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Case Study: Genentech's ECP-1 Bacterial Manufacturing Facility, Overall Winner, 2010 Facility of the Year Awards

Innovative Project Execution Outpaces Ambitious Schedule

by Rochelle Runas, ISPE Technical Writer

Introduction

Standing on a greenfield site once part of a shipping channel in Tuas, Singapore is an unassuming structure with a remarkable story. The structure was designed in four different locations spanning 12 time zones. It was built and shipped in pieces across thousands of miles of rough seas. It was reassembled at a site where six languages were spoken. All of this was accomplished ahead of a very ambitious schedule so that patients could have access to an important medicine.

This article presents the story of how innovative project execution and strong teamwork overcame numerous challenges in the making of Genentech's ECP-1 Bacterial Manufacturing Facility, Overall Winner of the 2010 Facility of the Year Awards. Genentech's win of this coveted award was announced at ISPE's 2010 Annual Meeting in November 2010 in Orlando, Florida, USA. Initially developed by Genentech, a wholly owned member of the Roche Group, the facility is now operating as Roche Singapore Technical Operations.

A Motivating Vision

The E. Coli Plant 1 (ECP-1) Bacterial Manufacturing Facility was built to increase production capacity of Lucentis® (ranibizumab injection), a novel therapy used to treat neovascular (wet) Age-Related Macular Degeneration (AMD). Wet AMD is a retinal disease that causes irreversible vision loss and is one of the leading causes of blindness in people over 55 years of age. Produced using *E. coli*, Lucentis inhibits the formation of new blood vessels which can grow under the retina and cause damage to the macula.

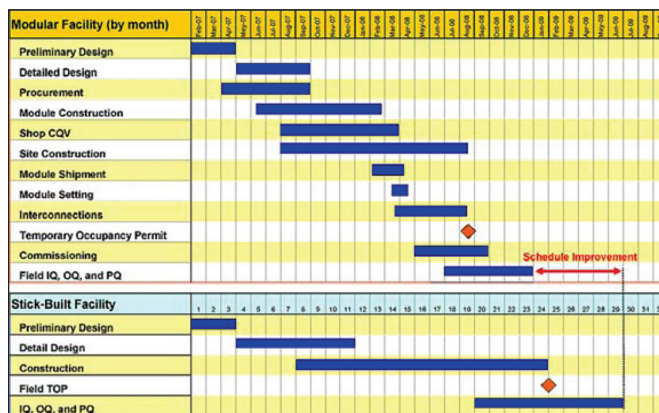
The 2006 FDA approval of Lucentis for the treatment of wet AMD was followed by rapidly escalating patient demand. Needing additional capacity to manufacture Lucentis drug substance, Genentech established a highly ambitious project schedule to construct a new production facility halfway around the world from its headquarters in South San Francisco, California, USA.

Project Overview

The project goals were to deliver a licensable manufacturing site that: provided for safe, reliable, and cost effective production; met construction safety targets; remained within the approved budget of \$217 million; and completed OQ within 24 months from engineering kickoff.

A worldwide selection effort yielded a 30-acre greenfield site bordering a shipping channel in Tuas, Singapore. Singapore was chosen for its knowledgeable, highly supportive business environment, a modern infrastructure, and improved cost structure. Additionally, Singapore houses a thriving pharmaceutical

Project completed in 23 months.





Buffer prep area in shop fabrication.

community, which enabled Genentech to benefit from a deep regional talent pool.

Meeting an ultra-fast-track schedule on an international project required a collaborative team to develop and execute an innovative strategy. A design build team – comprising contractor Jacobs Engineering Group located in Cincinnati, Ohio, USA, Charleston, South Carolina, USA, and Tuas, Singapore and contractor Bovis Lend Lease Pharmaceutical located in Tuas, Singapore, and owner Genentech located in South San Francisco, California, USA – developed a strategy utilizing large-bay modules integrated with traditional stick-build construction.

The project comprises a total building area approximately 102,000 square feet, more than 30,000 square feet of which is manufacturing space (modular construction) on two levels. Jacobs headed the module building work, which included process areas (including Grade C rooms), process equipment, and process utilities. Bovis headed the site/stick built work, which included production support areas, including administrative offices, a GMP warehouse, and a central utility building stick-built on the site. Additional site scope included infrastructure, such as roads, main utility services, landscaping, and an electrical substation.

Why Modular Construction?

“The decision to use modular construction was in large part to meet an aggressive schedule and we were able to take advan-

Advantages and Disadvantages of Modular Construction for ECP-1

Advantages

- Potential for faster schedule due to parallel construction
- Better QC and safety, as work occurs in a controlled environment
- Access to additional skilled craftsmen, who may be in short supply at the jobsite

Disadvantages

- Can be more expensive
- Requires considerably more coordination between the site and modular construction firms



Route from South Carolina to Singapore.

tage of the overlap in construction provided by this delivery methodology,” said Jon Reed, Vice President, Engineering, Genentech. “We were able to perform considerable activities on the site while at the same time the modular manufacturing building was being constructed in South Carolina.”

ECP-1 utilized 24 large bay structural modules measuring 25' W × 21' H × 45' L as opposed to the standard module size of 14' W × 12'6" H × 45' L. One large bay module is equivalent to roughly four standard modules. The use of large bay modules resulted in a 75% reduction in the number of modules, further accelerating schedule completion.

Nearly all acceptance testing and qualification work was executed before module shipment to Singapore, thus reducing the time to start up once the modules were installed at the ECP-1 site.

Two ocean shipments of the oversized modules were each transported almost 14,000 miles, enduring weather, the rough Atlantic Ocean in late winter, and traffic logistics. The total ocean transport time from Charleston, South Carolina to the site in Singapore was 45 days per shipment, which represented a significant block of time on the schedule's critical path. “We couldn't ship too early or too late,” said George Mackey, Project Director, Genentech. “We had to be exact.” Planning for dedicated “last on, first off” ocean shipping and pre-approval of all permits and customs documents was key to maintaining the planned project schedule. All modules arrived fully intact and on schedule.



Ocean transport of finished modules.

The site being located directly on a shipping channel indeed helped module transportation logistics. But regardless of the location in Singapore, Genentech would have used modular construction, “provided that a reasonably direct path from the channel to the jobsite was available,” said Reed. “With large modular construction there may be restrictions on transportation that would prohibit their use. However, modules can be adjusted in physical size to meet most transportation requirements.”

Modules were moved after midnight with police escort on roads that were closed to other vehicles. In advance of the move, trees were trimmed, lights removed, and utility lines relocated.

The construction site was prepared for the modules by setting drain piping, base plates, rigging and soil compaction (for the crane), scaffolding and safety barriers. Upon arrival at the site, each module was carefully lifted and set in place with a 500 ton crane/220 foot boom, and a dedicated team of tradesmen under Bovis’ direction.

Taking into account the process piping, ductwork, structural slab, flooring, wall partitions and ceilings, thousands of module/field connections had to be made. “A large team of craftsmen planned every detail of the field assembly work,” said Reed. “Upon module arrival, the teams executed like clockwork and completed their work flawlessly. No connections were out of tolerance by greater than 0.375 inches!”

Key project participants were pleased and impressed with the modular approach. “Large modules utilized for the process and clean utilities areas provided a ‘spaciousness’ that belied the

fact that the entire area was built as a series of module ‘boxes’ half way around the world, shipped, and then set in place and bolted together,” said Pat Sanders, Project Manager, Jacobs.

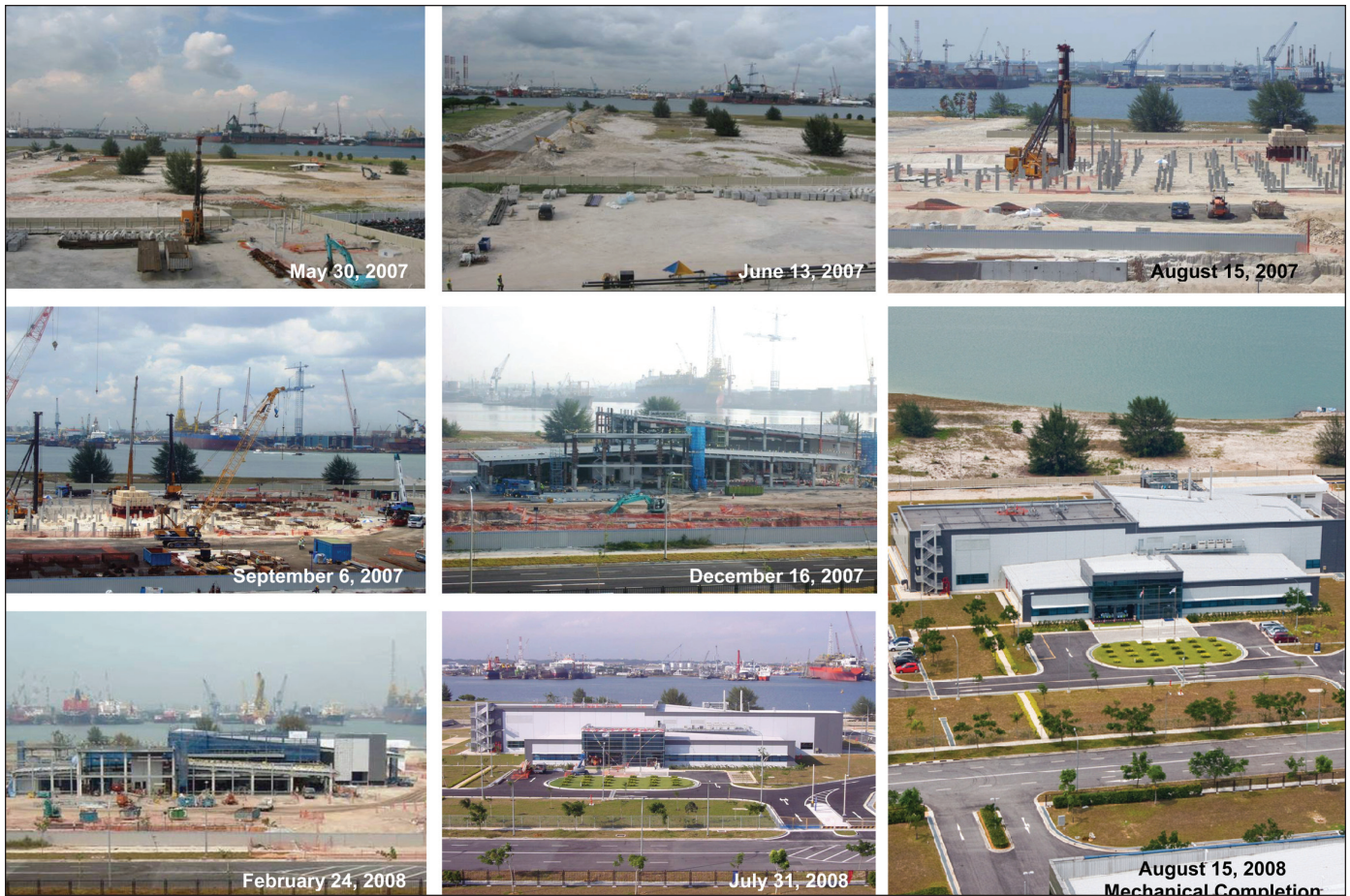
“Dealing with modules was easier than I expected simply because we had great quality in our information transfer from the Jacobs team in Charleston: ship books, schedules, interconnection scopes of work, etc.” said William McNamara, Project Manager, Bovis. “The accuracy of the build contributed to the ease of setting and interconnecting the modules.”

Mackey said several project company executives walked through the plant upon mechanical completion and the question often asked was: Where are the modules? “You cannot find the difference between the modules and site construction,” said Mackey.

Overcoming Unique Project Challenges

There were some challenges unique to the ECP-1 project that tested the team’s project management skills as well as its commitment to the project and all parties involved.

For example, the modules arrived in Singapore with more incomplete work than planned. “This was primarily due to the need to stay aligned with the ocean shipping timeline,” said Reed. “Coordination between the on-site construction work and the arrival of the modules was aggressively planned and missing the ship date would have delayed the overall project severely. Teams avoided finger pointing and blame and worked out a resourcing plan to deal with the problem and maintained schedule.”



Campus construction progress.

Another challenge was communications. "Working across 12 different time zones assured work was occurring 24/7, but effective communication was essential," said Reed. "While technology (videoconference, WebEx, email) was employed, the most effective tool was co-locating project staff together."

Also, six languages were spoken at the site. Daily team "toolbox" talks held in each language were communicated through multi-language signage throughout. "Multi-lingual superintendents were a must!" said Reed. "Even the cafeteria had separate menus and facilities to address the needs of our staff's appetites."

Mother Nature also proved challenging. Daily rains, frequent thunder/lightening storms, and constant high humidity made construction work difficult. Lightening detectors were required

safety equipment. "During module setting, we constructed a football-sized 'umbrella' that was held by a second crane over the open modules while they were being set on their respective foundations to prevent rain from getting into the open sides of the modules," said Reed.

Success Factors for the ECP-1 Project

Overall, the project was successful because of strong teamwork, effective decision making, and constant communication, according to Reed. Contracting partners that are aligned and staying focused on the mission are major factors, as well as having the site's General Manager, Jim Miller, as an integrated partner that supported the construction team and helped remove barriers along the way to keep project teams moving.

Facility of the Year Awards

Sponsored by ISPE, INTERPHEX and *Pharmaceutical Processing* magazine, the Facility of the Year Awards (FOYA) program recognizes state-of-the-art pharmaceutical manufacturing projects that utilize new and innovative technologies to enhance the delivery of a quality project, as well as reduce the cost of producing high-quality medicines. Now in its seventh year, the awards program effectively spotlights the accomplishments, shared commitment, and dedication of individuals in companies worldwide to innovate and advance pharmaceutical manufacturing technology for the benefit of all global consumers.

More information on the Facility of the Year Awards program can be found at www.FacilityoftheYear.org.

2010 Facility of the Year

Genentech's ECP-1 Bacterial Manufacturing Facility, category winner for Project Execution, was selected as the Overall Winner of the 2010 Facility of the Year Awards among four other Category Winners in 2010:

- **Biogen Idec**, winner of the Facility of the Year Award for *Operational Excellence* for its Large-scale Manufacturing (LSM) Technology Map Project in Research Triangle Park, North Carolina, USA
- **MannKind Corporation**, winner of the Facility of the Year Award for both *Equipment Innovation* and *Process Innovation* for its Technosphere® Insulin Manufacturing Facility in Connecticut, USA
- **Pfizer Biotechnology Ireland**, winner of the Facility of the Year Award for *Sustainability* for its Monoclonal Antibodies (MAbs) Small-scale Facility in County Cork, Ireland
- **Pfizer Ireland Pharmaceuticals**, winner of the Facility of the Year Award for *Facility Integration* for its Aseptic Facility Expansion Project in Dublin, Ireland

"FOYA is a good venue to showcase excellence in engineering and allows companies an opportunity to discuss new and innovative ways to provide these services to our industry, which ultimately benefit our patients and communities. Our organizations all benefit from learn-

ing about best in class methods or innovations around process design, sustainability, efficiency, and delivery innovations which drive better quality into our products, higher efficiencies in our production operations and more cost effective ways to deliver our services." – Jon Reed, Vice President, Engineering, Genentech, for Genentech's ECP-1 Bacterial Manufacturing Facility, Overall Winner of the 2010 Facility of the Year Awards.

2011 Facility of the Year

The 2011 Facility of the Year Category Winners are:

- **F. Hoffmann – La Roche Ltd**, winner of the Facility of the Year Award for *Process Innovation* for its "MyDose" Clinical Supply facility in Kaiseraugst, Switzerland
- **MedImmune, LLC**, winner of the Facility of the Year Award for *Project Execution* for its Frederick Manufacturing Center (FMC) Expansion facility in Frederick, Maryland, USA
- **Merck & Co., Inc.**, winner of the Facility of the Year Award for *Facility Integration* for its Global Clinical Supplies Manufacturing, Packaging and Warehouse expansion project in Summit, New Jersey, USA
- **Novartis Vaccines and Diagnostics GmbH**, winner of the Facility of the Year Award for *Equipment Innovation* for its "MARS Project" (Marburg Site) facility in Marburg, Germany
- **Pfizer Health AB**, winner of the Facility of the Year Award for *Operational Excellence* for its Project Pegasus – Bio 7 Manufacturing facility in Strängnäs, Sweden
- **Pfizer Manufacturing Deutschland GmbH**, winner of the Facility of the Year Award for *Sustainability* for its SPRING and E-MAP (Strategic Plant Restructuring and Energy Master Plan) project in Freiburg, Germany
- **Shire HGT**, Facility of the Year Award *Honorable Mention* for its Project Atlas, Building 400 facility in Lexington, Massachusetts, USA.

The Category Winners of the 2011 Facility of the Year Awards will be featured in a Supplement to the May/June 2011 issue of *Pharmaceutical Engineering*.



Multiple languages were spoken on site.

“The teamwork exhibited by our employees, partners, and leadership team was exceptional,” said Reed and Miller. “With an aggressive schedule such as this, we didn’t have time to spend talking about any one subject. It was imperative that we made good, timely decisions and that the teams quickly aligned and executed those decisions.”

As for success factors for projects employing modular construction, according to Mackey they are the same as those for projects using standard construction. “However, they demand flawless execution and attention to detail. Everything is on the critical path.”

A Worthwhile Premium

This decision to use modular construction came at a small premium, however to Genentech it was worth it to get the product to market. “Every day this facility was not in operation, we risked patients not having access to this important medicine,” said Reed.

“The operation of this facility improves the efficiency of our ability to produce Lucentis. Coupled with the close proximity to our much larger facility across the street, we are able to leverage a common workforce and didn’t have to duplicate many support facilities in this facility, such as a full service cafeteria, large meeting rooms, warehousing, etc.”

Conclusion

The guiding principle throughout the project was the need to provide patients with products that addressed an unmet medical need, and the end users with facilities that were fit to operate. The business requirements presented the team with significant schedule, cost, and execution challenges. However, by committing to a modular approach from the beginning, along with an early focus on site issues, outstanding project planning, execution techniques, and team development, the project beat the aggressive schedule target of 24 months by two weeks and 10.5% under budget. As a result, facility production capacity goals were met, delivering a high quality, licensable manufacturing site that continues to meet future Lucentis market demand. 