

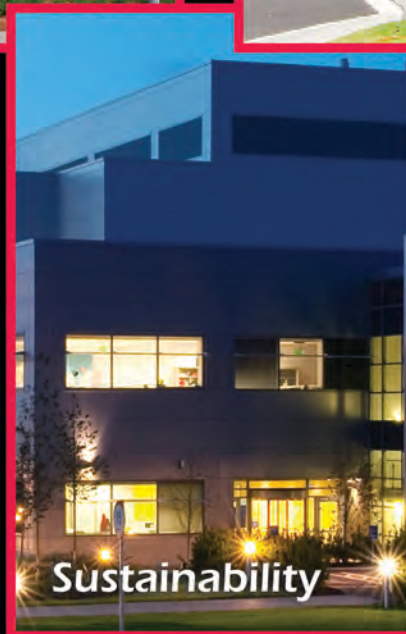
Supplement to

**PHARMACEUTICAL
ENGINEERING**

2010



Facility of the Year Awards CATEGORY WINNERS





Cover Photographs

Photos courtesy of Biogen Idec, Genentech, MannKind Corporation, Pfizer Biotechnology Ireland, and Pfizer Ireland Pharmaceuticals

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**ENGINEERING
PHARMACEUTICAL
INNOVATION**

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Supplement to PHARMACEUTICAL ENGINEERING®



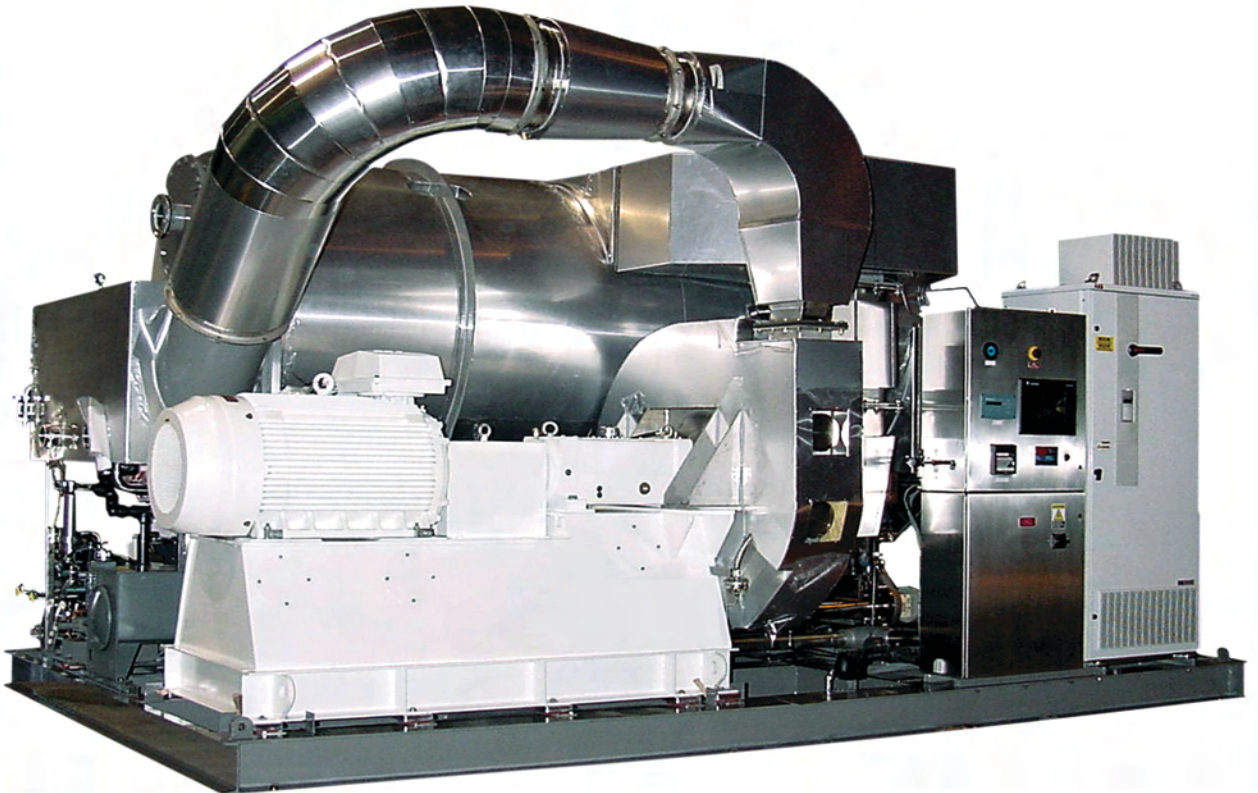
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2010 Facility of the Year Awards Program: Honoring Innovation in Pharmaceutical Manufacturing

The Facility of the Year Awards 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 sixth 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.

Five pharmaceutical manufacturing facilities constructed in Singapore, Ireland, and the USA were selected as Category Winners in the sixth annual Facility of the Year Awards (FOYA) program sponsored by ISPE, INTERPHEX, and *Pharmaceutical Processing* magazine. The winning companies and respective award categories are:

- **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
- **Genentech**, winner of the **Facility of the Year Award for Project Execution** for its **ECP-1 Bacterial Manufacturing Facility** in Tuas, Singapore
- **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



Biogen Idec: bioreactor buffer tank.



Genentech: fermentation suite.

- **Pfizer Ireland Pharmaceuticals**, winner of the **Facility of the Year Award for Facility Integration** for its **Aseptic Facility Expansion Project** in Dublin, Ireland

The Facility of the Year Awards program is truly global, as submissions over the past six years have been received from more than 25 different countries and territories. Each of the submissions was reviewed by an independent, blue-ribbon judging panel of global representatives from the pharmaceutical design, construction, and manufacturing sectors. These industry professionals included:

- **Chaz Calitri, Judging Panel Chairman**
Vice President, Global Engineering, Pfizer Global Engineering
- **Jim Breen**
Vice President, Project Management, Worldwide Engineering & Real Estate, Johnson and Johnson
- **Steve Dreamer**
Head of Global Pharma Engineering & Operational Excellence, TechOps, Novartis Pharma AG
- **Brian Lange**
Director, Quality Services, West Point Quality Operations, Merck & Co.
- **Geoff Monk**
Vice President, Global Engineering Services, Schering Plough
- **Shinichi Osada**
General Manager, Biopharm, Industrial & Logistics Systems Division, Hitachi, Ltd.



MannKind Corporation: centrifugal chillers and distribution piping in the CUB.

- **Andy Skibo**
Senior Vice President, Global Engineering, MedImmune
- **Ron Trudeau**
Vice President, Facilities Engineering Services, Baxter Healthcare

2010 Facility of the Year Events

There will be several opportunities to meet the 2010 Facility of the Year Award Winners and learn first-hand about the facilities being honored as “best in their class.” These events include:

- **INTERPHEX2010** – The Facility of the Year Awards Display Area is located at booth number 1059 in the exhibit hall of the Jacob K. Javits Convention Center, where during 20 to 22 April, Category Winners discuss the success stories associated with these pharmaceutical manufacturing facilities. For more information, visit www.interphex.com.
- **ISPE 2010 Annual Meeting** – Learn first-hand who the Overall Winner of the coveted 2010 Facility of the Year Award is during ISPE’s 2010 Annual Meeting, 7-10 November in Orlando, Florida, USA. For more information, visit www.ISPE.org.

At each event, a Facility of the Year Awards display will feature the 2010 Category Award Winners.



Pfizer Biotechnology Ireland: media preparation.

Visit www.FacilityOfTheYear.org for more information about the awards program and detailed information about each Category Winner’s project participants.

About ISPE

ISPE, the International Society for Pharmaceutical Engineering, is the Society of choice for 24,000 technical professionals working in or serving the manufacturing sector or drug development in the pharmaceutical industry in 90 countries. ISPE aims to be the catalyst for “Engineering Pharmaceutical Innovation” by providing Members with opportunities to develop their technical knowledge, exchange practical experience within their community, enhance their professional skills, and collaborate with global regulatory agencies and industry leaders. Founded in 1980, ISPE offers online learning opportunities for a global audience and has its worldwide headquarters in Tampa, Florida, USA; its European office in Brussels, Belgium; an Asia Pacific office in Singapore; and its newest office in Shanghai, China. Visit www.ISPE.org for additional Society news and information.




Pfizer Ireland Pharmaceuticals: in-line inspection machine.

About INTERPHEX

Now in its 31st year, INTERPHEX is the world’s most trusted source for leading-edge technology, education, and sourcing of the products and services that drive scientific innovation for Life Sciences manufacturing from drug development to market – accelerating regulated products for patient care globally. Held 20 to 22 April at the Jacob K. Javits Convention Center in New York City, New York, USA, the 2010 exhibition features more than 950 exhibitors, an expanded conference program, and a high-profile roster of industry professionals and speakers. For information, visit www.interphex.com.

About *Pharmaceutical Processing*

Pharmaceutical Processing magazine is the pharmaceutical industry’s leading information provider, reporting on a full range of innovative new products, equipment, technology and trends for 31,000 engineers and managers responsible for the development, manufacture, validation and packaging of pharmaceuticals. An official sponsor of INTERPHEX, *Pharmaceutical Processing* distributes critical information to these professionals in a timely manner through a full range of print, electronic and online media. For information, visit www.pharmpro.com. 

Biogen Idec

Realizing the Value of Renovation

Introduction

To upgrade the infrastructure of the company's bulk biologics production facility and reduce challenges associated with downstream processing bottlenecks, Biogen Idec completed the largest renovation of a licensed manufacturing facility in the company's 30-year history: **Building 22 Large Scale Manufacturing (LSM) Technology Map** project at Research Triangle Park, North Carolina, USA.

Winner of the **2010 Facility of the Year Award (FOYA) for Operational Excellence**, the upgraded facility provides a better than 300% increase in yield over its previous production output by incorporating new technologies and de-bottlenecking operations at an existing site at a fraction of the cost of building new facilities. The resulting higher throughput comes, in part, from facility and equipment improvements that achieve faster and more streamlined technology transfers and process changeovers within the multi-product facility.

The project team successfully implemented and achieved this strategic upgrade utilizing exceptional up-front project planning and management; integrated, lean design and construction techniques; and rolling plant shut-downs at a scale that few, if any, have attempted to execute at one time.

Value Proposition

Biogen Idec's capabilities and capacity for protein manufacturing are world-class in quality and scale. Biogen Idec has expertise in protein expression in mammalian cells and process sciences capability for cell culture and downstream processing. Biogen Idec is one of a few biotechnology companies with three licensed and dedicated biological bulk-manufacturing facilities. One of these facilities includes a 250,000-square-foot LSM plant in Research Triangle Park (RTP), North Carolina.

Since 2000, when the LSM plant was designed and constructed, significant investments have been made in the biopharmaceutical supply chain across the industry. Improvements

Biogen Idec

Category Winner – Operational Excellence

Project: Building 22 Large-Scale Manufacturing (LSM) Technology Map

Location: Research Triangle Park, North Carolina, USA

Size: 50,000 sq. ft. (4,645 sq. m.)

Total Project Cost: \$39,100,000

Duration of Construction: 4 months



Aerial view.

in media, process, and cell-line development are examples of methods that have significantly improved yields. This increase in titers and improved expression yields create pressure on downstream processing. This downstream processing bottleneck is consistently cited by pharmaceutical and biotechnology companies as one of the top three biomanufacturing challenges today.

As part of a broader initiative to operate as effectively as possible, Biogen Idec developed a "Manufacturing Equipment and Facility Technology Map" for each of its manufacturing facilities and corresponding infrastructure, which considered the age of the facilities, advances in new equipment and technologies, raw materials, cell lines, and operational excellence. In support of this long-term corporate initiative and to reduce challenges associated with downstream processing bottlenecks, Biogen Idec renovated its existing LSM plant.

In comparing what it would cost to build a new 90,000 L LSM facility to deliver titers in the >3g/L range vs. renovate the existing 250,000-square-ft LSM facility and take it from 1g/L to >3g/L, there were significant time and capital savings with renovation. Based on industry averages, the equivalent capital outlay of a new LSM facility is in the range of approximately \$500 million and would take at least 60 months to design/build/validate and license. In contrast, the renovation and upgrade of the LSM leveraged what was already operational and executed it in 18 months at a cost of \$39.1 million.

Facility and Equipment Improvements

The Building 22 Large Scale Manufacturing (LSM) Technology Map project enabled Biogen Idec to significantly update and improve current and future manufacturing capabilities,

Continued on page 8.



Congratulations, Biogen Idec
Category Winner, Operational Excellence
LSM Technology Map Project,
Research Triangle Park, NC

2010 Facility of the Year Award



IPS Booth #965
Facility of the Year
Display Area
#1059

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Cover Image: Courtesy of Biogen Idec



Modular 1000 L to 4000 L buffer hold tanks.

capacities, and efficiencies. Biogen Idec completed the largest series of manufacturing renovations in its 30-year history and has created one of the largest state-of-the-art bulk biologics facilities in the world. Highlights in facility, equipment, and technology improvements include:

- robust tech transfer and product changeover processes
- flexible manufacturing platform consistent across sites
- increased overall efficiencies with maximized throughput
- consistency from early stage through commercial capabilities
- increased titer capabilities from 1 g/L to >3g/L (+300%)
- platforms that grow and facilitate partnerships/collaborations
- operations that perform with speed, excellence, and discipline: overall manufacturing operations efficiency



Nutrient feed tank area.

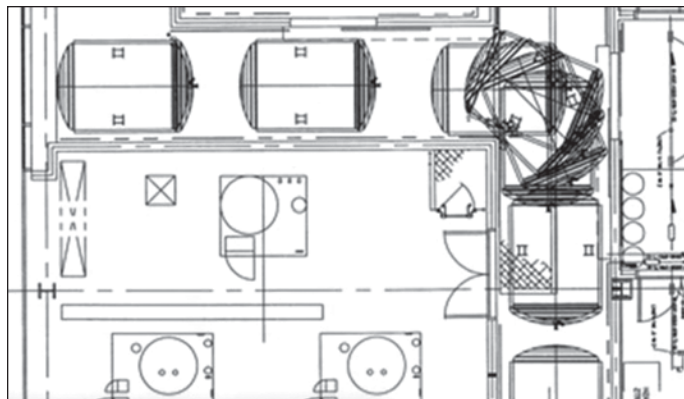
- avoidance of having to build new capacity to increase capacity
- increased SIP, CIP, Sampling and Addition Operations
- addition of large scale feed vessels – 3 × 6200 L and support infrastructure
- new mixing technology for media components
- replacement of 13 product hold vessels ranging in size from 2000 L to 9000 L utilizing modular construction for minimizing outages
- new final filtration (flat sheet) technologies

The following is a list of functional areas/systems that were modified:

- bioreactor vents and exhaust systems (new piping and filters)
- three new purification product hold arrays (three modules, nine vessels)
- purification hold array modifications
- two new 6000 L buffer prep vessel systems (stick-built)
- three new buffer hold vessels (two 6000 L, one 8000 L) (modular)
- two new 8000 L harvest buffer hold vessels (stick-built)
- three new 6000 L bioreactor feed vessels (stick-built)
- two new product hold nutrient vessels (stick-built)
- new lenticular depth filter systems for product isolation (modular)
- new “POD” filter (disposable technology) system
- modifications to four 20,000 L harvest and permeate tanks
- three heat transfer systems (skidded)
- utility upgrades

Notes from the Judging Panel – What Impressed Them

Their plan to deliver was what made this project so impressive. There is a lot here that big companies could learn from. Lots of skid-mounted equipment that equals a lot of scheduling issues.



Travel plan for 6000 L tank.

Unique Project Execution Strategy

The project execution strategy is unique due to the involvement of a building refurbishment, a conventional stick-build support facility, and modular process equipment, all at the same time. In addition, there were many constraints that impacted the project, such as limited windows for allowed shut-down (16

weeks) and the close tolerances for equipment access into the existing facility.

For a project with such limited execution time, the need to integrate the planning and work together was paramount. An integrated owner's team was established at the project inception and continually collaborated with all stakeholders.

Concludes on page 10.

Why Our Project Should Win

The following is an excerpt from Biogen Idec's submission, stating in their own words, the top reasons why their project should win the 2010 Facility of the Year Award:

- The facility, process, and equipment improvements deliver an increase in titer capabilities from 1 g/L to >3g/L. The result is a >300% increase over previous capacity.
- Value! In comparing what it would cost to build a new >3g/L facility vs. renovating LSM to deliver >3g/L, the equivalent capital outlay of the new facility would have been in the range of approximately \$500 million and would take approximately 60 months to design, build, validate, and license. In contrast, this project leveraged what was already operational and executed it in 18 months (with only a four month shut-down) at a cost of US \$39.1 million.
- The renovation also provides capability to establish late stage clinical/commercial capabilities and also provides harmonization between Biogen Idec's other global large scale manufacturing facilities.
- This lean transformation resulted in an overall increase in capacity by de-bottlenecking the process operations and addressed the downstream process operations and made significant efficiency improvements.
- The project incorporated lean project delivery methods utilizing 3D Building Information Modeling (BIM) of the process equipment layouts. The equipment was designed and modeled to within ¼" tolerance. The model was reviewed using real-time online software allowing stake holders in Denmark, Cambridge, Research Triangle Park, and Somerset, New Jersey to review for technical content, accessibility, ergonomics, and maintenance and operations.
- In addition, the "3D Model" was developed in conjunction with the equipment vendors and fabricators thus leveraging their expertise and eliminating duplication of efforts. The model was given to the contractors who then in turn utilized it to generate hundreds of isometric drawings saving several weeks of isometric submittal drawing time.
- Lean fabrication using modular skids and super skids were utilized. Components were assembled off site to speed installation, improve quality, and minimize environmental disruption.
- New technologies and increased capacity for mixing media components, additional large scale feed vessels (3 x 6200 L) with support and support infrastructure, replacements of 13 product hold vessels ranging in size from 2000 L to 9000 L utilizing modular construction speed installation, new final filtration (flat sheet) technologies and increased buffer preparation and hold capacities.
- Zero lost time accidents on more than 250,000 man hours logged.
- Utilizing a lean philosophy, the concept of "rolling shut-downs" reduced facility down time to a minimum. This optimized the production and eliminated the need to keep areas out of production when they didn't need to be.
- Excellent integrated collaboration among owner, architectural/engineering, and construction management project teams.



Modular skid.

Since this project was very strategic in nature, considerable up front planning was undertaken. The early planning was embraced by all operational functions at the RTP facility and the ensuing comprehensive execution plan was compared with recent outages at other companies. The outcome, if successful, would indicate a clear, competitive advantage for Biogen Idec. During the early planning, the use of modular construction and the systematic approach to commissioning and validation would result in shorter facility outages by months or even quarters when compared with benchmarks from other companies.

As a result, the project execution plan was divided into seven project phases consisting of the feasibility study, conceptual design, preliminary engineering, preconstruction, construction, commissioning, and validation. This project required substantial overlap and coordination of activities among engineers, contractors, commissioning, validation, and quality teams.

A rolling shut-down approach was implemented to minimize duration of production outage, and construction and commissioning and qualification was integrated to effectively manage transition from construction to manufacturing. Rolling shut-downs and turnover included post campaign cleaning, GMP documentation close out (e.g. batch records), post use calibration, system decommissioning, and safety lockout. Additionally, all change control activities needed to be documented and approved prior to start of decommissioning activities.

Key Project Participants

Architect: Integrated Project Services (Lafayette Hill, Pennsylvania, USA) *(See ad on page 7)*

Design Manager/Engineer: Integrated Project Services (Lafayette Hill, Pennsylvania, USA) *(See ad on page 7)*

Construction Manager: Yonkers Industries (Cary, North Carolina, USA)

Award Category – Operational Excellence

Winners in this category exemplify the application of modern management techniques aimed to improve operating efficiencies, promote excellent quality, consistency, and yield competitive cost of goods from existing and new facilities, processes, and manufacturing operations.

Successful Construction Approach

A lean design approach was developed that leveraged the capital project supply chain by integrating the A/E, CM, vendors, fabricators, owner, and key trades contractors. The integration was the key to developing the proper sequencing of work by selecting stick built and modular skids in anticipation of erection durations. In addition, maximizing off-site fabrication also was used to accelerate the schedule. Another technique essential to the construction sequence and meeting schedule was to perform as much of the work in the grey space boundary prior to production outage.

Conclusion

The renovation plan was designed to meet current and future manufacturing and clinical needs and comply with cGMP and regulatory requirements. By utilizing modular and stick built techniques, Biogen Idec was able to significantly compress the schedule – completed the construction within a four month shut-down – and reduce construction costs and speed products to market. Through exceptional up-front project planning and management; integrated, lean design, and construction techniques; and rolling plant shut-downs, the project resulted in:

- flexible manufacturing platform consistent across sites
- increased overall efficiencies with maximized throughput
- consistency from early stage through commercial capabilities
- increased titer capabilities from 1 g/L to >3g/L (+300%)
- platforms that facilitate and grow partnerships/collaborations
- operations that perform with speed, excellence, and discipline
- avoidance of having to build new capacity to process higher yields

LISTEN.
THINK.
SOLVE.®



The Rockwell Automation EMEA Life Sciences team would like to congratulate Pfizer Ireland Pharmaceuticals on being awarded the 2010 Facility of the Year award for Facility Integration and we are delighted to be associated with the ISPE FOYA winning facility for the 2nd consecutive year.

If you require an Automation/MES partner or are looking for further information on how we could assist you in delivering an award winning facility please visit our websites,

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Genentech

Innovative Project Execution Outpaces Ambitious Schedule

Introduction

Genentech's **ECP-1 Bacterial Manufacturing Facility** was built in Tuas, Singapore to increase the production capacity of Lucentis® (ranibizumab injection), which is used to treat patients with wet age-related macular degeneration. Genentech established a highly ambitious schedule that would be the defining challenge: to take a project from engineering kick-off through initiation of GMP qualification batches in 24 months. Winner of the **2010 Facility of the Year Award (FOYA) for Project Execution**, the facility was initially developed by Genentech, a wholly owned member of the Roche Group, and is now operating as Roche Singapore Technical Operations.

Meeting an ultra-fast-track schedule on an international project required a collaborative team to develop and execute an innovative strategy. With its contractors Jacobs Engineering Group and Bovis Lend Lease Pharmaceutical, Genentech developed a strategy utilizing large-bay modules integrated with traditional stick-build construction. The team also developed a parallel work strategy that enabled a 90% overlap of design and construction efforts, leading to significant overall schedule savings.

As with any project of this size and complexity, the Genentech team encountered numerous challenges, but overcame each through outstanding project execution techniques. The team's planning, dedication, and innovation enabled delivery of a fully integrated, high-quality facility in record time.

Vision for an Unmet Medical Need

Wet Age-Related Macular Degeneration (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. The 2006 FDA approval of Lucentis for the treatment of wet AMD was followed by rapidly escalating patient demand. Genentech elected to increase Lucentis manufacturing capacity by constructing a new production facility that could meet future business needs with ability to accommodate increased throughput and

Genentech

Category Winner – Project Execution

Project: ECP-1 Bacterial Manufacturing Facility

Location: Tuas, Singapore

Size: 102,000 sq. ft. (9,476 sq. m.)

Total Project Cost: \$194,000,000

Duration of Construction: 14 months



Aerial view of exterior.

a changing product mix.

A worldwide selection effort yielded a 30-acre greenfield site in Tuas, Singapore, because it offered a knowledgeable, highly supportive business environment, a modern infrastructure, and an improved cost structure. Additionally, Singapore houses a thriving pharmaceutical community, which enabled Genentech to draw from a deep regional talent pool.

The project comprises a total building area greater than 102,000 square feet, more than 30,000 square feet of which is manufacturing space on two levels. Production support areas, including administrative offices, a GMP warehouse, and a central utility building were stick-built on the site. Additional site scope included infrastructure, such as roads, main utility services, landscaping, and an electrical substation.



Module fabrication shop.

Continued on page 14.



Congratulations Genentech!

Winner of the 2010 ISPE Facility of the Year Award for Project Execution

Genentech Biologics Manufacturing Facility *Tuas, Singapore*



Bovis Lend Lease is proud of its partnership with Genentech and the exceptional team that helped deliver the design and challenging fast track execution of this facility.

Whether providing up front consultation or comprehensive EPCMV services, our goal is always the same – delivering safe, sustainable, innovative solutions with profitable outcomes for the life science industry.

Bovis Lend Lease: proud partner of ISPE's Facility of the Year Award recipient for Project Execution for the second consecutive year.



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Ocean transport of finished modules.

Accelerating the Schedule with Modular Construction

An early stage study indicated that a modular approach offered numerous advantages and concluded that it was the only viable method to meet the schedule requirements. Merging modular and stick-built construction, 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 in size to four standard modules. Utilizing

modular construction shortened the duration for overall project execution because:

- Modular construction allowed for progression of significant structural, mechanical, electrical, and architectural works in parallel with Singapore site construction. Normally these occur in sequence.
- Experienced hygienic craft labor was available at Jacobs' module shop in Charleston, South Carolina, USA.
- Productivity benefited from the controlled environment in the shop, which also reduced the density of field craft in confined areas.
- Genentech was able to execute FAT and qualification in the same controlled module fabrication shop, prior to shipment.
- Charleston location facilitated Genentech involvement to resolve engineering and design issues and ensure quality control.

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. Planning for dedicated "last on, first off" ocean shipping and pre-approval of all permits and customs documents were keys to maintaining the planned project schedule.

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



Modules staged in final layout.

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. Temporary weather protection was applied until the modules were connected with each other and the site infrastructure.

The speed and flexibility of panel installation both in Charleston during primary fabrication and in Singapore during module interconnection, contributed to achieving the overall schedule targets. The quality and consistency of the panels and finishes was excellent, and they made the long ocean journey without a scratch.

Significant Contributions in Project Execution

Meeting an ultra fast track schedule on an international project required a collaborative team to develop and execute an innovative strategy, and Genentech found this team in Jacobs and Bovis.

A project execution plan was established prior to preliminary engineering that recognized each company's strengths and experience for each task. The plan called for Jacobs and Bovis to

form two design build teams; Jacobs led the US-based design and construction of complete manufacturing area modules, while Bovis managed Singapore-based design-build of infrastructure and non-process areas, as well as module setting and hook up. This parallel work strategy enabled more than 90% overlap of design and construction efforts, resulting in significant overall schedule savings.

With design activity taking place in four locations spanning 12 time zones, the project team selected "typical" design tools and procedures to eliminate learning curves, and their online, real-time model allowed immediate design review and comment. This online, real-time data model allowed immediate design review and comment. This online process proved so effective that planned on-site reviews were greatly reduced, saving travel costs and time, as well as the lag between design and design approval.

Equipment and instrument procurement could not proceed quickly enough, which meant that critical vendor design data would not be available to support the design and module fabrication schedule.

Concludes on page 16.

Why Our Project Should Win

The following is an excerpt from Genentech's submission, stating in their own words, the top reasons why their project should win the 2010 Facility of the Year Award:

Outstanding Project Execution

- The project team successfully delivered a high quality E. coli drug substance facility in record time – preliminary engineering to initiation of GMP qualification batches in less than 24 months! This was the fastest schedule in Genentech history, and was more than 10 months faster than industry benchmarks.
- The project achieved a perfect safety record. Module fabrication and site construction utilized nearly two million man hours with zero lost time incidents and zero reportable accidents.
- The focus on quality engineering, quality construction, and team collaborations resulted in precise alignment between thousands of module connections at the Singapore site. In no case was there any connection misalignment greater than 3/8 of an inch.
- Modeling of the GMP process modules maximized use of Plant Design System (PDS®) 3D in Cincinnati to reduce obstacles and to ensure that field interconnections had proper alignment. The stick-build design was executed with AutoCAD 2D in Singapore.
- The project utilized large bay modules, a first for the pharmaceutical industry. The large bay modules resulted in a 75% reduction in the number of modules, further accelerating schedule completion.

Unique Project Challenges Overcome

- Two ocean shipments of oversized modules were each transported almost 14,000 miles, enduring weather,

rough seas, and traffic logistics. All modules arrived fully intact and on schedule.

- Outstanding communications made this successful project possible, despite the team spanning 12 time zones with team members in Singapore, San Francisco, Cincinnati, Charleston, and various vendor shops.
- Nearly all acceptance testing and qualification work was executed before module shipment to the Singapore site, thus reducing the time to start up once the modules were installed at the ECP-1 site.
- The team drew strength from what could have been obstacles arising from the diversity of languages, customs, standards, and practices in this multinational project.
- The team surmounted labor availability issues in Singapore by leveraging pre-existing subcontractor relationships, while still maintaining cost effectiveness. All subcontracts were bid on a lump sum or unit price standard.

Exceptional Project Management

- The project set new standards for team collaboration, teamwork, and team leadership.
- From the outset, Jacobs, Bovis, and Genentech formed a seamless partnership without boundaries or corporate egos.
- The tone of the project was set early with each team member committed to providing any and all resources required in order to deliver this facility in record time.
- Decision making occurred quickly and at the lowest levels possible.
- Emphasis was placed on meeting post-construction, FDA licensure-critical compliance deliverables to assure the GMP Lucentis Qualification batch schedule.

Notes from the Judging Panel – What Impressed Them

The project execution was fantastic.

Completion in 24 months! They had three geographic regions working on this project and they all came together with no items off more than three eighths of an inch. Good use of large box modules, done very well. They had some severe logistical challenges.

Award Category – Project Execution

Winners in this category exemplify the application of novel tools and approaches to delivering projects that improved efficiencies, overcame unusual challenges, promoted effectiveness, and organized stakeholders and project team participants in ways that led to successful outcomes.

The risk to the schedule of potential rework was mitigated through the development of a process that:

- established a design basis for each component (equipment/instrument) on the project
- tracked the vendor information for each component and its impact on design previously completed
- managed the impacts from a separate contingency fund established for this issue

A Unified Team Approach

The guiding principle throughout the project was the need to provide patients with products that addressed unmet medical needs, and the end users with facilities that were fit to operate.

Key Project Participants

Designer/Architect/Engineer: Jacobs Engineering Cincinnati (Cincinnati, Ohio, USA)

Construction Manager: Bovis Lend Lease Pharmaceutical Pte Ltd. (Singapore) *(See ad on page 13)*


Many design decisions were resolved by answering the question “what’s best for the patient?” These simple, but powerful words had long been part of the Genentech culture and were immediately embraced and followed by the contract members of the team, as well.

Effective communication with open and honest discussion of issues and concerns among all parties was an obvious requirement for this project to succeed. The project management team established an atmosphere of trust early, thus ensuring that team members did not overreact when potential problems or bad news arose. This allowed the team to be informed about issues early, while options to mitigate the situation were still open.

Although the project was highly collaborative, Genentech was at the top of the organization chart and had ultimate responsibility for all strategic decisions. Effective decision making with a well defined process and clear accountabilities was another critical success factor that made it possible to attain the aggressive schedule.

Performance was measured daily and formally reported weekly to Genentech and the rest of the team. This report highlighted overall cost trends, schedule status, progress, and productivity by discipline/task/module, staffing, change management, and safety. Through timely analysis of this data, the team identified negative trends early enough to implement mitigation steps and effectively kept the project on its schedule and cost targets.

Conclusion

The business requirements of the ECP-1 project presented the project 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 a \$217 million budget. As a result, facility production capacity goals were met, delivering a high-quality, licensable manufacturing site to meet future Lucentis market demand. 



Modules set on foundations.

Bayer AG
Pfizer
Lek Pharmaceuticals
GlaxoSmith Kline
Smithkline Beecham Pharmaceuticals
BRI
BASF AG
Interbio
Sandoz
ARC International
Eden-Waren
TMI
Miles, Inc.
Biotechnikum
EuroCetus
Sclavo SpA
Pasteur Merieux Connaught
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Lonza AG
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MannKind Corporation

Changing the Face of Bulk Lyophilization

Introduction

MannKind Corporation's signature drug, an ultra rapid-acting insulin therapy, was developed to offer the millions of people suffering from diabetes a non-invasive treatment option. At the heart of the drug lies MannKind's proprietary Technosphere® molecule that can deliver not only insulin, but also a wide variety of other macromolecules into systemic circulation through the pulmonary route. The Technosphere particle and Technosphere® Insulin (TI) were so revolutionary and specialized that no existing facility in the world was capable of producing them. For this reason, the company designed and built its own **Technosphere Insulin Manufacturing Facility** in Danbury, Connecticut, USA.

It is the custom process line the facility houses that impressed the judging panel and inspired them to award this project the **2010 Facility of the Year Award for Process Innovation**. MannKind engineered an innovative manufacturing process line from start to finish and at every point in this process, designed new technology or applied innovative adaptations to existing technology to meet their needs.

Yet another distinguishing feature of MannKind's facility is a first-ever solid-dosage pharmaceutical adaptation of a cryopelletizer for which the judges awarded the **2010 Facility of the Year for Equipment Innovation**. MannKind worked with Cryogenic Equipment Services to modify the cryopelletizer to create uniform pellets from the slurry so that the water could be removed quickly and consistently during the bulk lyophilization process. This revolutionary adaptation dramatically improved the quality of the drug and the efficiency of its production.

Innovation for a Top Priority

According to the Centers for Disease Control and Prevention, 7.8% of the U.S. population is afflicted with diabetes, as is a staggering 10.7% of Americans aged 20 or older. Diabetes costs our nation more than \$170 billion annually, and more

MannKind Corporation

Category Winner – Equipment Innovation and Process Innovation

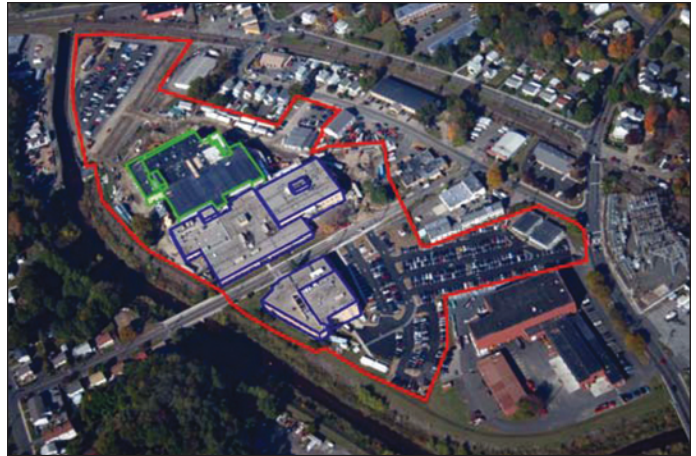
Project: Technosphere® Insulin Manufacturing Facility

Location: Danbury, Connecticut, USA

Size: 251,876 sq. ft. (23,400 sq. m.)

Total Project Cost: \$163,100,000

Duration of Construction: 20 months



Aerial view during construction: expansion outlined in green and connected to Building 1 outlined in blue.

importantly, it is responsible for tens of thousands of premature deaths each year.

MannKind Corporation, a diversified biopharmaceutical company engaged in the development of novel therapeutics for the treatment of major disease states, has made the treatment of diabetes its top priority.

MannKind's lead product, inhalable insulin, is based on the company's Technosphere particle technology: an inhalable powder designed to provide efficient conveyance of pharmaceuticals to the respiratory tract for delivery into the systemic circulation. Technosphere particles have an approximate mean particle size of 2.5 microns and are formed by the intermolecular self-



Specialty reactor designed to form Technosphere particles.

Continued on page 20.



Where does energy efficiency fit into the equation?

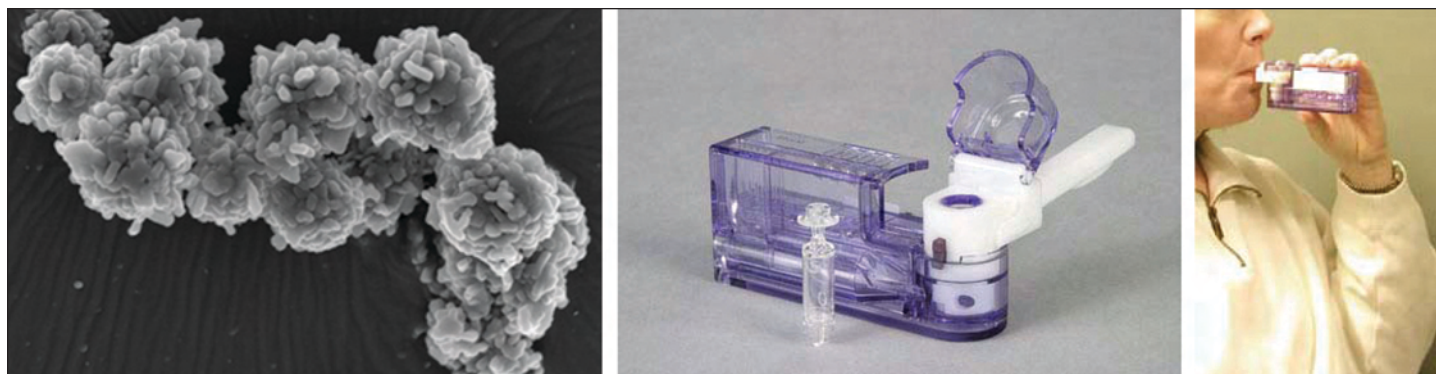
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Answers for infrastructure.

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The Technosphere particle (average particle size 2.5 microns in diameter), cartridge and inhaler, and inhaler in use.

assembly of a small organic molecule. A wide variety of small organics, peptides, proteins, and other macromolecules can associate with the particles to create a variety of innovative oral inhalation products.

Technosphere Insulin Inhalation Powder (TI) is delivered by means of the reusable, high-resistance, breath-powered MedTone® inhaler, discreetly sized to fit into the palm of a patient's hand. The innovation represented by Technosphere Insulin's formulation and drug delivery system made it necessary for it to be manufactured on proprietary equipment in a proprietary process. Commercial scale-up of existing laboratory techniques was not cost-effective, and the TI cartridges, still under design, were incompatible with existing powder filling technology.

In early 2005, MannKind initiated conceptual design of an expandable manufacturing facility for TI. At the time, the company was producing TI for clinical trials in a small pilot plant, and the first Phase 3 clinical trials of TI were being planned.

In anticipation of the preparation and submittal of its first New Drug Application (NDA), MannKind designed and built a \$163 million facility to manufacture TI. This included not just the building itself, but also the creation or novel adaptation of multiple pieces of process equipment.

Process Overview

MannKind's facility is divided into two main parts: 1) a bulk manufacturing facility where the Technosphere particle is made, combined with insulin to make TI,

freeze dried, and packed into containers that can be stored prior to filling; and 2) a filling-packaging facility where the finished cartridges are produced from the bulk TI powder.

The process begins with raw materials (acetic acid and FDKP) to form the Technosphere particle in solution. Using a tangential flow filter, the particles are washed using diafiltration and the concentration of the particles is increased by removing liquid. Insulin is added to the suspension to form Technosphere Insulin suspension. In a process called cryopelletization, the suspension is flash frozen to make pellets that are dried in a bulk lyophilization process to remove the liquid components. Dry TI powder removed from the lyophilizers is packed into containers that are later affixed to the fillers during cartridge filling. Filled cartridges are individually packaged into foil envelopes, and then assembled into kits to provide to patients.

Cryopelletizer

After the Technosphere particle is formed, insulin is added to a process vessel that contains the Technosphere particle suspension pumped from a tangential flow filter operation. Insulin is adsorbed onto the Technosphere particles to form TI, still in an aqueous suspension.

Once the TI particles are formed, the suspension is flash-frozen and then lyophilized (freeze dried) in bulk to obtain the dry powder. Simple quiescent freezing would allow the product to agglomerate while freezing, which would result in inefficient drying and/or meltback and possible loss of pharmaceutical usefulness. Therefore, the project team needed to create a new method of flash-freezing.



Cryopelletizer with the top section raised for inspection.

This led to the selection of the cryopelletizer, which flash-freezes the TI suspension into small pellets within a defined size range and solves the agglomeration problem.

Though cryopelletization has been applied in processing of cellular material from bioreactors, its use appears to be novel in the formulation of a solid dosage form delivery as an aerosol. According to the vendors and engineers involved in the project, MannKind's large-scale application, applicable to most bulk lyophilization processes, is unique in the pharmaceutical industry.

In the laboratory, cryopelletization can be accomplished by dripping the product suspension into a pool of liquid nitrogen to form small frozen pellets. Although this method produces good product on a small scale, the technique is not commercially viable. Commercial-scale production required the application and modification

Award Categories – Equipment Innovation and Process Innovation

Equipment Innovation

Winners in this category exemplify the novel application of commercially available and custom developed process manufacturing and facility management tools, which yielded superior results, advanced processing understanding, and improved competitive position. Includes imaginative collaboration with vendors/suppliers/manufacturers.

Process Innovation

Winners in this category exemplify the application of novel process manufacturing techniques on existing and new facilities, including fundamental scientific processing approaches and related applied science-based solutions to existing and new challenges.

Notes from the Judging Panel – What Impressed Them

For Process Innovation they were quite creative in what they accomplished. For Equipment Innovation, they designed a lot of the equipment from scratch.

Continued on page 22.



& KLING STUBBINS

Congratulate MannKind Corporation

Winner: 2010 Facility of the Year Award for Equipment Innovation

Winner: 2010 Facility of the Year Award for Process Innovation

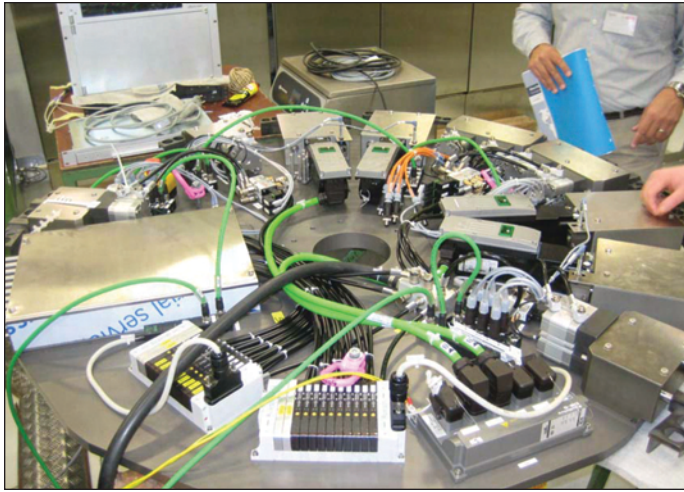


When it came to developing a state-of-the-art facility for the production of their revolutionary and highly specialized new signature drug, MannKind turned to industry leaders, CRB and KlingStubbins. The team delivered a striking and unique design that fused form and function with process efficiency.

Congratulations MannKind for being the first facility in the history of the awards to win in two categories and thank you for allowing us to be a part of the team!

www.crbusa.com

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Powder filler.

of equipment previously used, to the best of the project team's knowledge, only in the food processing industry.

Together with Cryogenic Equipment and Services (CES), MannKind designed a unique method to cryopelletize our product on a commercial scale. As with the laboratory technique, it

Key Project Participants

Designer/Engineer: CRB (Plymouth Meeting, Pennsylvania, USA) (*See ad on page 21*)

Architect: KlingStubbins (Philadelphia, Pennsylvania, USA) (*See ad on page 21*)

Construction Manager: Torcon, Inc. (Red Bank, New Jersey, USA)

Additional Suppliers:

- Automated Control Concepts (Neptune, New Jersey, USA)
- Dynamic Systems, Inc. (Raleigh-Durham, North Carolina, USA)
- Cryogenic Equipment Systems (Bissegem, Belgium)
- Integrated Process Technologies (Devens, Massachusetts, USA)
- Serail (Le Coudray, France)
- Siemens Building Technologies (Pine Brook, New Jersey, USA) (*See ad on page 19*)

utilizes liquid nitrogen to flash-freeze the product suspension, but rather than dropping or spraying the suspension into a pool of liquid nitrogen, it meters it into a liquid nitrogen stream. Internal components in the machine separate the frozen pellets from the nitrogen, recirculate the liquid nitrogen, and add

Why Our Project Should Win

The following is an excerpt from MannKind's submission, stating in their own words, the top reasons why their project should win the 2010 Facility of the Year Award:

- Our adaptations of cross-sector technologies for novel application in the pharmaceutical industry not only make the production of the innovative Technosphere® particle possible, they also make possible multiple new drug therapies in the future. Our cryopelletization technology can improve the production of hundreds of drugs worldwide that require bulk lyophilization in their manufacture; and our innovative, non-invasive drug delivery system can transport a potentially endless variety of macromolecules into systemic circulation via the lungs. Additionally, though our new facility was purpose-built for a drug with blockbuster potential to treat diabetes, it was also designed with tremendous flexibility and can be customized and expanded to suit new product needs and increased demand.
- Extensive use of standardization, automation, 3D design, field bus technology, S88 methodology, simulation software, labor-versus-automation cost analyses, and preinstallation testing permitted significant schedule accelerations and reductions in the overall project cost and the cost of post-installation issues, errors, and malfunctions. The resultant documentation and understanding gained from these techniques also greatly accelerated the commissioning and validation process and the development of SOPs.
- Our culture of empowerment and accountability, small-business flexibility, and unwavering focus resulted in

a superior quality facility that was completed on time and 11% under budget despite numerous stumbling blocks and challenges (renovation of an in-use facility necessitating phased construction, environmental remediation, multiple equipment customizations, overseas sourcing, regional challenges, company infancy, lack of pipeline funding, lack of capital construction experience, process equipment design occurring in parallel with facility construction, etc.).

- Our innovative use of multiple scheduling and communication tools, many not commonly found in pharmaceutical construction and one completely custom-designed in house, sets a standard for future capital construction projects in our industry and others. Our integrated, nimble SCoRe management system, combined with Primavera scheduling, PIMS, SharePoint, block-sequential diagramming, process mapping, and other techniques, resulted in a highly energized and empowered workforce, a stellar safety record, and the discovery of many creative solutions that may otherwise have been overlooked in a lesser management/communication environment.
- Our unrelenting commitment to our region and our environment informed our choices from start to finish. From the removal of 15,700 cubic yards of contaminated dirt, to the selection of energy-efficient equipment, to the final touches of recycled and recyclable sustainable furniture, sustainability was at the forefront of our decision-making processes during facility construction and beyond.



Cartridge filling line.

make-up nitrogen to replace that which evaporates.

Once conceived, the process of design, construction, testing, and operation led to several improvements to the overall process. Application of lean manufacturing principles eliminated the need to store frozen pellets and handle them multiple times: the pellets were formed, loaded onto chilled trays, and delivered into the freeze dryer. This method saved large capital investment in storage and transportation equipment for frozen pellets.


MannKind's pioneering efforts in cryopelletization and bulk lyophilization allowed the introduction of a dosage form never before used for any active pharmaceutical substance. The same general process can be applied to future APIs. MannKind's cryopelletization technique offers significant reductions in process

time and cost and significant improvements in the consistency of the resultant pellet size.

More Equipment Innovation

In addition to the new lyophilization technique, MannKind also made unique adaptations to the specialty mixer where the TI particle and the insulin are combined; designed a highly cost-effective method to move bulk powder from the lyophilizer to the filler; and designed a filling system that could work at high speed, while remaining safe for the operators and supremely precise in the metering of the bulk powder.

Conclusion

MannKind's Technosphere particle technology represents a radical leap forward in the pharmaceutical industry; together with their custom-designed, breath-powdered inhaler, it forms an entirely novel drug delivery method for a wide variety of therapies. Due to the innovative and highly specialized nature of the Technosphere Insulin (TI) particle, it was necessary for MannKind to conceive a new process technology for the production and packaging of the drug. Through innovative adaptations of cross-sector technologies for novel application in the pharmaceutical industry, not only did MannKind make the production of the TI particle possible, they also make possible multiple new drug therapies in the future. The cryopelletization technology can improve the quality and production of drugs that require bulk lyophilization in their manufacture. 



Daldrop + Dr. Ing. Huber congratulates Pfizer Biotechnology Ireland and Pfizer Ireland Pharmaceuticals on their „Facility of the Year Awards 2010“

The consistent implementation of the Daldrop + Dr. Ing. Huber SHELM EQ® Cleanroom system played an essential part in the successful applications of our clients for the Facility of the Year Awards. Daldrop + Dr. Ing. Huber are specialists for designing and constructing high efficient HVAC-Solutions as well as cleanroom floor, wall and ceiling systems.



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Pfizer Biotechnology Ireland

A Green Approach to Biotech Facility Design

Introduction

Pfizer Biotechnology's Ireland's **Monoclonal Antibodies Small-Scale Facility (MAbs SSF)** in Shanbally, County Cork, Ireland, represents Pfizer's first biotechnology greenfield development.

From inception through implementation, this clinical trial product facility incorporated industry best practices for sustainability and Pfizer's green building guidelines into its design, including: extensive re-use of existing assets, waste minimization procedures, recycling utilization in both construction and operations, the inclusion of energy-efficient fixtures and equipment, and minimized air change rates to meet comfort conditions and classification standards.

The project, winner of the **2010 Facility of the Year Award for Sustainability**, was executed with an excellent safety record and delivered on target according to a very aggressive timeline of 29 months from start of preliminary design to completion of PQ, 35% better than the biotechnology industry benchmark average.

Project Overview

Driven by a critical business need, Pfizer Biotechnology Ireland built the MAbs SSF to supply late state clinical trial material. The facility also serves as a strategic biotechnology manufacturing center of excellence and is planned to support the rapid development of new biotechnology products.

The initial product to be manufactured in the facility is Tanezumab, a humanized monoclonal antagonistic antibody with indications for osteoarthritis and chronic lower back pain in Phase III clinical trials.

The facility includes a warehouse with space adequate to meet the raw material and finished goods storage requirements of the manufacturing facility, and a combination of laboratories and administration offices within the same building to house the quality control laboratories and site staff. All facilities are incorporated within one structure. Other features of the facil-

Pfizer Biotechnology Ireland

Category Winner – Sustainability

Project: Monoclonal Antibodies Small-Scale Facility (MAbs SSF)

Location: Shanbally, County Cork, Ireland

Size: 133,000 sq. ft. (12,356 sq. m.)

Total Project Cost: \$189,613,542

Duration of Construction: 19 months



Aerial view of exterior.

ity include a technical services laboratory with a planned use to support technology transfers through, for example, lab pre-qualification) work for new products, process characterization, manufacturing support, and process validation.

The site was chosen for a variety of reasons, including its proximity to the adjacent Pfizer Ringaskiddy site which allowed the new facility to use spare capacity of the existing Waste Water Treatment Plant and fire main system rather than building a new treatment plant or bringing in new tanks and pumps for fire water retention.

The major elements of the project's approach to sustainability are detailed below.

Existing Asset Re-Usage

The choice of Shanbally as the site for the project and the fact that it was a previous manufacturing site with ready adjacency to the Pfizer Ringaskiddy API facility presented significant opportunity for asset re-use. The following highlight the green benefits and opportunities of this location:

- use of Pfizer Ringaskiddy (adjacent API site) Waste Water Treatment Plant spare capacity rather than the provision of a new treatment plant for process waste water and sanitary effluent treatment
- re-use of existing assets, e.g., existing tankage north of site for fire water retention
- use of gas, electrical, and city water supplies already on site

Notes from the Judging Panel – What Impressed Them

A top-tier sustainability project. Well done, well executed. Advanced automation, 3D, PAT, a lot of cutting-edge technology to make the facility happen. Their benchmarking data was exceptional.



Utilities area.

- use (through extension) of Pfizer Ringaskiddy Fire Main System rather than the provision of a new system with associated tanks/pumps, etc.
- 5,000 cubic meters of crushed rubble from an old adjacent facility were used in the building substructure
- 4,000 cubic meters of rock and stone which were excavated in the course of the works were crushed on site and used as backfill beneath the building and roads
- 2,000 cubic meters of topsoil were set aside and re-used for landscaping works
- 30,000 cubic meters of excavated material have been used on site for general fill and landscaping

Continued on page 26.

Pfizer Biotechnology Ireland Small-Scale MAb Facility • County Cork, Ireland

*Fluor Congratulates Pfizer Biotechnology Ireland
on Its 2010 Facility of the Year Award for Sustainability*



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HVAC plantroom.

Award Category – Sustainability

Winners in this category exemplify the application of novel approaches, tools, and techniques intended to improve effective use of energy, minimize waste, reduce carbon footprint, incorporate green manufacturing techniques, reduce environmental impact, and result in more efficient processing, utilities support, and business advantage.

Utility, Electrical, and Architectural Design – Environmental Considerations

Utilizing best practice and Pfizer's Green Building guidelines, a large number of energy efficient features were applied in the design as well as items which were commonly applied across the majority of the utility system (e.g., utilization of variable frequency drives, metered parameters fed back to energy monitoring system, high efficiency motors). Specific measures undertaken include:

Boilers and Steam/Condensate System

- economizers on boilers
- heat recovery from blow down to pre-heat make-up water
- automatic oxygen trim, gas boilers, and low NOx burners
- All condensate systems are designed for return of condensate to central receiver/deaerator (excluding clean steam condensate).

Chilled and Cooling Water

- water cooled chillers (preferred over air cooled units) based on energy consumption
- Cooling water designed such that RO water waste stream, regeneration, and reject can be used as feed-water for make-up.
- automatic cell isolation/flow management and temperature control – automatic control of cooling towers designed based on climate conditions

Key Project Participants

Designer/Architect/Engineer: Fluor Enterprises, Inc. (Greenville, South Carolina, USA) (*See ad on page 25*)

Construction Manager: Jacobs Engineering, Ltd. (Cork, County Cork, Ireland)

Clean Water Systems

- For sanitization purposes, ozone is used on RIW rather than heat/steam.
- Final treatment on Purified Water systems is electro-deionized.
- Meters provided to monitor all water usage.
- Point of use coolers are utilized rather than loop coolers.

Compressed Air Systems

- Compressors are water cooled with all air intakes externally ducted.
- Air drying regeneration achieved by separate blower rather than air compressor.
- pipe sized to minimize pressure drops/pressure at source

HVAC

- use of Variable Air Volume (VAV) air distribution systems in office type areas
- use of outside air economizer cycle for office areas
- low velocity/friction rate duct design to reduce fan horsepower
- use of direct drive fans, high efficiency motors, and VFD's on supply and return air fans
- chilled water coils sized for low velocity across coil face in order to reduce fan HP
- cycle operation of air handling units serving office type areas during unoccupied periods, based on setback temperature

Plumbing

- use of low flow/water conserving plumbing fixtures

Electrical Systems and Energy Management Systems

- The sites electrical distribution system is metered for every area and major use point.

- All utility meters and instrumentation can be tied into an energy monitoring system in order to monitor and control the major utility systems for a site.
- A lighting management system has been installed in the facility across all floors. This ensures lighting is only operational in occupied areas. This has a projected cost saving of \$83,234 per annum compared to a traditional switched system.
- use of energy efficient light fixtures and motors

Architectural

- All offices and desks are adjacent to exterior glazed walls.
- extensive use of glazing/glass walls in the facility to maximize the amount of natural light in the processing suite and make the building a more pleasant working environment
- An ecoseal grey insulated roof membrane has been used to reduce heat island effect.
- Building orientation optimized for solar gain.

Pre-Ops Energy Savings Study

An energy saving study was built into the early C&Q stage of the project, involving the sustaining operations personnel. Detail of set points and operating ranges were examined for all plant utilities and HVAC systems. Some key recommendations were incorporated back into the design. These included room temperature reduction throughout the facility. Air change rates for classified areas were challenged and minimization was successfully implemented (Grade D). The cooling tower water temperature was set to track the ambient wet bulb to allow for greatest efficiencies.

Process Chemistry

The processes, based on the Pfizer platform, have been developed such that solvent utilization is very limited in the processes. Beyond small quantities of ethanol in which chromatography resins are stored (between uses), the entire process is aqueous based.



Cell culture harvest train.

Concludes on page 28.



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Waste Management

The facility also operates a total waste management system. There is intensive recycling of all appropriate components under this system, i.e., fluorescent tubes, batteries, waste electrical and electronic equipment, cardboard, paper, cans, and glass.

Emissions

There are no major emission points from the facility, as defined by the Irish Environmental Protection Agency. There are only two minor emission point (boilers), both of which are significantly less than the 5 MW threshold.

Conclusion

Driven by a critical business need, Pfizer Biotechnology Ireland's project mission was to deliver a new cGMP multi-product mammalian cell culture manufacturing facility for monoclonal antibodies under an aggressive timeline and budget. Not only did the project team accomplish this mission, it also incorporated industry best practices for sustainability and Pfizer's green building guidelines into the facility's design, making the MAb's SSF a model sustainable biotech facility worthy of recognition. 

Why Our Project Should Win

The following is an excerpt from Pfizer Biotechnology Ireland's submission, stating in their own words, the top reasons why their project should win the 2010 Facility of the Year Award:

People/Team

- The overall team approach to the delivery of the project reflected a strong belief in the experience, strength, and capability of the core project team.
- At various points along the way, the team has been supplemented with highly capable design and construction partners.
- In the later stages of the project, there was full integration of the start-up resources and the sustaining operations team.
- It is a measure of the overall success of the job that each phase can be independently gauged as a success, in isolation from the other phases.
- This team have delivered an extremely high level of performance to achieve the results highlighted above.

Excellence in Project Execution

- It was recognized that extraordinary performance would be necessary to achieve the aggressive targets set to meet a critical business need for Pfizer.
- The project has excelled in delivery and exceeded Pfizer internal and industry benchmarks for all the major categories of safety, quality, schedule, and costs.
- New and innovative approaches to project challenges have been successfully implemented.
- A complex biotech facility has been designed, constructed, commissioned, and qualified to a point where batch production can proceed in less than 2.5 years. This represents a 35% improvement against the average time for this scope.
- The overall cost is almost 20% less than the project budget (excluding contingency). It also represents a 35% improvement against the average cost (\$/sq.ft), based on the industry benchmarks established for similar projects.
- A truly global project.

Operational Excellence

- Bearing in mind that this is Pfizer's first green field biologics facility, it is a significant achievement to complete a successful start-up in a timely manner. It is an even more noteworthy achievement when one considers the range of innovative operational approaches and structures that the plant has chosen to implement from inception.
- The project and sustaining operations team embraced Right First Time (Six Sigma) and Lean concepts and tools.
- A diverse operations team were brought together from various companies and geographic locations. They have operated in a non-traditional 'flat' organization which is focused on team performance.
- The Team successfully achieved all of this, despite a very challenging timeline, establishing a culture of operational excellence, flexibility, quality, and delivery.

Safety and Quality

- In terms of safety, based on overall construction person-hours of almost one million, the safety record achieved as zero lost time incident rate.
- The facility quality is of an excellent standard in terms of architectural finish, equipment, documentation, and systems. Re-work levels for mechanical and electrical were less than 1%.
- This plant represents the next step in the improvement of cleanroom design and construction for projects within Pfizer in Ireland.

Balance of Flexibility, Technology, and Sustainability in a Cost Conscious Manner

- The project has been constructed using a mix of technologies, both fixed and flexible.
- As well as being designed and constructed with sustainability and 'green' technology in mind, it has incorporated automation solutions in keeping with a modern biotechnology facility.
- Through this mix, the plant has maintained the capability to provide a competitive cost of goods, comparing favorably with biopharmaceutical contract manufacturing organizations.



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Pfizer Ireland Pharmaceuticals

Facility Integration at its Finest

Introduction

Pfizer Ireland Pharmaceuticals' **Aseptic Expansion** project in Dublin, Ireland – winner of the **2010 Facility of the Year Award for Facility Integration** – is notable for the way in which it successfully integrates a new production module with existing manufacturing operations and the surrounding residential neighborhood.

To respond to community and environmental issues associated with building a manufacturing facility so close to neighboring residential properties, the project team used a series of site analyses to optimize the current and future use of a very tight suburban site. The proposed design was specifically tailored to respond to its context and minimize the impact on the neighboring residences. Many other measures, along with extensive consultation with local residents groups, resulted in an aesthetically pleasing facility that meets Pfizer Ireland Pharmaceuticals' business need for additional freeze drying capacity, while demonstrating excellence in facility integration.

A Need to Increase Capacity

Located on a 17-acre site in Pottery Road Dun Laoghaire, the Pfizer Dublin Manufacturing facility has been in operation since 1970. Currently, Dublin is a global sourcing unit for both Vfend and Zithromax and is approved in the EU/US for both products. Pharmaceutical production has increased from an original volume of 750,000 vials to five million vials in 2008, increasing to 11 million vials in 2014.

In 2004, an overview of the freeze drying network within Pfizer concluded that there was a need for additional freeze drying capacity within Pfizer Global Manufacturing. A significant expansion of the Pfizer Dublin site was approved to provide additional capacity.

The project involved the construction of one new production module (PM2) containing four freeze dryers and the following support facilities: laboratories, warehousing, central utilities building, dispensary, and personnel and administrative support

Pfizer Ireland Pharmaceuticals

Category Winner – Facility Integration

Project: Aseptic Expansion

Location: Dublin, Ireland

Size: 177,066 sq. ft. (16,450 sq. m.)

Total Project Cost: \$254,674,792

Duration of Construction: 29 months



Aerial view.

areas. The facility was designed to manufacture products for global markets and is registered to be a global sourcing unit, working to FDA, EU, and JP standards.

A Desire to Be Considerate Neighbors

In early 2005, the foundations for the new aseptic facility in Dublin were started. The Dun Laoghaire site, which was originally built on reclaimed land, has a significant incline rising 12 meters from front to rear of the site. The new manufacturing facility was built at the back of the site and part of the design brief was to integrate the new plant with the existing buildings, while minimizing the impact on the surrounding residential neighborhood.

This required excavation of a significant hole in the site to reduce the profile of the building. Approximately 85,000 m³ of soil was excavated and reformed into large earth mounds (berms) around the site. When the building was constructed, significant time and effort was put into integrating it with the surroundings through the thoughtful landscaping of these berms.

Other significant contributions to the integration of the facility with the local community included: consistent color scheme in grey to neutralize impact on the landscape; curved roofs and plan elements for variety and liveliness and also to enhance the visual impact; and glazed areas and attractive design features on the buildings to raise the aesthetic content of the site.

A site master planning exercise completed during the conceptual phase of the project provided for significant future expansion space at the Dublin facility through the demolition of an existing Cadbury Adams gum based plant. In the short term, this space has been converted into a colleague garden.

Notes from the Judging Panel – What Impressed Them

They took so much time and effort into putting it together and consideration of neighbors. Very well-thought out.



Courtyard view of link corridor to PM2.

The site master plan also made provision for future expansion through the construction of a central utilities building with capacity and equipment space to support future modules.

Another key component of the project was the integration of the new facility (PM2) with the existing facility (PM1). A new warehouse was constructed as part of the project with adequate

space to meet the raw material and finished goods storage requirements of both production modules, thus freeing up the original warehouse space for conversion into an administration area. This administration area is now located at the heart of the site and is central to both production modules.

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View of PSF integrated with PM1 from colleague garden.

Design Process for Success

Pfizer approached each decision for this facility using a structured and rigorous assessment process. Thus site selection, site due diligence, and site master planning tackled the macro issues and likewise the internal facility scoping and planning tested the optimization of the

Award Category – Facility Integration

Winners in this category exemplify the application of good design practices and superior conceptual planning which led to excellent integration of facility and process, yielding efficient, clean, pleasant environments promoting business advantages for staff and enterprise, encouraging excellent processing outcomes. Synergistic merging of process and building to create environment of form and functional excellence.

operations and logistics. A good example of the complexity and thoroughness of this process is the site master plan described below.

Site Master Plan

Every successful project takes into consideration the receiving site and the scale and demands of the project. In Pfizer’s case, the site was difficult as highlighted by the following facts:

- narrow site with lots of neighbors
- visually and environmentally vulnerable (especially the landfill area)
- adequacy of space for existing and project demands and future growth
- steeply sloping site for both fill area (piling) and good ground
- good services availability
- Currently very tightly planned. Additionally, a desire to improve parking/plant boundary definition and

security, municipal authority plans for frontage road realignment, desire to improve fire/ambulance services access, and an own door access required by electrical utility company for the new HT station.

A series of site analysis and options diagrams sought to optimize the use of these valuable suburban lands, as well as to respond to neighbor and environmental issues.

The use of the site was further complicated by the existence of a third party legacy gum manufacturing plant occupying the center of the site; although its capacity was scheduled for eventual transfer to another site, it would remain operational for the duration of the construction works.

The analysis of these and many other options clarified how best Pfizer should develop the site. Two sets of criteria, “the

The Classics	The Criticals
Cost	Neighbor response and environmental (including road safety etc.)
Schedule/phasing	Facility integration/production/logistic synergies
Disruption	Management span and control
Expandability	Predictable growth patterns

Classics” and “the Criticals” were used in this assessment as shown.

This structured process of reviewing five and 20 year site planning options together simplified the decision making. Each option was reviewed to consider the implications both on manufacturing and the neighboring context. The final site was selected with consideration to manufacturing adjacency and synergy with the existing Pfizer facility and the rising topography to screen the new buildings.

Designed to Minimize Impact

The site design was developed to minimize its impact on its neighbors with the following characteristics:

- The overall manufacturing program is divided in five distinct buildings, each with smaller massing and impacts, but linked to a coherent site manufacturing pattern.
- Each building in turn is given a distinct shape to further break down the



Primary neighbor elevation: the top photo shows the existing views, the middle photo shows the effect of the berms, and the bottom photo shows the final effect of the landscaped berm. Up to 14 of these composite images were developed and discussed with the neighbors for their feedback and agreement.

visual scale and optimize its manufacturing function.

- The new buildings and structures are consistently colored grey to prevent

them forming a monolithic mass with the existing brown structures and to neutralize its color in the landscape.

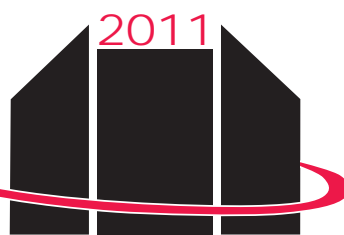
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The Facility of the Year Awards program is an annual program that recognizes state-of-the-art pharmaceutical manufacturing projects that utilize new and innovative technologies to both improve the quality of the project and to reduce the costs of producing high-quality medicines.

The Awards program is unique because it provides a platform for the pharmaceutical manufacturing industry to showcase its new products and accomplishments in facility design, construction, and operation.

The program, its Category Winners, and the Facility of the Year Award winner will be recognized through high-profile attention and media coverage from ISPE, INTERPHEX, and *Pharmaceutical Processing* magazine.

www.FacilityOfTheYear.org



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ISPE, INTERPHEX, and *Pharmaceutical Processing* magazine are looking to recognize projects that demonstrate global leadership by showcasing cutting-edge engineering, innovative new technology, or advanced applications of existing technology.

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For additional information about the Awards program and submission procedures, visit www.FacilityOfTheYear.org. You may also contact Amanda Gilmer, ISPE Marketing Associate, by tel: +1-813-960-2105 ext. 274 or by email: agilmer@ispe.org.



Key Project Participants

Designer/Architect/Engineer: Jacobs Engineering (Dublin, Ireland)

Construction Manager: Jacobs Engineering (Dublin, Ireland)

Major Equipment Suppliers:

- IMA Edwards (Dongen, The Netherlands)
- Robert Bosch GmbH (Crailsheim, Germany)
- ATEC Pharmatechnik GmbH (Sörup, Germany)
- STERIS FINN-AQUA (Tuusula, Finland)

- The buildings have large glazed areas and attractive design features to raise the aesthetic content of these industrial buildings. Curved roof and plan elements add variety and liveliness, enhancing the visual impact.
- The main buildings are cut into the existing site to lower visual impact. The car park can become multi-storey in the future.
- The earth released by this deep basement cutting is used to generate a large scale attractive bermed structure to fully enclose the site, and in particular, to build a local attractive planted hillock beside the nearest residences so that their views are predominantly of landscape structures rather than buildings.
- The bermed and landscaped enclosure of the site also would significantly reduce and remove any residual noise or night lights from the site.
- A new safer car and truck entrance was integrated into the site plan, including improved fire truck access.



Micro laboratory.

Conclusion

Pfizer Ireland Pharmaceuticals' Aseptic Expansion represented a unique proposition for modern pharmaceutical companies: How to act sustainably to support new products on a long standing established site in a residential suburban area. Through a rigorous and inclusive design process, Pfizer successfully integrated a new production module into its existing manufacturing site in terms of manufacturing capacity, effectiveness and flexibility, social and neighbor integration, and economics and city planning. (1)

Why Our Project Should Win

The following is an excerpt from Pfizer Ireland Pharmaceuticals' submission, stating in their own words, the top reasons why their project should win the 2010 Facility of the Year Award:

- The successful integration of a new production module, warehouse, central utilities building, and personnel support facility with existing operations (an aseptic manufacturing suite, a bioprocess suite, and QC laboratories) with no impact to manufacturing output during construction and qualification, while delivering improvements in quality, cost of goods, and colleague engagement.
- The sympathetic integration of the new facility within the surrounding residential area. An extensive process of consultation with local residents groups resulted in an aesthetically pleasing facility, carefully blended into the suburban landscape. The project team organized weekly follow up meetings with the local residents to continue the dialogue during the full execution of the project.
- State of the art equipment was used throughout the facility, including two highly automated compounding suites, vial washing/depyrogenation tunnel, pressure/time filling equipment, automatic loading/unloading of

pass through freeze driers, capping in grade B background, highly innovative inline inspection equipment, fully automated stopper processing.

An innovative solution to the industry wide issue of sticking stoppers was the combination of a specific surface structure of the freeze dryer metal shelf and coating with a Teflon-containing layer.

- The maximization of sterility assurance through the novel integration of the Atec Stopper Processor and a Restricted Access Barrier System (RABs) filling machine.
- The project involved the construction of a new production module and warehouse on reclaimed land on an existing Pfizer site. In addition to making use of vulnerable land, the considerable resources dedicated to conceptual planning resulted in a waste management strategy that has delivered an increase in the sites recycling from 15% to 85%.

In order to minimize the energy consumption, a lot of attention went to the optimization of the air changes in the clean rooms. The project team worked out an optimum proposal that balances the reduction the air changes and the assurance of the air quality in the cleanroom.

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