

This article presents a detailed narrative on the design drivers and delivery methodology for Genentech's recently completed fill-finish facility in Hillsboro, Oregon.

Just in Time. An Approach for a cGMP Fill-Finish Facility

by Andrew Cunningham

Designing and constructing a technically complex yet efficient, fully integrated fill-finish facility is no small task. The timeframe can be long, the costs can be high, and the stakes with numerous stakeholders involved, can be even higher. But this case study of one biotherapeutic company's new fill-finish facility in Hillsboro, Oregon, provides practical insights and steps for success for "just in time" delivery of a fully operational and cost-effective ground-up manufacturing facility in a shorter timeframe than typically witnessed by industry standards. The end goal of this project was to bring a licensed fill and finish facility online to ensure reliable supply of product to patients through innovative design, sustainable technologies, and effective use of capital. By all accounts, the "just in time" process and mindset facilitated this, laying the groundwork for a shift in the way the industry approaches and completes complex projects.

Background

Prior to constructing the new fill-finish facility, the company had three existing manufacturing

facilities online, all of which were in northern California. The building of the new facility was driven by the company's need to address specific fill and finish operational conditions: lack of supply chain capacity; the risks associated with all operations concentrated in a single, high-risk seismic zone; and operational inefficiency, due to production in multiple facilities. In addition, locating in Oregon provided a favorable tax climate as a single-sales factor state, which bases its sales tax upon profit apportioned to revenue of in-state sales relative to total sales. When licensed, the facility will be used for the filling and packaging of commercial biotechnology therapeutics from bulk drug substance and will assume commercial filling operations from another of the company's facilities

The facility was to be designed and constructed in two years with qualification and licensure taking an additional 18 months. Planning for the project began in 2006. Forward-looking in scope, the company required that the facility include space for expansion to accommodate increased production and to be responsive to future needs and new product lines. The facility had to meet

Figure 1. The construction sequence of the facility was governed by completing B5 first, followed by B4, utilizing the high bay space for material storage followed by the manufacturing, utility, and administration buildings.



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current and unforeseen regulatory requirements for both international and United States markets, and be capable of processing both liquid and lyophilized biopharmaceutical products on an annual basis.

Other goals for the project were to build only what is required to support the company's immediate fill and finish needs, employ lean principles with limited redundancy throughout the process, minimize on-site inventories based on high turnover rates and shortened cycle times, and integrate off-the-shelf, demonstrated technologies. Leveraging equipment technology to minimize construction costs and improve quality control to satisfy multiple markets was an important tenet of both the design and engineering phases of this project.

Meeting Conditions, Achieving Goals

Part of the facility's fast-track success was the clear vision company executives laid out before initiating the design of the facility, as well as the initial engineering work the company completed on the front end; this was crucial in adhering to the fixed budget the company set for the new facility. With the high-level scope of the facility already mapped out, the design teams began to develop the basic design and core elements, breaking the big picture into smaller pieces of a puzzle.

In relation to the fill-finish facility, "just in time" is indicative of both the lean manufacturing practices utilized within the facility, as well as the design and construction processes. It also incorporates strong partnering with local government for fast-track approvals and ensuring excellent relationships and adequate high skilled local labor. As the design process overlapped with the construction, as soon as information became available, it was handed to construction crews for

implementation. Due to the speed of the construction timeline, the project was essentially divided into smaller pieces, defined by construction trade.

While the goal was to complete construction of the facility within 24 months, the timeline was driven, in part, by Oregon's climate, where the rainy season lasts November through February; in short, the building needed to be watertight by the end of October 2007. Additionally, toward the conclusion of the Basis of Design, the company added a distribution center to the project, which corporate executives required to be completed first to satisfy immediate supply chain requirements for storing and shipping finished product being produced by Contract Manufacturing Organizations (CMOs).

This presented an interesting challenge. Given the six-month lead on steel at the time and the constrained overall schedule, a steel order was placed in March 2007, using an estimate of the gross tonnage needed for the project, while final plans were still being developed. With the mill order in process, the design team began focusing on the detailed structural design in line with the intended construction sequence. In tandem with this effort, the architectural team focused on the exterior envelope design, developing alternate options for the review of company executives and the City of Hillsboro. The City successfully partnered with the company, allowing fast track approvals at each stage of the project. In addition, the local Labor Council collaborated early on to provide highly skilled trade labor. Ultimately, working in close conjunction with the subcontractors, the exterior skins of the buildings were erected in quick succession to the completion of the steel frame, moving sequentially from (Figure 1 - building aerial) Building 5, the distribution center; to Building 4, the warehouse; then to Building 2, the three-story cGMP-manufacturing facility at the center of the campus; and finally Building 3, a utility building, and Building 1, the main office administration area. From initial ordering of steel to commencement of exterior envelope, the process took five months.

While team leaders were assigned for every technical and functional area of the facility, they relied on the expertise of their consultants and vendors, allowing subcontractors to work within the cost models and design parameters to provide available goods and materials.

Regular meetings, including a minimum of 17 standing weekly meetings, allowed work groups to collaborate, troubleshoot, and prioritize issues within the larger scope of the project. These meetings were organized in a hierarchy of management; project managers and major decision-makers came together in one meeting; work groups, such as those for structural engineering and architecture in another; and design process engineers in yet another. This allowed issues and concerns to move laterally as well as vertically without slowing down certain parts of the ladder with unnecessary information and details. In all, by eliminating handoff points, minimizing work-in-progress staging areas, and passing control of the plan details to specialized design teams, the overlap of the exterior construction and design-bid-build phase of the process manufacturing facilitated an integrated workflow to ensure on-time delivery.

Project Statistics

- Five months from start of design to groundbreaking
- Goal: 24 months from concept design to mechanically complete; actual time: 22 months
- Designed 1,500 square feet per day
- 17 weekly standing meetings covering company's core team review, facility, project management, process, Civil, Structural and Architectural (CSA), mechanical, electrical, plumbing, site, design team coordination, multiple trade discussions, individual work groups, and intermittent all hands meetings
- 1 million construction hours worked
- 520 highly skilled and motivated trade workers on site at height of construction
- Local government collaborative accelerated approval process
- Mechanically Complete, Operationally Qualified (MCOQ) in 4.5 months within the given time frame.

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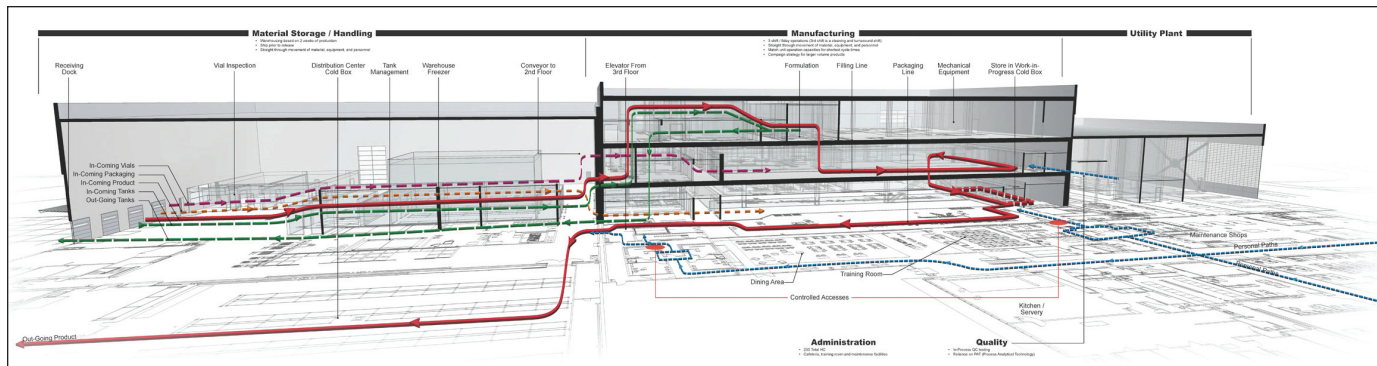


Figure 2. The uni-directional flow of the finished product is represented by the red line with raw product and materials entering through the warehouse, moving into the three-level manufacturing building and then stored in the distribution center prior to being shipped.

Additionally, commissioning and qualification reviews were started early in the design process with the company's quality assurance group actively involved in the development of the plans; as such, there was no direct hand-off from design-build to the validation process. Validation occurred as an integrated part of the design and construction process, where Factory Acceptance Tests (FATs) were leveraged as part of the validation strategy.

As previously mentioned, the company had three specific operational goals to achieve with the construction of the fill-finish facility. How these goals were achieved is outlined in detail.

Supply Chain and Operational Efficiency

Supply chain and operational efficiency are inextricably linked within the project as evidenced by Building 2's top-to-bottom workflow schematic - *Figure 2*. At a high level overview for this article, supply chain relates to the global supply of product to patients around the world, from raw material supplies delivered to the facility for processing or use in the manufacturing process, and distribution of finished product from the facility to patients. Operational efficiency is the internal organization within the facility and the work patterns of people, raw materials, products, or waste streams in support of the broader supply chain.

Location Risks

To mitigate the location risks associated with having all the company's original manufacturing facilities in an active seismic zone, among other factors, Genentech conducted an extensive site analysis and selected Hillsboro, Oregon as the facility's home. The location offered the ability to serve the West Coast market and remain in proximity to the company's main campus in California. A suburb of Portland, the location provided a high quality workforce, good business relationships, and a great place to live for facility staff. The community also had a welcoming, collaborative political environment conducive to the project's fast-track approval process, and offered tax incentives and rebates for the use of energy-efficient technologies and training programs.

General Design for the Facility

Design studies revealed the need for a 300,000-square-foot, three-story, super-block building, a single building that housed all the facilities the company needed under one roof, instead of multiple buildings scattered around the campus. This design accommodated a single, continuous, straight-through process of materials, equipment, and personnel, as well as matching unit operation capacities for shortest cycle times. Manufacturing also required a campaign strategy for larger volume products.

In addition to manufacturing, the building needed to contain warehouse and distribution spaces, a quality control laboratory, administration offices, and a central utility building. Massing the building into one super-block reduced the travel and circulation time between different areas of the building. It also condensed the building's footprint to save construction dollars.

Product Flow

The diversity of the company's biopharmaceuticals portfolio proved an interesting challenge; the design needed to accommodate flexibility in vial sizes, along with capacity. To respond to the supply chain capacity issues, the new facility was sized to accommodate three production lines with mixed 3cc to 100cc vial capacities. The facility's manufacturing sector included two filling lines with shell space provided for a future syringe line and two future freeze dryers. The manufacturing process moves materials, equipment, and personnel in a simple uni-directional flow, reducing the chance for cross-contamination. This allows for the product to move in one direction through the fill-finish process rather than backward and forward in an inefficient manner.

At the company's California headquarters, where the manufacturing process was long housed, operations were developed and spread out through the site, creating inefficiencies. By contrast, the new fill-finish facility's efficiency begins at the gate with a rational flow of vehicles onsite to assist with clear security checkpoints in and out of the facility. As for materials, upon arriving at the receiving dock at ground level, frozen product is moved via elevator to the third-floor freeze-thaw area and formulation space, and vials after inspection are delivered to the second floor.

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Once the product is formulated, it moves down to the second-floor filling line (Figure 3); this process design element leverages gravity feed, a critical component so that every last drop of product is utilized. Following inspection, the product then moves down to the first floor where the filled vials move to the packaging line. Prior to the packaging line, Work in Progress (WIP) cold storage boxes are available for filled vials awaiting packaging; this eliminates the need to temporarily transport the product to the cold box in the distribution center at the end of a shift. The finished product exits through the cold box to the shipping area of the distribution center; so all

Delivery at a Glance

Delivery Goals

- A single point of responsibility for budget and scope control – integrate general contractor into process
- Facilitate early shipping of product – design and construct distribution center in 16 months
- Schedule required interior construction to proceed in winter – complete the building exterior before rainy season
- Phased validation of equipment to support licensure – sequential handover of process systems
- Maintain the aggressive construction schedule – integrate undefined long lead items into the building

Delivery Strategy

- Approved plan to meet function and budget – early review and fix plan layout
- Quality Assurance Approval – sign off on process and equipment flows
- Best value delivery team – bid individual scopes based on URS/design packages
- Accelerate and motivate workforce capacity to meet schedule – engage multiple design-build subcontractors to develop scope
- Stand alone design packages – identify construction sequence
- Communication strategy – robust meeting schedule
- Integrated design team – Building Information Modeling (BIM)/roundtable meetings/review process
- Ability to control cost; individual budgets were allotted to different parts of the project, such as the exterior skin, the landscape, etc., which gave the contractor and designer a better perspective on the money available and what could be done with it.

Operational Efficiency

Process designed to maximize operational efficiency by building in:

- Single Point Location
- Production Capacity
- Flexibility
- Quick Batch Turnaround
- Equipment Technology



Figure 3. The fill line incorporated depyrogenation through capping within the isolator, including sterile stopper loading and automated lyo loading/unloading with all controls through an HMI.

materials, raw and finished, enter and exit through the same side of the super-block building.

Right-Sizing

To support the just-in-time methodology of the facility, staging areas were efficiently sized, circulation zones were created, and equipment and effective personnel adjacencies were established. For instance, fill suites and inspection areas were positioned adjacent to each other with view windows to facilitate easy communication and monitoring of the process, and the facility was designed so FDA inspectors can easily view the technical areas without needing to gown up.

The adjacent warehouse was right-sized for supply expectations to keep a two-week supply of raw materials; this minimizes on-site inventories based on high turnover rates and shortened cycle times. This also fulfills the company's goal of risk mitigation, be it a shortage of products and raw materials or a localized breach, such as an earthquake in the area of the company's headquarters, without stockpiling product.

Planned Expansion

On the north side of the building, expansion space was allotted to accommodate two additional production lines. This was a critical component of the company's recent merger with another major pharmaceutical company. Prior to acquisition, a supply agreement between the companies committed this firm to producing fixed quantities of three specific pharmaceuticals sold throughout the world by the acquiring company. Additionally, in 2007, the partner company completed a fill-finish plant in Switzerland. These sister facilities were designed to be compatible with one another and serve as back-up should either need to go offline.

Operations required three shifts per day with a five-day work week. The third shift was responsible for cleaning and turning around the production area for use during the following day's first and second shifts.

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Figure 4. Isolator technology provides improved user comfort, due to reduced gowning requirements, while maintaining critical environmental control.

Technology Solutions

Technology plays a large role in any complex pharmaceutical manufacturing facility, and at this location, it is an integral part of the design. One of the company's initial goals was to leverage off-the-shelf, demonstrated technologies to both minimize construction costs and improve quality control to satisfy multiple markets, which were important tenets of both the design and engineering phases of this project. It also required entrusting subcontractors, equipment vendors, and other partners to take the lead on individual components and systems to assist in streamlining the facility.

Design

In determining the needed technology for the facility, an early and detailed definition of the equipment URS was developed by the company's process engineer leads; the vendors then provided solutions and the project team helped to integrate all the needs. Validation and qualification were phased by system as each building block became mechanically complete.

Maintaining sufficient resources and leveraging the Factory



Figure 5. Inspection lines are visually connected to the fill suites to ensure ease of communication. Within the inspection suite, there is the capability for both automated and manual inspection.

Acceptance Test (FAT) process to expedite IQ/OQ accelerated the turnover process.

Isolator Technology

To reduce the size of the class 100 areas, isolator technology was integrated into the facility. Isolator technology ensures environmental control and reduces contamination risk during aseptic processing. Key features of this filling system include mass flow technology and a filtration skid that can be cleaned and sterilized in place. In addition to accommodating vials, isolator technology offers lyophilization capability - *Figure 4*.

Because the last facility the company built utilized Restricted Access Barrier Systems (RABS), isolator technology was new to the firm. Based on this, every effort was made to thoroughly understand potential product implications so the isolators could be utilized to their fullest capacity. Grade A isolators in the fill suites minimize personnel gowning time and maximize operators comfort. The facility has segregated integrated isolator fill lines with one liquid/lyophilization line providing overlap fill operations.

Additionally, isolator technology offered numerous cost benefits, including lower fill room air classification with reduced HVAC costs and less environmental monitoring. Contamination risks are also reduced, eliminating human intervention in a critical zone and increasing sterility assurance. Isolator technology also hastens turnaround time for cleaning, sterilizing, and parts change-out.

Quality Controls

Quality control is absolutely critical in the pharmaceutical industry as is knowing where your product has gone once it heads out the door. Operational requirements for ensuring quality include in-process testing. At the fill-finish facility, fully automated inspection lines were built in to the ends of the fill lines; manual inspection is also an option. The rate for the auto-inspect line is equivalent to the fill rate; the semi-automated line is 30 vials per minute. By comparison, the manual inspection line moves at a rate of five vials per minute - *Figure 5*.

Additional quality controls include the use of SAP technology to track filled and finished products awaiting shipment from the distribution center's cold box. This provides a clear record of the product and its status should quality issues occur.

Other Solutions

The just-in-time nature of the operations required minimizing space requirements and maximizing labor efficiencies, other technological solutions included equipment integration and streamlined production efficiency. For instance, high bay storage racks served by wire-guided forklift trucks keep raw materials consolidated in a smaller footprint. A direct supply of vials moves from the warehouse through a conveyor system to the fill area, reducing handling. The facility was designed to be paper-free; digital controls and the use of digital tablets allow supervisors to be close to the production line rather than working in remote offices. With the knowledge that

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Figure 6. The main arterial circulation street in the administration building provides natural daylight into the interior spaces along with providing visual connections between the lab and office areas.

staff would be working in controlled areas, combined with the restrictive winter climate, it became important for the facilities' culture to provide open, interactive spaces - *Figure 6*. The main spine through the administration building and large cafeteria seating area, named the Great Hall, with its fireplace and capability for large-screen projection, are envisioned as key social hubs to provide the workforce with a refuge for relaxation - *Figure 7*.

Budget and Savings

In total, including land, fees, construction, equipment, design, and in-house staff costs, this fill-finish facility cost \$400 million. Relative to industry standards, this price point is within the bounds of what is expected for a project of this size and scope.

To create a target budget, first the scope of the project was



Figure 7. The Great Hall was conceived to provide a collaborative and community building environment incorporating multiple amenities. Functions include the cafeteria seating area, training room break out space, viewing windows in the manufacturing building, and a fireplace with a large format projection screen.

established based on satisfying the company's operational and business needs; from there, high-level area requirements and equipment lists were developed. A fair market value was then assigned to needs to determine a target budget. Through the early stage of the project, the overall needs and scope were refined before fixing the final goals, resulting in the actual budget to further develop the project. By employing lean principles in the development of the building and operational needs, the project was engineered to deliver best value.

To reach "best value," changes needed to be made along the way. This project was set up with a budget by system; a fixed amount of money was allotted to the exterior skin, the finishes, the landscape, and more. This compartmentalization made for more efficient decision-making during design and construction and helped strike a balance between budget and schedule.

Some times budget ruled, and sometimes schedule. For example, it may have cost a bit more to get the distribution center up and running in 16 months, but the benefits outweighed the costs so schedule was the driver there. Additionally, more time could have been spent in designing the structural system, but it was critical to get steel fabrication and erection started so the building could be made watertight before the winter rains. This resulted in using steel that was readily available and not specifically rolled for the project, which had schedule benefits. Conversely, some items of equipment could have been procured cheaper, but given the operational needs or quality goals, there was value in spending more. Prior to final sign-off on the interiors, the project had to save \$6 million, resulting in cost cutting of some of the systems and finishes in the building. Here cost became the driver in hitting an established budget.

All this begs the question: What were the cost savings in this fast-track approach? Initial savings were realized for the design-portion of the project. The company solicited a bid for only design early in the process before deciding to go design-build, saving the company more than \$10 million. Other savings achieved relate to the schedule; the project could not have been achieved in the same time frame if a sequential design-bid-build strategy was implemented. For example, by getting the distribution center done well before the completion of the remainder of the facility, the company was able to start shipment of product sooner. While there may not have been cost savings identified in construction, there were enhanced occupancy benefits resulting in revenue.

Lessons Learned for Success

In the end, design and construction of the facility was completed in less than 22 months, two months prior to the final deadline and nearly eight months faster than the industry average - *Figure 8*. At the peak of construction, there were more than 520 workers on site. These workers surprised even the company's longtime project staff with their capacity to work through the most severe weather to "get their job" done in furtherance of the project. It is a true tribute to the collaboration with the local trades that this project was delivered ahead of schedule.

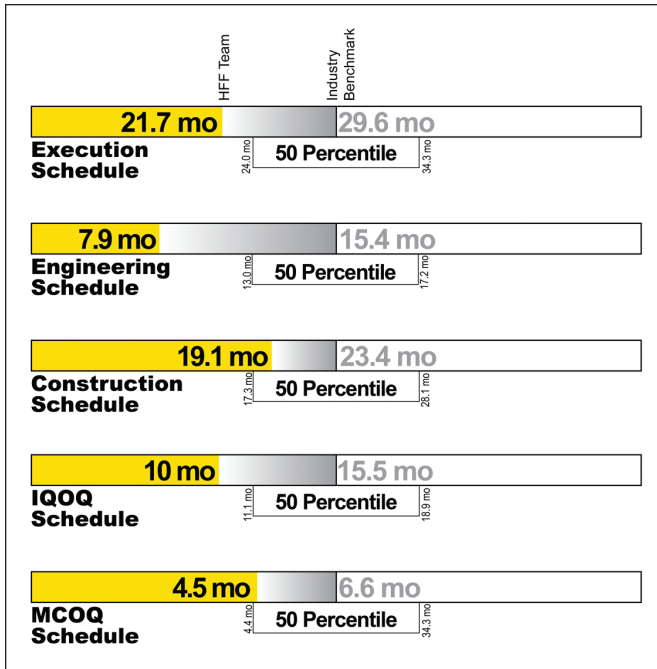


Figure 8. The design-build relationship facilitated an accelerated delivery process resulting in completion within the top 80th percentile of industry standards

The facility has already shipped more than one million vials of biotherapeutics through the distribution center, which has been fully operational since July 2008. While commissioning and qualification reviews were started early in the design process and occurred as an integrated part of the design and construction process and FATs leveraged to validate equipment before coming onsite, full validation of the facility's system remains ongoing as planned for in the original schedule.

In support of the accelerated pace of work, the tight turn-arounds, and the sheer number of decisions made across all levels, the following are seven lessons that helped all parties involved achieve success:

1. A Team with a Can-Do Mentality

In its team selection process, quality, their ability to meet regulations, and price were only cursory parameters for the evaluation and selection of design and construction partner. The company sought designers and a contractor who would be collaborative and innovative in the way they worked and how they worked together. In order to create solutions in a fast-paced project, it is critical to have a team approach rather than a number of individual groups working in separate silos. For solutions to be explored and options presented to the client, all team members had to be working toward a common goal, not at odds with one another. Included in this team approach were regular defined interaction and updates with both local government and labor trades to keep them aware of and to advance project goals and schedule deadlines. In the end, the chosen contractor, which had never done a facility of this magnitude, was selected as it brought the best value to the table with all these parameters, but particularly innovation and collaboration in mind.

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2. Clear Project Goals and a Strategic Vision

In a visioning session at the start of the project, the facility director explained the building's function of producing cancer-curing therapeutics and cited examples of how products produced in the facility would save lives. The notion that the faster the building was completed, the more lives could be saved was a powerful one. This single act identified that it wasn't just about building a building, but coming together as a group to provide a solution to improve the quality of patients' lives. The facility director's continued involvement in creating a project vision was critical to buy-in by the local community. To that end, there were many clearly identified milestones along the path, which were shared with key community stakeholders to keep them aware and help guide the process, chart progress, and maintain budget control. If any of these items began to deviate from the desired course, a recovery plan was put in place to realign the goal.

3. Clear Decision-Making Process

In a project of this size, there were many disciplines and people required to execute all the necessary tasks; it was important to make sure that no one person became a bottleneck in the process. Sometimes there may be competing goals, be it from a budget, schedule, or function point of view. The project structure was organized with tiered levels of decision-makers, corresponding to the various discipline groups ranging from process equipment to quality to construction and design with strong alignment and interactions with legal, corporate relations, and government affairs. Within each corporate engineering group, various levels of oversight existed with one level reporting up to another should a decision not be attainable. Ultimately, the company's core team had the ability to sanction changes and resolve project-defining issues.

4. Clear Roles and Responsibilities

Given the scope and schedule of the project and once the basis of design was defined, it was imperative that a "divide and conquer" approach was adopted. The design disciplines operated in work groups to develop each of the scopes, and then met on a regular basis as a large group to collaborate and review interdisciplinary coordination. Each group had a clear development schedule with milestones that were tied into the integrated construction strategy.

5. Balance Cost vs. Function for all Design Solutions

Although the phrase 'least cost scope' was repeatedly used, it also was imperative to align the budget allocation with the functional requirement. Not all items were created equal and having a hierarchy of equipment, spaces, finishes, and materials to work with not only resulted in a judicious use of resources, but also added to the richness and variety of the environment. Designing appropriately was as critical as maintaining budget.

6. Phased Sequencing and Schedule Execution

A key strategy was having the contractor engaged early in the process as a single point of contact that understood the project goals and drivers. The design team collaboratively designed the schedule with the contractor to benefit these goals. This resulted in a distinct approach to engage the construction process, harnessing the abilities of the team to hasten the overall schedule and meet the vision by allowing a fast acceleration of the workforce.

7. Flexibility in Solutions

Satisfying a fast-track schedule requires flexibility with the design solution, budget application, and schedule impact. The team worked to balance all these items, while still addressing the least cost scope directive. Function was a key driver in all decisions, along with availability of resources, be it material or labor.

Given the complex nature of this fill-finish facility, these same seven tenets easily can be applied to any construction project for coordinated delivery in a time-constrained manner.

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About the Author



Andrew Cunningham, RIBA, LEED AP, Principal, Flad Architects has more than 22 years of architectural experience covering a wide range of project types, including pharmaceutical and R&D facilities for private and public sector organizations. Focusing primarily on project management and client service, recent projects include Genentech's

Hillsboro Fill Finish facility and the Brewery, Winery and Food Pilot Facilities at UC Davis. Cunningham has been an active member of his local community Planning Commission for eight years and has previously presented a number of seminars for ISPE, Interphex, and BayBio.

FladArchitects, 650 California St., 8th Floor, San Francisco, California 94108, USA. 