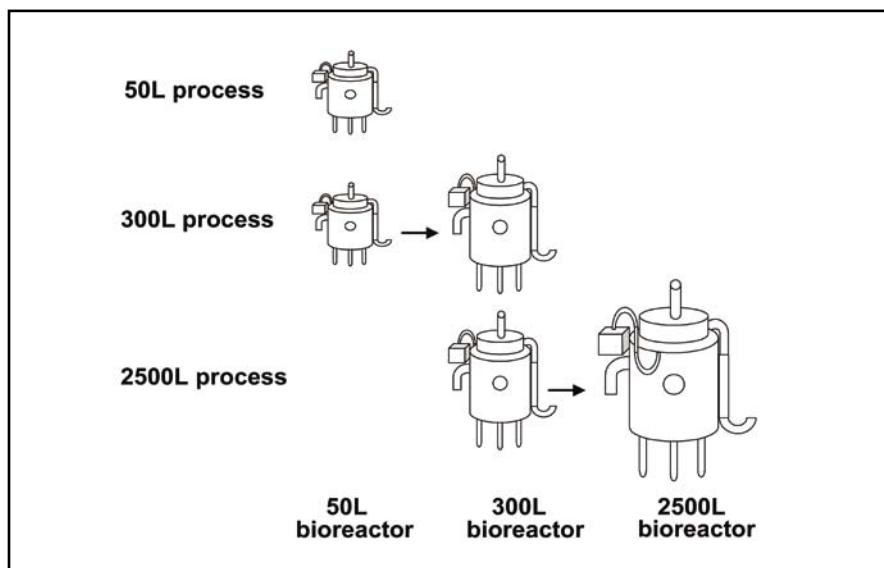


Figure 2. Proposed bioreactor process train in the new facility: The new facility has two identical bioreactor trains, each comprising a 50 L, a 300 L, and a 2,500 L bioreactor. The facility offers the flexibility for three possible processing schemes that involve varied combinations of 50 L, 300 L, and 2,500 L bioreactor processes. The two-train configuration along with the three process schemes covers the production needs of various clinical stages and enables concurrent manufacturing of two different products.

facility, the answer became a combination of both, as revealed in Scope No. 2. Scope No. 3 further compounded the complexity of the design by requiring that it support multi-product, concurrent manufacturing.

Scope No. 4 saved some site selection efforts by concentrating on the existing building infrastructure. However, this decision came with a price when meeting the challenge of Scope No. 5.

With limited human resources, Scope No. 6 presented a significant hurdle. For a typical multimillion-dollar construction project, the owner’s key team members, (primarily the project

leader, project manager, and engineering manager) would be required to dedicate 100% of their time to the project, but at the same time, maintain responsibility for managing day-to-day operations.

Site Selection

Figure 1 shows the Immunomedics facility layout in which two possible sites were evaluated: Site #1 was the vacant space (shown in green) adjacent to the down-stream purification area, and Site #2 was the open space in the northeast corner of the facility (shown in blue). At first glance, Site #1 ap-

Table 1. Project Guidance Table.

1	Must be cGMP facility with the capacity for meeting Phase III and early launch material needs
2	Must be flexible in accommodating early development work and supporting multi-product concurrent manufacturing and campaigning
3	Built on the existing infrastructure
4	Integrate into existing site without affecting current clinical manufacturing
5	Must meet FDA ^{2,3} and EMEA ⁴ facility design guidelines
6	Must meet the minimum NIH biosafety level BSL I requirements ⁵
7	Must meet EPA and local biowaste disposal standards
8	Must meet all federal and local building and fire codes
9	Contract engineering firm to design, build, commission, and certify the facility

Table 2. Project Scope.

1	Speed to market; lead monoclonal antibody drug produced in a cost effective and approvable facility
2	The cell culture bioreactor facility to support primarily Phase III and product launch; also has the flexibility to accommodate some early development works
3	The facility should have capabilities to support multi-product concurrent manufacturing and campaigning
4	Built at the existing building site
5	Construction of the new facility without interfering with the current ongoing Phase II clinical manufacturing and other operations
6	Managing the design and building of the project without exhausting the current limited human resources

peared to be the better choice because its location would make it convenient to integrate the space into the existing purification operation. In addition, the space could be readily accessed from the neighboring small-scale tissue culture laboratories.

However, several concerns prohibited this plan. First of all, it was nearly impossible to excavate through the adjacent operating space so that we could connect the existing drainage system. Secondly, this site was entirely surrounded by operational space, much of which involved purification steps in class 10,000 areas. This created a difficult burden on the project execution plan, which would have to preserve the controlled environment in the adjacent clinical manufacturing areas during construction. In addition, it was going to be quite difficult to transport the bioreactor equipment to the project area from outside the building. Although the remote nature of Site #2 presented some operational challenges, it was the most feasible to support a fast-track installation. Therefore, we selected Site #2 for the project.

Defining the Manufacturing Process

The sole purpose of a biotechnology facility is to house the operations that will be performed; so the facility design must be specifically focused on the processes. One of the challenges we experienced with this project was that the process was not yet well-defined. Information was limited on the product yield at larger scale, and we were uncertain as to how successful our process scale-up would be. Despite these difficulties, the cell culture team created three possible processing schemes with various combinations of 50 L, 300 L, and 2,500 L bioreactors (Figure 2). The 50 L scale was to be used primarily for early process development. The 300 L scale, which uses the 50 L bioreactor as a seed vessel, was to serve the needs of Phase I and II trials. The 2,500 L scale, which uses the 300 L bioreactor as the seed vessel, was for Phase III and commercial production. The process flow diagram of the 2,500 L scale bioreactor is shown in Figure 3.

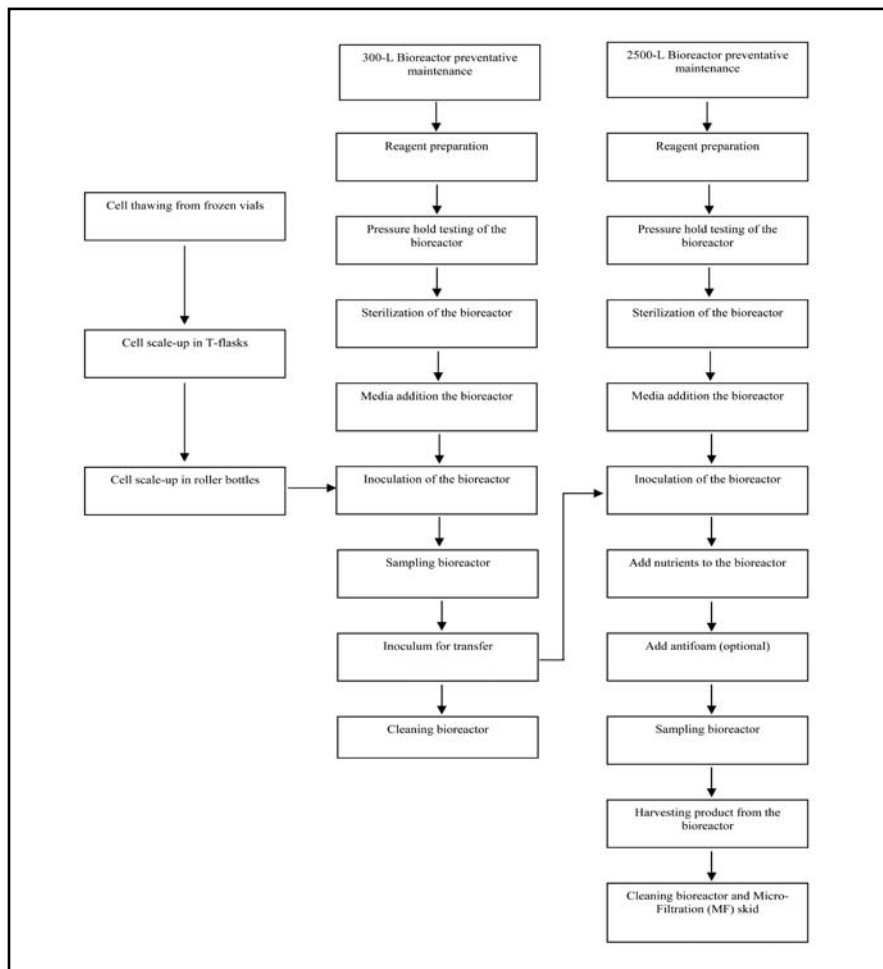


Figure 3. 2,500 L fed-batch bioreactor process flow diagram: Each block represents a critical unit operation.

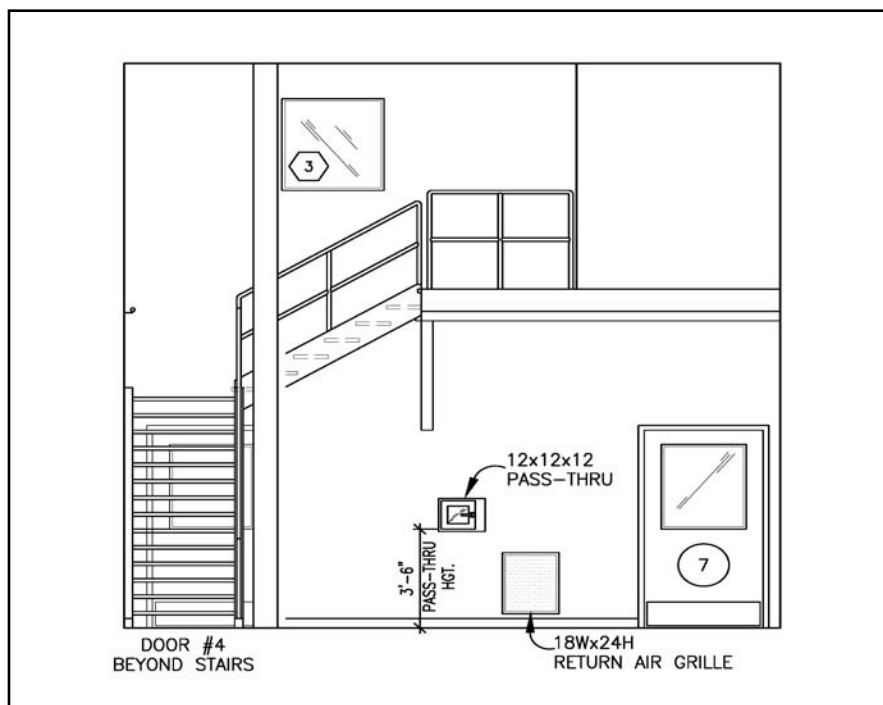


Figure 4. Elevation view showing first and second level process areas.



Figure 5. Front view of the 2,500L bioreactor: This 2,500L bioreactor was designed more vertically than horizontally to take advantage of the 25-foot high bay ceiling space. Most utility piping was routed above the facility and down to process equipment, thus reducing much of gray space otherwise needed for utility piping at the ground level.

The final design incorporated two identical bioreactor trains with 50 L, 300 L, and 2,500 L bioreactors, and met the project requirement for multi-use and concurrent manufacturing capabilities.

Facility Design Challenges

Early in the project, three major design challenges were identified that could affect the project timeline: A) limited space; B) integration of a new facility into an existing operating facility with limited utilities; and C) a design that would permit the manufacturing of multiple products simultaneously. In the following section of this article, the approaches to overcoming these challenges are discussed. Since the limited project timeline was managed through good project planning, execution, commissioning, and validation, it was not included in the scope of this article.

A) Limited Space

The initial estimation of space needed, as compared to the available site, quickly revealed a tight space constraint. Listed below were some of approaches taken by the project team to overcome this challenge. They were achieved from both facility design and process design:

A-1. Prioritizing space planning: Setting the priority for each functional area helped the design team to resolve conflicts resulting from areas competing for the same limited space. After evaluation of the area needs, it was determined that the process trains received the highest priority, the cold rooms and support labs were given mid-range priority, and the ancillary spaces (airlocks, gown rooms, process drainage) were given lowest priority. Early in the design phase, we identified the need for a new process-waste inactivation system dedicated to this new facility. This fea-

ture would allow any waste processing to take place outside the bioreactor, therefore freeing bioreactors for more valuable production time. Listed below are the functional areas identified to be built on site:

- Bioreactor suites
- Inoculum preparation
- Supplement/Buffer preparation
- Analytical support
- Intermediate coldroom storage
- Staging
- Waste processing

A-2. Looking at available cubic feet vs. available square feet: The site location presented limited floor area but ample total volume. With a 25-foot high overhead clearance to structure, the design team had to think vertically instead of horizontally. Large overhead volumes were required within the production suites to accommodate reactor vessels; however, support spaces required minimal overhead clearance. This led to the idea of creating an intermediate second floor level for inoculation prep above the first floor non-production areas (Figure 4).

Narrow profile stairs were installed at the perimeter of the production suite to access the second floor areas, with an airlock located at the top of the stairs for air separation and pressure cascade out of the inoculation prep area. The design team considered the future need for equipment replacement by utilizing a removable modular wall and corresponding removable rail on the stairs to accommodate equipment that could not travel through the airlock.

A-3. Be creative in designing the equipment insometric arrangement: To further alleviate the space shortage on the ground level, the equipment suppliers were asked to design their equipment within a given footage. For example, our bioreactor supplier designed the 2,500 L bioreactor vertically, rather than horizontally, to take advantage of the 25-foot high bay ceiling space (Figure 5). For mobile equipment, the width and height were often dictated by door openings and minimal clearance requirements from the floor. The length was often dictated by the turn-

ing radius required for maneuvering a unit within the suites (Figure 6). All these restrictions were defined on paper so that we could accurately create the equipment user requirement specification. The suppliers were notified of this requirement in the Request for Proposal (RFP) documentation. The dimensional constraints forced the suppliers to explore as many different design options as practically possible.

A-4. Creating an effective floor plan:

The dimension of the equipment cannot be reduced without end. When a minimal design limit was reached before it started to incur a cost impact, the floor plan was manipulated to accommodate the particular equipment's needs. Creating an effective floor plan and designing the equipment configuration was an iterative process. Each variable was analyzed and fed back to the other to ensure that the final design accommodated both floor plan requirements and process efficiency.

These examples illustrate the trade-offs that occurred during this process: The initial process design called for a permanent, centralized, clean-in-place (CIP) station, with fixed pipe distribution loops to the bioreactors. This design offered the best convenience for performing CIP operation. However, the initial space estimation for housing the CIP station and the distribution loops was very space prohibitive, and it would require elimination of one of the functional rooms, which was unacceptable. In the end, the design team gave up the "permanent station" option and accepted a "mobile CIP cart" option. This alternative freed much-needed space within the facility. The cell culture team agreed to sacrifice some operational convenience, and the floor plan was modified to accommodate the maneuvering needs of the mobile CIP cart.

In another example, a permanent steel platform was initially proposed to provide access to the 2,500 L bioreactor. Unfortunately, the support structure of the platform would obstruct the ground accessibility of process equipment to the bioreactor. The platform option was eventually replaced by the mobile manlift option. In addition, a structural

beam with columns was integrated into the floor plan to support a half-ton hoist for use with each 2,500 L bioreactor.

In both of these examples, process needs gave way to facility needs. However, in many other situations, the facility yielded to the process requirements. For example, overhead clearance on the 2,500 L bioreactor required significant ceiling height in the production suites. The design team accommodated this requirement by installing the cleanroom ceiling tight to the building structure near 25' AFF. This forced all of the mechanical systems, excluding terminal HEPA filtration, to be located on the roof directly above the cleanroom areas. Outdoor air handling and condensing equipment was selected to create the cleanroom environmental conditions of temperature, humidity, cleanliness, and pressure cascade. Significant portions of the ductwork distribution system were located above roofline to minimize conflicts in the limited interstitial space.

A lack of gray space in the program, coupled with limited overhead interstitial space for process piping created a challenge for utility distribution to the

bioreactors. Ultimately, most piping was routed above the facility and down to process equipment.

A-5. Use of modular walls to minimize the footprint of the structure and maintain maximum usable space: The design specifications called for room finishes that were smooth, durable, and cleanable. The floor plan required maximum use of space for process needs. To meet these criteria, the design team based the architectural features of the project around a pre-engineered modular system. This system provided minimal wall thickness, thereby eliminating the traditional space losses due to "stick-built" construction methods. In addition to providing a net benefit to usable space, the modular architectural system delivered factory generated room finishes. These predictable details not only provided benefits to the validation timeline, but also created the opportunity for clean construction and alleviated trade congestion on the project site. Consequently, we significantly improved the field construction timeline.

By utilizing the modular wall system we could easily introduce creative floor



Figure 6. Mobile Clean-In-Place (CIP) cart: The dimension of the cart was carefully sized for easily maneuvering the unit within the suites.

plan arrangements that maximized usable space. The diagonal separator wall between the entry gown room and the buffer prep room is an example of floor plan engineering that focused on proper flow of materials while maintaining code-compliant movement of personnel. Swinging doors were eliminated and replaced with high speed rollup doors in areas where door swing could not be accommodated (*i.e.*, material airlock).

B) Integration Challenges

Even though the project site provided direct exterior access and less impact to existing spaces, significant challenges existed. As shown in Figure 1, the location helped to protect the existing process operations during construction, but in turn, isolated this facility from existing infrastructure systems within the building. Listed below were some of the key issues that we faced.

B-1. The construction area was limited within perimeter walls: No additional space surrounding suite was available for use by construction team. Even though the project site was afforded access to two perimeter building walls, no additional space within the facility could be used for staging of materials or logistical support. The construction team opened up two 8' x 8' entrances on both north and east walls of the construction site for movement of construction materials and equipment. These temporary openings provided access to the project area from the surrounding parking lots which served as staging areas during construction.

Significant underground changes were required for the project's structural requirements and drainage needs. Fourteen structural footings and hoist beams were created within the footprint of the scope area for support of the second floor areas. In addition, two large

bioreactor vessel footings and a pit (18' long x 6' deep) with all process drain lines were created for the waste inactivation system. The project team rotated from location to location through the process steps of cutting, excavating, forming, and backfilling each of these structures with limited access to the outside. These steps were performed with small-scale equipment by skilled labor forces, all focused on creating minimal disruption to the surrounding operating spaces.

B-2. Construction took place during ongoing operation of the existing facility: Construction debris and noise were significant challenges during the demolition and structural installation segments of the project. Temporary construction barriers were installed around the premises of the project site and the transport hallways to protect the surrounding areas. During construction, only limited access was granted

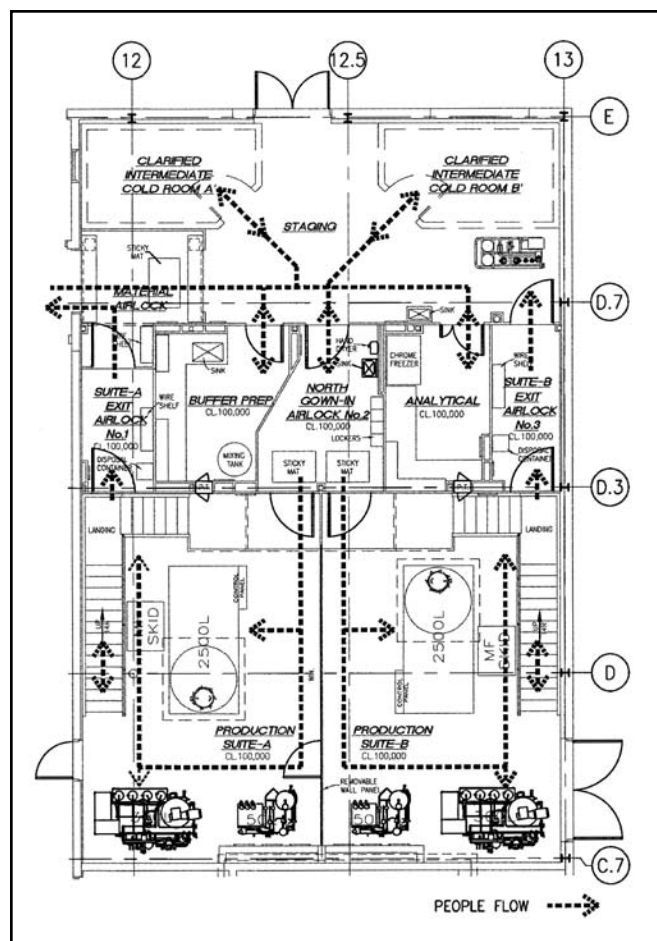


Figure 7.1. First floor personnel flow in the large-scale bioreactor facility.

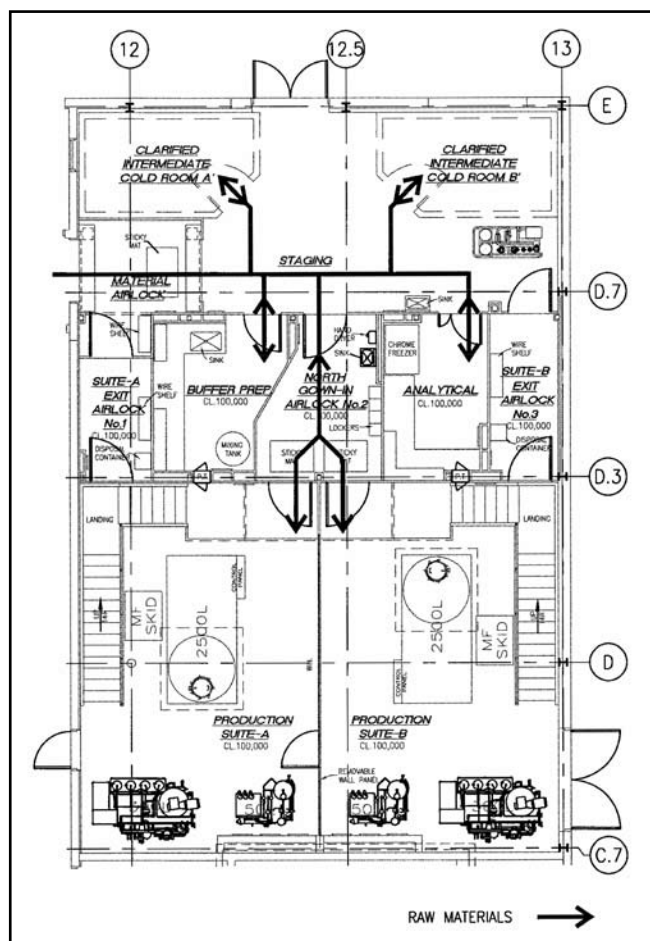


Figure 7.2. First floor raw material flow in the large-scale bioreactor facility.

ed between the project site and the remainder of the operating facility. Once the heavy structural and mechanical scope of the project was completed, the installation of the modular architectural system was performed under clean conditions, which minimized the impact on the new process equipment and utility systems. Sections of the modular wall system were left out until process equipment was rigged into place, with the final prefinished wall sections simply plugging into place.

B-3. Internal transport issues from cell culture suite to existing purification suites, which are physically separated: Direct piping transfer between cell culture and purification suites was not feasible due to the extent of piping required to link the spaces. This large, dead span would create an unacceptable level of product loss in the transfer, and cleaning/sterilizing functions would be a challenge. Our alternative approach for

this was based on a transport container with an internal sealed product bag. This sealed transport concept facilitated transfer between remote locations and required only a sanitization step before entering the purification suites.

B-4. Lack of process chilled water available for bioreactors: Chilled water capacity within the facility was limited both in capacity and proximity. In an effort to minimize initial project scope and prevent the need for a dedicated process chilled water system, we explored the possibility of utilizing city water for cooling within the bioreactors. This utility was available in sufficient capacity and was closely linked to the project site; however, the city water could reach 60° F during certain times of the year. By working with the bioreactor manufacturer to assess performance of cool-down time as a function of incoming water temperature, we determined that the performance was

within an acceptable range for operation. Therefore, we utilized city water as the source of cooling instead of providing a dedicated chiller to serve the process.

B-5. Limiting existing utility capacity for use: The entire utility infrastructure was evaluated to determine if sufficient existing capacity was available for use. Where the existing capacity did not meet the process requirements, we sought first to expand existing systems. Several upgrades were made to expand capacity, including tapping into the existing single stage, water-for-injection (WFI) still and adding multiple stages to serve the new process, adding a storage tank and WFI distribution system dedicated to the new cell culture suites, adding boiler capacity to the loop, adding a redundant compressed air system, and adding a new, clean steam generator.

The project team analyzed the use of deionized (DI) water to reduce the con-

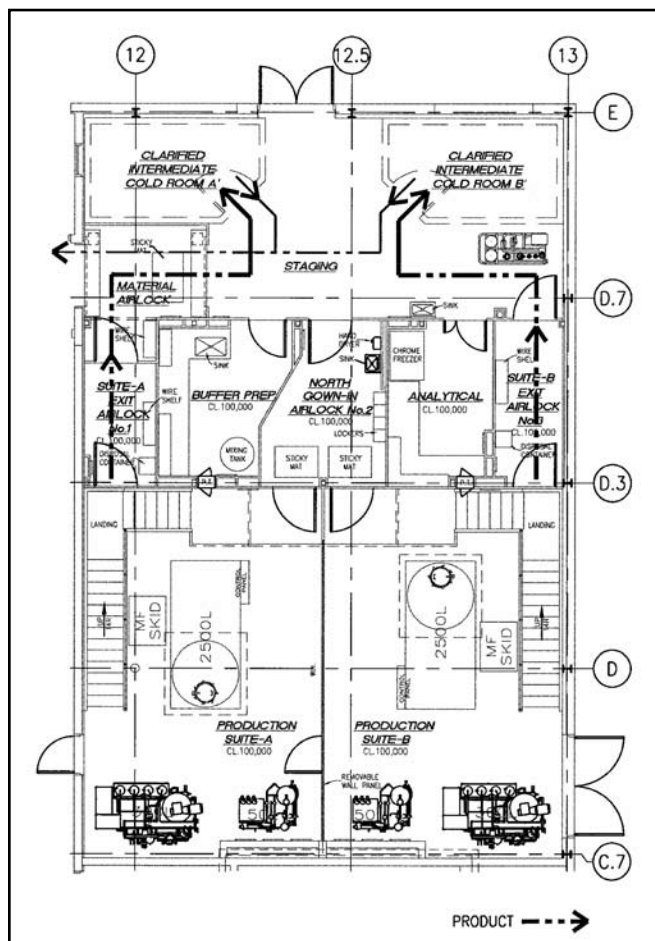


Figure 7.3. First floor product flow in the large-scale bioreactor facility.

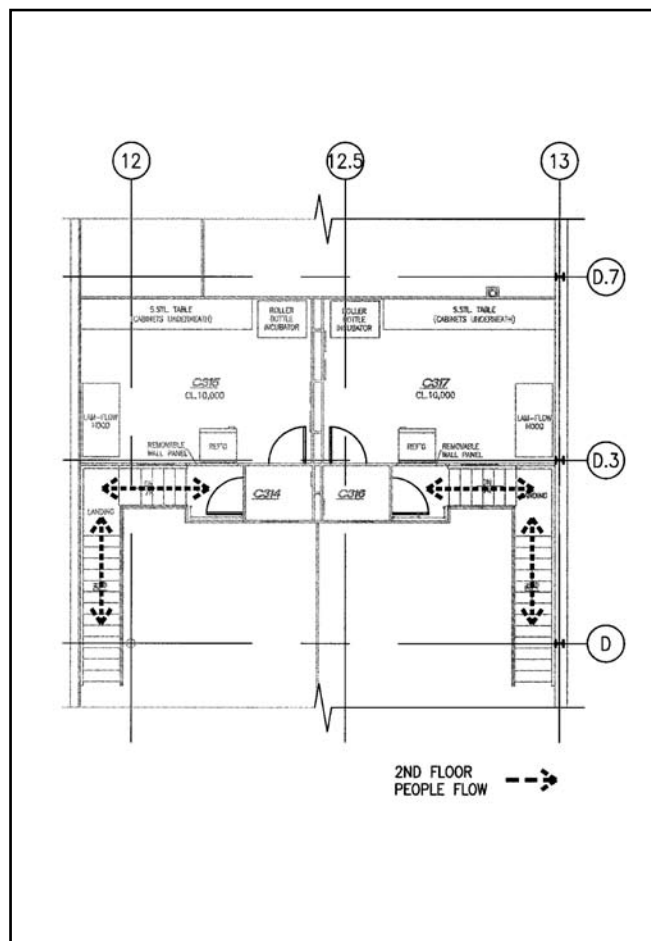


Figure 8. Second floor personnel, and material flow in the large-scale bioreactor facility.

sumption of WFI during CIP operation; however, the cost saving derived from reduced WFI usage did not outweigh the extra cost of constructing, maintaining, and monitoring a separate DI water system. Therefore, DI water was not utilized for the new cell culture suites.

C) Multiple Products and Concurrent Manufacturing

Numerous challenges exist when processing multiple products concurrently within a facility, particularly those associated with potential product cross-contamination/mix-ups^{6,7} and utility sizing.

C-1. Independent floor plans: To prevent potential risk of product or processing cross-contamination associated with concurrent manufacturing, the areas in which different products are produced require proper segregation. As a result, two bioreactor trains were architecturally segregated into separate production suites, each with its own entrance and exit (Figure 7.1). The access to the suites is further managed through electronic passkeys to only qualified personnel. Airlocks were located at critical access points serving as additional barriers to control the flow of materials and personnel in the areas. Cleanroom gowning and degowning procedures were followed by production staff before entering or exiting the production areas. In addition, each production suite was further equipped with both a dedicated inoculum prep room and a dedicated intermediate product storage coldbox.

C-2. Independent HVAC systems: The design specifications required separation of airflow between the suites to further eliminate the concern of airborne cross-contamination, so the mirror image production suites were each equipped with their own independent HVAC system. Because the systems were dedicated to each suite, the mechanical design could accommodate recirculation airflow to help reduce the overall utility consumption. Make-up air was drawn from outdoors to provide the appropriate level of fresh air for occupants, to generate the required level of pressure cascade, and to feed the exhaust airstreams exiting the space. This

design approach reduced the operating burden, as compared to a 100% fresh air HVAC system, while still eliminating airborne cross-contamination.

C-3. Design of pressurization to prevent cross-contamination: The bioreactor is designed and operated as a closed system; however, to add another layer of protection to the process and ensure consistent quality of environmental conditions, the production suites and supportive areas were designed as class 100,000 (ISO 8) and the inoculation rooms were designed as class 10,000 (ISO 7). All classified areas were under routine environmental monitoring.

Proper pressure cascade was designed into the HVAC systems to manage relative airflow within the facility. This cascade addressed contamination control and cross-contamination control. Further procedural control was created through the use of door interlocks.

C-4. Independent process drainage: In order to prevent waterborne cross-contamination between suites, we developed dedicated process drainage from each suite to the waste inactivation system. The design specifications required that the inactivation system be sized to accommodate the entire process flow so that no waste processing would be necessary within the bioreactor itself. To avoid potential corrosion of piping by process waste due to extreme pH and temperature, stainless steel materials were utilized for all process drainage.

C-5. Staggering concurrent manufacturing to reduce peak usage:

• Time lag to reduce peaks on usage. A detailed schedule was created for running two bioreactor trains at the same time while sharing boiler, WFI, gas, air, and drain capacity. This analysis prevented us from exceeding our capacity limits during production.

• Limited CIP to one train at a time. This alleviated peak WFI usage.

• Limited SIP to one 2,500 L bioreactor at a time. This alleviated peak steam usage.

• Peak usage vs. operating usage. The bioreactor equipment manufacturer provided only peak usage values for utility sizing. The project team studied and agreed upon diversity factors for

utility sizing in an effort to predict actual utility usage.

Design Results and Discussion

The design outcome of the facility, with its people flow, is shown in Figure 7.1. Figures 7.2 and 7.3 show the first floor raw material flow, and first floor product flow within the bioreactor facility. People enter the facility from the main entrance airlock to the staging area. From there, they can go to the buffer prep room, the analytical room, the clarified intermediate coldboxes, or enter production Suite A or Suite B via a common north gown-in room. Once in the production suites, people can exit the production suites via respective exit airlock or access the second floor inoculum prep rooms by staircase, as shown in Figure 8. The separation of the entrance and exit corridors of the suite ensures a one-way traffic pattern in and out—a necessity for enhancing the cleanroom environmental condition and helping prevent possible product cross-contamination across the two suites. It should be noted that the double doors at the north wall of staging area and east building wall of the Suite B were installed for construction access and were since sealed off after completion of the project. The two doors, one between the two suites and the other on the west wall of Suite A, are for emergency exit and are tightly sealed, remaining closed during normal operation.

In conjunction with the engineering controls that were built into the design (as previously described), several procedure controls were also developed to further guard against possible product cross-contamination and potential mix-ups. Fully validated cleaning procedures are followed to ensure that the equipment and facility are clean from operations. A validated facility sanitization process maintains the facility at desirable microbial levels, which, together with the other environmental conditions, are routinely monitored. A product changeover procedure that is supported by a validated cleaning method and an effective sanitization procedure prevent product carryover from lot to

lot. Procedures were also implemented to train, qualify, and regulate the operators rotating between the two suites.

A cGMP documentation practice, with a good labeling system, is in place to further prevent the potential material and product mix-up. Taking the above-mentioned integral approach of both engineering control and procedure control, we believe that the risk of potential product contamination, cross-contamination, and mix-ups can be prospectively minimized or eliminated from our multiproduct facility.

Early in the conceptual stage of this project, flexibility was built into the design of process, equipment, and facility. The process was developed utilizing as much standard, off-the-shelf material, parts, and software as possible. The bioreactors were designed as a closed system and meet BL2-LS containment per NIH/CDC guidelines. This design standard far exceeds the biosafety requirement for manufacturing of monoclonal antibody. A dedicated waste inactivation system enables automated biowaste decontamination ensuring safety compliance to BL2-LS level or higher. All of this design flexibility was aimed at building the facility to be easily and readily retrofitted to receive other

mammalian cell types, including those for vaccine production.

The facility meets the challenges for capacity, flexibility, contamination control, cost-effectiveness, and cGMP compliance. The facility has been fully validated and currently in use for Phase III clinical production of Epratuzumab.

Conclusion

Designing a cGMP cell culture facility is a complex process that requires effective planning and strong leadership to integrate many—often conflicting—requirements from various functional groups, into the overall design. Our experience in building Immunomedics' cell culture facility was no different. Success was delivered on this project by combining strong support from the corporate quality team with creativity, perseverance, and design expertise from the project team and our contractors. Such a project experience has left us with high expectations for future construction projects.

ACKNOWLEDGEMENTS

The authors are thankful to the Immunomedics board of directors for their strategic guidance and support from various functional departments of cell culture, valida-

tion, quality assurance, financing, and regulatory. The following Immunomedics team members deserve special acknowledgement: Jerry Shi (Validation), and Brad Stasny (Cell Culture Production). Thanks to the team of AES Clean Technology, Inc.: Ralph Melfi (Project Development), Bob Short (Project Management), Bob Bright (Architectural Engineering), and Kevin Koffke (Mechanical/Electrical Engineering), for their contributions to the project. A part of this work was financially supported by a grant from New Jersey Economic Development Authority.

REFERENCES

1. Levin J. Facility Design for Biotechnology Products in the new millennium. *BioProcess International* 2005; 3-1:18-23.
2. Code of Federal Regulations, Title 21, Part 600, Subpart B.
3. Code of Federal Regulations, Title 21, Parts 210 and 211.
4. Guidance for Industry Q7A. Good Manufacturing Practices Guidance for Active Pharmaceutical Ingredients, Center for Drug Evaluation and Research, ICH, August 2001.
5. NIH Guidelines for Research Involving Recombinant DNA Molecules, Appendix K, Physical Containment for large scale uses of organisms containing recombinant DNA molecules, April 2002.
6. Roscioli N, Vargo S. Facility design issues—a regulatory perspective. In: Rathore AS, Sofer G, editors. *Process validation in manufacturing of biopharmaceuticals: guidelines, current practices, and industrial case studies*. Florida: CRC press; 2005. p 329-393.
7. Hill D. Current regulatory issues in facility design. Slides presented at University of Maryland Baltimore County; 2005 Spring; Baltimore, MD.

Facilities for Mammalian Cell Products

From Design Through Operation

9th Annual Meeting

Hilton North Raleigh ☞ Raleigh, North Carolina ☞ October 16–18, 2006

Featuring a tour of

BIOLEX
THERAPEUTICS



Sponsored By

MILLIPORE  Life Sciences

Topics Include:

- Multi-Product Facilities
- Material & Personnel Flow
- Product Change Over
- Project Management
- Organizational Structure
- Regulatory Issues / Licensing
- Containment Issues
- Plant-Wide Automation
- Modular System Construction
- Process & Utility Systems
- Validation Strategy
- Paperless Manufacturing

To Register Now: Visit us at www.wilbio.com, Call us at 757.423.8823, or Email us at info@wilbio.com