

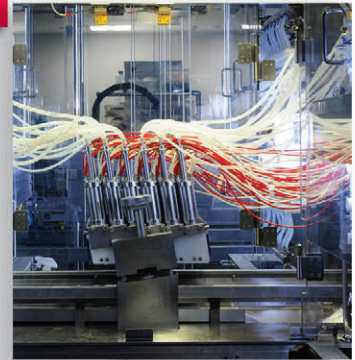
Facility Integration



Project Execution



Equipment Innovation



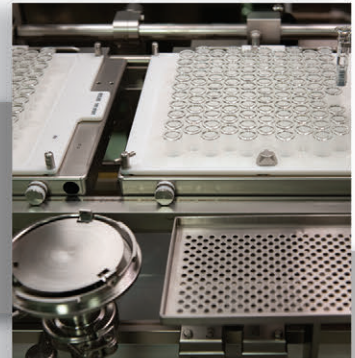
Operational Excellence



Sustainability



Process Innovation



Facility of the Year Awards
CATEGORY WINNERS

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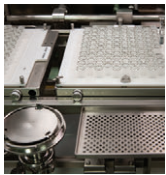
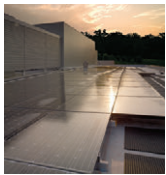
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2013 Facility of the Year Awards Program: Winning Projects Reflect Response to a Changing Industry

The Facility of the Year Awards (FOYA) program is the industry's premier awards program dedicated to celebrating innovation and accomplishments in facility design, construction, and operation.

The 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 entering its 10th 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 patients worldwide. The FOYA program is sponsored by ISPE, INTERPHEX, and *Pharmaceutical Processing* magazine.

"The FOYA program is about recognizing the pharmaceutical industry's innovation and technical advances in facility manufacturing, which ultimately is about helping patients who need and depend upon us for a reliable supply of quality medications," said Chaz Calitri, Vice President of Network Performance at Pfizer and chair of the 2013 FOYA Judging Panel.

"The six facilities honored by this year's award program embody innovation, exemplified by advances in areas

including flu vaccine manufacturing, which is very relevant in parts of the world right now where outbreaks have occurred, threatening public health. All of this year's honorees are to be commended for their important contributions to our industry and, most importantly, to improving people's lives."

The winning projects, selected from 27 well-qualified entries, reflect how industry is adapting to changes calling for more efficient, cost-effective manufacturing that brings new drugs to patients faster and with higher quality. Whether focused on vaccine or clinical manufacturing, recurring themes throughout all projects are staying ahead of trends and technology and preparing for rapid response.

The winning companies and respective award categories are:

- **Merck & Co., Inc.**, winner of the Facility of the Year Award for *Operational Excellence* for its Vaccine and Biologics Sterile Facility (VBSF) in Carlow, Ireland
 - **Morphotek, Inc.**, winner of the Facility of the Year Award for *Sustainability* for its Pilot Manufacturing Plant in Exton, Pennsylvania, USA
 - **Novartis Vaccines and Diagnostics**, winner of the Facility of the Year Award for *Process Innovation* for its United States Flu Cell Culture Facility in Holly Springs, North Carolina, USA
- The Facility of the Year Awards program is truly global, as submissions over the past nine 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 consisting of global senior-level executives from all aspects of the industry. These industry professionals included:
- **Chaz Calitri, Judging Panel Chair**
Vice President, Network Performance, Pfizer, Inc.
 - **Jim Breen**
Vice President, Worldwide Engineering and Technical Operations, Johnson and Johnson
 - **Steve Dreamer**
Head of Global Pharma Engineering
 - **Biogen Idec**, winner of the Facility of the Year Award for *Facility Integration* for its Flexible Volume Manufacturing (FVM) Facility in Research Triangle Park, North Carolina, USA
 - **F. Hoffmann – La Roche**, winner of the Facility of the Year Award for *Project Execution* for its Technical Research and Development (TR&D) Building 97 in Basel, Switzerland
 - **MedImmune**, winner of the Facility of the Year Award for *Equipment Innovation* for its UK Automation Upgrade Project in Speke, Liverpool, UK



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- **Brian H. Lange, P.E.**
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- **Shinichi Osada**
General Manager, Hitachi Ltd.
- **Andy Skibo**
Executive Vice President, Operations, MedImmune
- **Ron Trudeau**
Vice President, Facilities Engineering Services, Baxter Healthcare
- **Jon Reed**
Vice President, Global Engineering, Genentech
- **Georgia Keresty**
Chief Quality Officer, Johnson and Johnson
- **Karen Kinney**
Director, Sustainable Facilities, LEED AP/Project Management and Engineering, BD
- **Sanjit Singh Lamba**
Managing Director, President, Global Brands Unit and Head, Global Procurement Strategy, Eisai Knowledge Center

2013 Facility of the Year Events

The Overall Winner – selected from the Category Winners – will be revealed at

The Facility of the Year Award is sponsored by:



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ISPE's Annual Meeting in November. There will be several other opportunities to learn first-hand about the facilities being honored as "best in their class." These opportunities include:

- **INTERPHEX2013** – Attendees will be able to meet the Category Award Winners at the Facility of the Year Awards Display Area 23-25 April at the Jacob K. Javits Convention Center in New York City, New York, USA. Team members from winning companies will be on-hand to discuss the success stories associated with these pharmaceutical manufacturing facilities. More information, including registration information, can be found at www.interphex.com.
- **ISPE 2013 Annual Meeting** – Category Winners will give presentations about their winning projects during ISPE's 2013 Annual Meeting, 3-6 November in Washington, D.C., USA. The highly anticipated announcement of the 2013 Facility of the Year Awards Overall Winner will also take place during the Keynote Session of this event. Information and updates on this global event can be found at www.ISPE.org.
- **Feature Articles** – Comprehensive coverage will appear in *Pharmaceutical Processing* magazine and *Pharmaceutical Engineering* magazine at www.pharmaceuticalengineering.org.

Visit www.facilityoftheyear.org for more information about the awards program and comprehensive details about each of this year's award-winning projects and their support teams.

About ISPE

ISPE, the International Society for Pharmaceutical Engineering, is the world's largest not-for-profit association serving its Members through leading scientific, technical and regulatory advancement throughout the entire pharmaceutical lifecycle. The 20,000 Members of ISPE


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Journey through FOYA from Past to Present

The annual Facility of the Year Awards (FOYA) program is one of the most rewarding and gratifying experiences of my entire professional career. I remember the first meeting 10 years ago sitting among leaders from ISPE and Pharmaceutical Processing Magazine. Jon Tomson and Andy Signore, leaders in the ISPE volunteer community, presented the envisioned concept that after much networking and idea generation turned into a formalized plan. Thus began the Facility of the Year Committee, followed by the Judging Panel – which were the first steps toward making the program a reality.

I've had the pleasure of working on the Committee since its inception, working alongside ISPE's Scott Ludlum for eight years and now Bill Koenen of *Pharmaceutical Processing*. Through the evolution of the program, there's always been a special bond and camaraderie between the three sponsors of the program: ISPE, INTERPHEX, and *Pharmaceutical Processing Magazine*.

From the spring to the late fall, this is a celebration of the best technical and engineering work done worldwide in the pharmaceutical manufacturing industry. For me, nothing professionally matches the feeling of being onsite at INTERPHEX and being part of initiating this unmatched celebratory journey. INTERPHEX hosts the "coming out party" for the five (and sometimes more) category awards winners that celebrates the technical innovation that is critical in helping patients worldwide – which is such a "cool thing." The winners are onsite at the FOYA Pavilion to answer questions and share best practices in a dedicated area on the INTERPHEX show floor. On Wednesday evening, the category awards winners are honored at an intimate awards banquet dinner at the Yale Club in New York City.

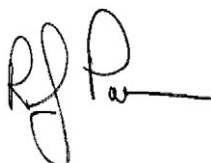
Throughout the year, *Pharmaceutical Processing Magazine* features articles detailing technological advances and best practices demonstrated by the category awards winners in engineering innovation. The recognition of the category award winners culminates with the announcement of the overall winner each year at the ISPE Annual Meeting in November. Seeing the faces and emotions of the project leaders and teams is very gratifying to me.

As we start over again, those that have won have not been forgotten, but a new season of FOYA begins. New submissions, new innovations, new winners, new journeys! Looking from the past and to the future, I am truly grateful to be a part of this program. I've seen so much great work over the past nine years that I am confident the future of innovation means more patients living longer and happier lives.

And to be a part of it, I will state it one more time, WOW how cool is that!

Please join us to celebrate the category awards winners at INTERPHEX, April 23-25, 2013 at the Javits Center in New York City.

I look forward to seeing you there,



RJ Palermo
Vice President of Strategic Initiatives, INTERPHEX
www.interphex.com

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Biogen Idec

Breaking Tradition to Create Flexibility for Clinical Programs

Introduction

The **Biogen Idec Flexible Volume Manufacturing (FVM) Facility** was constructed to manufacture variable batch sizes to address demand focused primarily on clinical trial material for therapies in the company's focus areas of neurodegenerative diseases, hemophilia, and autoimmune disorders.

Located in Research Triangle Park (RTP), North Carolina, USA, the facility is proving the success of an alternative manufacturing paradigm utilizing a hybrid of traditional fixed equipment manufacturing and end-to-end disposable manufacturing.

The manufacturing methods employed at the FVM Facility provide for a flexible multi-product environment with less capital investment, reduced utility demands, and increased speed through the product pipeline compared to traditional manufacturing methods. Biogen Idec's bold new methods and resulting success earned them the **2013 Facility of the Year Award for Facility Integration**.

Project Overview

The initial goal of the FVM Facility, constructed in an existing

Biogen Idec

Category Winner – Facility Integration

Project: Flexible Volume Manufacturing (FVM) Facility

Location: Research Triangle Park (RTP), North Carolina, USA

Project Mission: Optimize facilities usage through Flexible Volume Manufacturing.

Size: 10,000 sq. ft. (929 sq. m.)

Duration of Construction: 16 months



Cell culture single-use bioreactor with utility panel.

warehouse space, is to serve as a prototypical facility for proving the concepts of single-use technologies as a closed system.

The FVM Facility integrates into Biogen Idec's RTP campus, utilizing fixed equipment in existing areas in the 2K Small Scale Manufacturing (SSM) and 15K Large Scale Manufacturing (LSM) facilities without impact to existing manufacturing, creating a hybrid network of fixed and single-use equipment to accommodate variable product demands.

The facility covers a 10,000 square foot area comprising an inoculum prep lab, a cell culture suite, and two purification suites. The overall area is flexibly designed as General Pharmaceutical Manufacturing Space (GPMS) that is easily and fully upgradeable to either ISO 7 or ISO 8 classified space.

Biogen Idec's team based their success on the application of the following concepts and approaches:

- Flexibility and adaptability for clinical programs
- Integration with existing site operations

Congratulations to **Biogen Idec** on the **Facility of the Year Award** for Facility Integration

Biogen Idec's Flexible Volume Manufacturing (FVM) Project, located in Research Triangle Park, North Carolina



biogen idec

The FVM facility supports Biogen Idec's commitment to developing and delivering effective and innovative therapies to patients worldwide by providing adaptability and flexibility in manufacturing, particularly for early stage clinical products. Working with Biogen Idec, the CRB team provided **architectural and engineering services** for the entire FVM facility and successfully executed **construction management services** on the build-out of the cell culture suite.



"We are extremely honored to have worked with Biogen Idec on this world-class facility and winning this prestigious award. Knowing that our talent and expertise are contributing to our client's success and helping them efficiently and safely bring much needed medications to patients who need them is what drives us." — *Jeff Biskup, CRB President and CEO*

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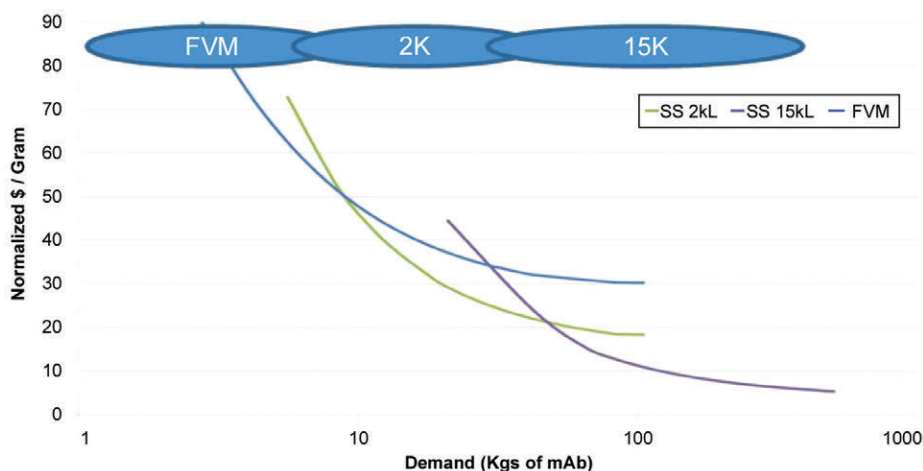


Figure 1. Cost of Goods for Operating FVM vs. 2K (SSM) vs. 15K (LSM) facilities.

- Operational approach
- 100% single-use flow path in a validated closed system

Flexibility and Adaptability for Clinical Programs

The very nature of clinical manufacturing, smaller batch vol-

ume requirements, and less predictable outcomes require an adaptable, flexible facility and manufacturing platform. The business need is to do this in a more cost-effective solution while reducing time to delivery of the clinical material.

Figure 1 compares cost of goods for operating in the FVM Facility vs. the fixed, stainless steel equipment in SSM (2KL) and LSM (15KL). Smaller batch volumes (<10 kg product) are typical for clinical batches and specialized orphan drugs. From a cost standpoint, smaller batch volumes lend themselves to production in the FVM Facility compared to the SSM and LSM production facilities at the RTP site. Conversely, when large product volumes and throughput are required, the SSM and LSM facilities are more cost-effective.

The FVM Facility allows the flexibility to produce just what is required to meet the immediate clinical program needs by adapting the volume of the production bioreactor. If only a small batch of material is required, this facility uniquely facilitates the ability to minimize costs by flexible production volume



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— As stated in JP Rev. 16



and the concomitant reduced need for expensive adsorbents, filters, and hold volumes during downstream processing. Once the program is ready to move forward, more drug substance can be manufactured at the required quantities and in the facility appropriate to meet the need. A hybrid network of manufacturing facilities allows Biogen Idec to optimize use of its manufacturing assets with regard to overall cost of manufacturing.

Integration with Existing Site Operations

Biogen Idec strategically selected the location of the FVM Facility to leverage existing cell culture, media and purification solution preparation capabilities. For example, the FVM purification suites can accept harvested cell culture from the adjacent SSM (2KL) facility, increasing the equipment utilization of the existing, stainless steel bioreactors. Additionally, process media and buffers are prepared in existing stainless steel preparation vessels without impacting other concurrent production. Thus,



Cell culture overall.

existing warehouse storage (for media/buffer materials), weigh-out dispensaries and solution preparation areas of the facility are also leveraged to support the new single-use purification and cell culture suites in FVM. This hybrid model of using

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Purification single-use chromatography in operation.

existing network and new single-use technologies allows Biogen Idec to effectively accommodate demand variability, without negatively impacting SSM and LSM manufacturing schedules.

Operational Approach

Biogen Idec's ultimate goal is the capability to build a mobile prototype flexible manufacturing facility that can provide bulk drug product for human use, breaking with the traditional fixed equipment and cleanroom investment paradigm. Dependence is greatly lessened or eliminated for capital-intensive structures associated with traditional manufacturing, such as stainless steel vessels and extensive distribution piping (including Clean-in-Place and Steam-in-Place), complex automation systems or extensive facility support infrastructure including heating, ventilation and air conditioning (HVAC) support for classified spaces.

To retain flexibility for future applications of single-use technology, 3D design was utilized to ensure accessibility,

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 2013 Facility of the Year Award:

- **Flexibility and adaptability for clinical programs.** The additional FVM production capabilities and novel manufacturing strategies provide a cost-effective means to quickly react to the variable requirements of clinical programs, from a standpoint of both batch volumes and timeframes. The goal is to create the flexibility required to enable rapid delivery of clinical supply while maintaining cGMP compliance and allow Biogen Idec to advance more drug candidates. Ultimately, this approach is about accelerating innovative treatments for debilitating diseases through the pipeline to benefit patients who need them.
- **Full utilization of existing production spaces.** The FVM Facility provides a cost-effective means for delivering and maximizing a blend of single-use systems and fixed equipment assets, taking advantage of existing production spaces. As an example, process media and buffers are prepared in existing adjacent areas, in fixed vessels, without impacting current production. In addition, the FVM purification suites add downstream processing capacity utilizing existing cell culture bioreactors in the adjacent SSM facility. Thus, existing capacity in other areas of the RTP site is leveraged with the added FVM production capacity, via the new single-use purification and cell culture suites.
- **Manufacturing – 100% single-use flow paths in a closed system.** Single-use, closed technology is utilized for all phases of drug substance manufacture – inoculum prep, cell culture, and purification through final product transfer and dispensing. Proving this technology and operation methods to be successful opens up the possibility to adapt the manufacturing environment to General Pharmaceutical Manufacturing Space (GPMS). This may provide a tremendous benefit in that it integrates seamlessly into a hybrid manufacturing network. Such a network allows balancing facility utilization to more efficiently produce life changing therapeutics for the patients we serve.
- **Deployable proof-of-concept facility.** The design concept of the FVM Facility, or a similar-type facility, can effectively be constructed anywhere. With a greatly reduced reliance on the typical parameters associated with traditional manufacturing, such as stainless steel vessels, complicated piping distribution systems, and extensive facility support infrastructure, FVM is a tangible solution for localized manufacturing requirements in emerging markets. With a validated proof of concept, regional facilities can be deployed with minimal capital investment requirements and shortened readiness timelines.
- **Minimize impact to site utilities.** While the FVM Facility is designed to be fully upgradeable to ISO 7 and ISO 8 classified spaces, if required, the intended outcome is to design and plan for the typical industry approaches without necessarily utilizing them. Production occurs in a GPMS environment and HVAC and CIP requirements are substantially reduced. Consequently, utility usages of steam, chilled water, tower water and electricity are also minimized. In addition, air locks for the production spaces become non-existent, increasing effective manufacturing floor space.



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CONGRATULATIONS BIOGENIDEC
Winner of the 2013 Facility of the Year Award for Facility Integration





Single-use ultrafiltration skid.

movement space, and “plug and play” layouts. Ceiling mounted utility systems allow the capability to service equipment with no fixed connections, allowing replacement of equipment with other different equipment relatively easy.

100% Single-Use Flow Path in a Validated Closed System

The FVM Facility demonstrates that closed systems can be maintained through the entire manufacturing process, utilizing “closed system disposable technology,” procedural con-

Key Project Participants

Designer/Architect/Engineer: CRB Consulting Engineers, Cary, North Carolina, USA (See ad on page 11)

Construction Managers:

- DPR Construction, Morrisville, North Carolina, USA (See ad on page 15)
- CRB Builders, Cary, North Carolina, USA (See ad on page 11)

Piping and HVAC Subcontractor: Gamewell Mechanical, Salisbury, North Carolina, USA

Major Equipment Suppliers:

- Finesse, Santa Clara, California, USA
- Sartorius Stedim, Bohemia, New York, USA
- GE, Piscataway, New Jersey, USA
- Pall Life Sciences, East Hills, New York, USA

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.* ”

trols, and in-process testing. This opens up the opportunity to consider operating in General Pharmaceutical Manufacturing Space (GPMS).

A traditional cleanroom/ISO 8 classified space is designed with a number of air locks strategically located to segregate air flows and maintain pressurization of the clean and dirty spaces, as well as upstream and downstream spaces. Similarly, product transfer and dispensing rooms supplied with 100% outside air are typically included within the clean space. While the FVM Purification Suite is currently designed to allow for future personnel and material entry air locks, a goal of the FVM Facility is to prove that constructing these physical separations and barriers is not required when using validated closed processing systems. Air locks and product transfer and dispensing rooms were not constructed in the FVM Facility, and air handlers are operated to provide air changes appropriate to GPMS conditions.

Conclusion

By applying the concepts and approaches above, Biogen Idec’s FVM Facility is proving the success of an alternative manufacturing paradigm utilizing a hybrid of traditional fixed equipment manufacturing and end-to-end disposable manufacturing. Biogen Idec is implementing the technologies of today, combining innovative solutions with common sense approaches to accelerate products through the pipeline in a cost-effective, efficient manner, bringing innovative treatments for debilitating diseases to the patients who need them. ①

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F. Hoffmann-La Roche Ltd.

Formula for Success in Project Execution

Introduction

The **Technical Research and Development (TR&D) Building 97** project was initiated to consolidate the Roche research and development groups for oral solid dosage and parenteral liquid dosage forms for clinical studies into one facility.

Embedded in the city of Basel, Switzerland and adjacent to a residential area, the project had to meet stringent authority requirements and ensure a good working relationship with the local neighbors during the building life cycle. The project addressed several issues, including meeting the different requirements of two user groups consolidated under one roof; building in a tight urban area environment; and a complex permitting approval.

Roche earned the **2013 Facility of the Year Award for Project Execution** for their excellence in overcoming these challenges within budget and schedule and building a facility that meets the requirements and expectations of Roche users and the Basel community.



Aerial view of building 97 and Basel site in background.

F. Hoffmann-La Roche Ltd.

Category Winner – Project Execution

Project: Technical Research and Development (TR&D) Building 97

Location: Basel, Switzerland

Project Mission: Build a high quality galenical TR&D facility at Basel site, at lowest possible cost, while meeting all user requirements.

Size: 239,723 sq. ft. (22,271 sq. m.)

Duration of Construction: 33 months

Project Overview

In addition to housing development of suitable dosage forms for new pharmaceutical molecules for clinical development and market, TR&D Building 97 will supply drug products for clinical Phase I to III studies worldwide. Formulations for a major part of Roche's portfolio will be developed and supplied from this facility. Key elements of the facility are:

- Liquid filling lines for vials including freeze drying and pre-filled syringes
- Solids processing units (e.g., granulation, tableting, coating, encapsulation, etc.)
- Laboratories, offices, archives, and storage areas
- General and process infrastructure including clean media generation and distribution
- Capability to handle highly active compounds

External Requirements

Because the building is located next to a residential area, there were significant expectations regarding appearance, architec-

tural integration, and Roche's place in the community. Roche was required to file a master development plan, which had to be agreed upon by the general city council. In addition to the standard permitting related activities, Roche's plans needed to be reviewed and approved by a special city architectural board.

The agreed upon master development plan contains Roche commitments exceeding the norm in favor of good citizenship and the best possible city integration:

- Limited and stepped building heights linked to distance from boundary limits (avoiding shadows on neighbor buildings)
- Building shapes and appearances (optical integration)
- Transparency (free space between buildings) and green zones (plants and trees)

These agreements formed the basis for the facility design and at times challenged the internal needs of the facility users who were attempting to achieve optimal operational functionality and layouts.

Internal Requirements

The two user groups from technical research and development required different functionalities that had to be consolidated



Finished construction pit in a very tight construction area.

in one building. A plan was needed to bring together functions that needed to interact with each other, but were historically scattered throughout the Basel site. The following were the internal requirements:

- Process area for production of oral dosage forms for clinical trials (GMP, Class E)

FREEZE DRYING SYSTEMS

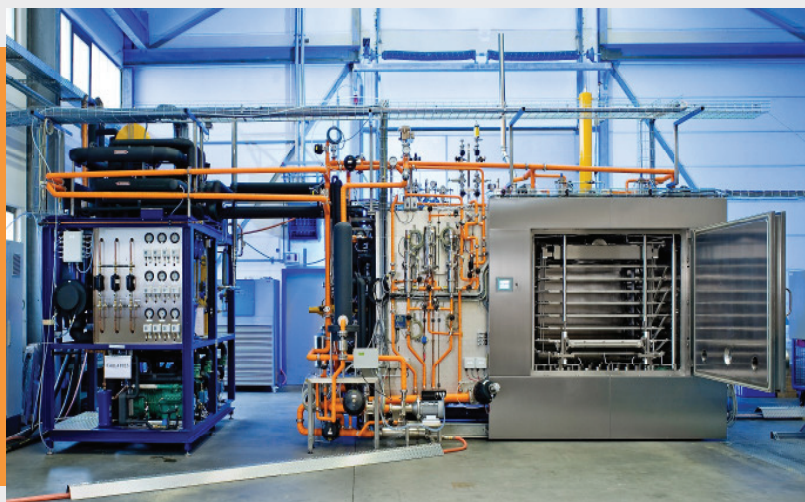


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35102 Lohra – Germany

phone: +49 6462 6080
mail: info@hof-sonderanlagen.de
hp: www.hof-sonderanlagen.com



Civil phase nearing completion 2009.

- Process area for production of parenterals for clinical trials (GMP, Class D-A, sterile)
- Process area for production of liquid filled capsules (GMP, Class E)
- Adaptable area for new and special technologies
- Laboratories within a controlled zone for oral dosage form research and development
- Laboratories for toxicity studies within a controlled zone
- Requirement for handling highly active substances up to Class 3A

Why Our Project Should Win

The following is an excerpt from Roche's submission, stating in their own words, the top reasons why their project should win the 2013 Facility of the Year Award:

- **High stakeholder satisfaction level**
 - Very challenging requirements fully implemented
 - Very positive feedback by all, users love their new facility
 - Outstanding quality of the facility recognized by all
 - Great architectural design appreciated by neighbors, city and Roche
- **Excellent project execution**
 - Forming, motivating, and leading large, integrated, and cross functional teams
 - Outstanding management support based on trust and competency
 - Establishing excellent relationships with all authorities. Successfully managed all internal and external neighbors
 - Achieved maximum functionality and quality on a minimum of available space
 - Despite all odds, undercut budget significantly and maintained delivery schedule on the day

- Modern, open space office
- Storage space, GMP and non-GMP

The following were additional challenges to internal requirements:

- Reliably define battery limits of and transition between areas (different GMP controlled zones, different laboratory categories, general areas, e.g., offices)
- Maintain the defined and validated pressure cascade between areas and rooms (670 rooms, 99 air locks) at all times
- Exploit synergies for personal and material flow
- Shared functions and rooms, e.g., gowning and dispensing areas

The project team succeeded in enabling two different GMP zone-concepts within the controlled production areas for solid dosage forms and for parenteral dosage forms. By designing the two different types of areas adjacent and connected to each other, the team was able to raise efficiency and avoided unwanted redundancies.

Strategy to Meet and Exceed Requirements

The project team credits their success to detailed planning, clear structures, continuous and in depth involvement of all stakeholders, excellent management support, and superior teamwork. High emphasis was given to:

- **World leading technology through collaborative equipment innovation**
 - Implemented functionalities beyond market availability through engaged innovation
 - Innovation involved all stakeholders aiming at sustainable results
 - Significant number of innovative and "first in industry" process functionalities implemented
- **Facility integration – complex functionalities with high synergies**
 - New home for final dosage form technical R&D exceeds expectations
 - Successfully integrated multiple zone grades while maintaining maximum synergies
 - 670 rooms, 880 doors, 99 air-locks, 239 cleanrooms, labs offices, etc.
- **Architectural landmark and clear commitment to the location of Basel**
 - Facility fits excellently into Roche site and city of Basel
 - Architectural landmark and highlight
 - High level commitment through agreed site development plan
 - High and very positive recognition of this unique facility by all



M+W GROUP



Roche, Basel (Switzerland)

Your Partner for Design and Construction

Congratulations to Roche Facility of the Year Award in Project Execution

M+W Group has been a reliable engineering partner for Roche in several projects. At the galenical TR&D project in Basel (Switzerland), M+W Group scope included concept, basic and detail design, procurement, construction management, commissioning and qualification.

As a leading global engineering and construction company M+W Group provides comprehensive process solutions for the Life Science and advanced technology sector. Locations in more than 30 countries covering all of Europe, Asia, and the Americas combine international experience with local support.

We would like to take this opportunity to offer our sincere thanks for the successful cooperation.

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www.pi.mwgroup.net

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Branch Office Switzerland
Gewerbestr. 12
CH-4123 Allschwil/Basel
ch.pi@mwgroup.net

- **Project definition.** Through an extended front-end planning phase, Roche was able to deliver a complex project tailored to user needs, with optimal functionalities. In the project goals, schedule was given lowest priority. Compliance with cost and quality targets was rated higher. The target schedule was built to allow best possible definition of tender packages.
- **Execution planning.** Thorough execution strategies and an excellent team delivered a high quality project fast, safe, and significantly below budget.

Roche's local procurement department handled all procurement activities involving 285 packages, of which required 189 equipment and construction contracts. The procurement plan included providing a flexible packaging strategy adaptable to the available market. Packages were mostly placed at or well under budget, which was a direct success of the well-executed procurement by Roche professionals.

A sophisticated construction site logistics and security plan was developed to address a tight construction space that posed challenges for logistics, safety, and construction methodologies. Full time logistics and security supervisors kept every movement under control.

- **Review and approval steps.** In depth reviews and rigorous change management was implemented. As part of regular project progress reviews, systematic risk assessments were executed and the resulting corrective actions were taken.
- **Quality assurance.** Continuous quality monitoring focused on outstanding results and high user satisfaction.

Key Project Participants

Designer/Architect: Herzog & de Meuron Basel Ltd., Basel, Switzerland

General Planner (A&E) and Construction Manager (building and infrastructure): M+W Group GmbH, Stuttgart, Germany
(See ad on page 21)

Construction Manager (process): Chemengineering Technology AG, Münchenstein, Switzerland

Civil/Structural Contractor: ERNE AG, Laufenburg, Switzerland

Piping Subcontractor: BIS Rohrbau Grenzach GmbH, Grenzach-Wyhlen, Germany

HVAC Subcontractors:

- E. Kalt AG, Basel, Switzerland
- Tschantré, Basel, Switzerland

Building Controls: Honeywell AG, Dielsdorf, Switzerland (See ad on page 23)

Process Controls:

- Penta-Electric AG, Münchenstein, Switzerland
- OctaveSoft GmbH, Basel, Switzerland
- Actemium Schweiz - Controlmatic AG, Pratteln, Switzerland

Main Equipment Suppliers:

- Groninger & Co. GmbH, Crailsheim, Germany (See ad on page 45)
- Robert Bosch GmbH, Waiblingen, Germany
- DIOSNA GmbH, Osnabrück, Germany
- Glatt Maschinen- & Apparatebau AG, Pratteln, Switzerland
- KORSCH AG, Berlin, Germany
- a1 safetech AG, Muttenz, Switzerland

***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. ”*

Cross-functional expert teams made up of engineering and user representatives were formed for vendor pre-qualification, vendor inspections and factory acceptance tests. Tremendous effort was put into guiding and monitoring equipment vendors to assure functional and quality requirements were met.


During construction, installation work quality was closely monitored. Regular walk downs by designated expert teams, as well as joint walk downs with the construction manager discovered quality issues quickly, allowing timely corrective action. Also during walk downs, users were involved. This led to a high level of mutual trust and quality for the facility. During all qualification steps, engineering, quality assurance, and users worked collaboratively, leading the suppliers to meet set quality targets.

- **Organizational setup and team environment.** A Roche core team led the project from inception to hand-over. Full-time professionals held leadership positions. The team was heavily supported by discipline experts and various site functions. The user representatives were an integral part in the project team from definition all the way to acceptance. Very close collaboration with the city's building authorities was key.

Several off-site team building events and project execution planning workshops were held to develop plans and align project participants across all functions.

During the design and qualification phases, close contact with the pharmaceutical regulatory authorities was kept. Several informal "plan inspections" were executed, helping to align expectations and minimizing inspection risks.

Conclusion

Through excellence in project execution, the TR&D Building 97 project team succeeded in satisfying all stakeholders, while meeting the target hand-over date and staying 11% below the approved budget. The team built a high quality facility that not only meets or exceeds both user and site requirements, but serves as a key site for Roche in the area of innovative formulations. 

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MedImmune

Redesigning Egg-based Bulk Vaccine Manufacturing

Introduction

Recognizing that their existing egg-based bulk vaccine manufacturing process would not support a rapid increase in production of its influenza vaccine Intranasal, MedImmune, the global biologics research and development arm of AstraZeneca, implemented the **UK Automation Upgrade Project**, a series of innovations to their existing equipment line in Speke, Liverpool, UK.

The MedImmune team redesigned the egg-based bulk vaccine process from a series of manual steps to a fully automated system. Their creative efforts streamlined and reduced the time required for the harvest process; reduced the incidence of production contamination; and reduced or eliminated waste in every area of the manufacturing train. Because of its work to drive a paradigm shift in the egg-based vaccine industry, the Facility of the Year Award Judging Panel recognizes this project as winner of the **2013 Facility of the Year Award for Equipment Innovation**.



Secondary candling system.

MedImmune

Category Winner – Equipment Innovation

Project: UK Automation Upgrade Project

Location: Speke, Liverpool, UK

Project Mission: Build and license a fully automated manufacturing facility

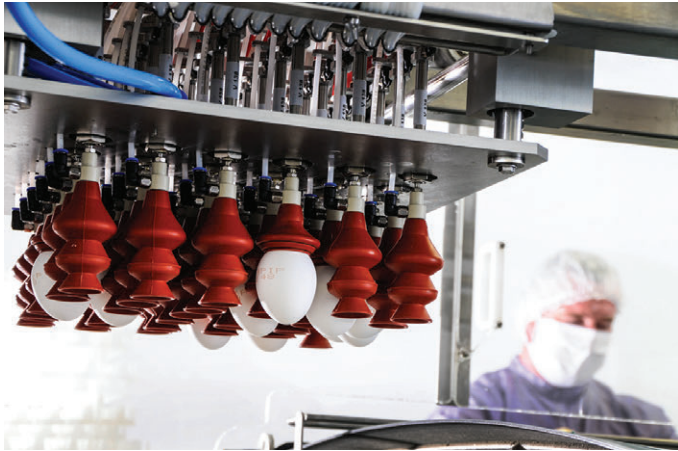
Size: 47,000 sq. ft. (4,366 sq. m.)

Duration of Construction: 7 months

Project Overview

MedImmune's Live, Attenuated Influenza Vaccine (LAIV), Intranasal, is the only live nasal spray indicated for active immunization against influenza disease in eligible individuals two to 49 years of age in the US, and in eligible children 25 months to less than 18 years of age in the EU.

In addition to facing the tight timelines of the seasonal influenza business, MedImmune encountered a lack of commercially available equipment to support unique process requirements. Their solution: redesign each discrete processing step into a fully automated and integrated production train. While doing so, the team made significant innovations to equipment for automated candling, isopropyl alcohol (IPA) spray, decap inspection, harvesting, and isolation.



Candling reject station.

The Candling System

In the existing process, eggs were visually inspected via candling in a darkened room, where trays of eggs were manually removed from trolleys by operators and placed on special tables for inspection by trained personnel. Damaged, infertile, or otherwise unsuitable eggs were discarded and remaining eggs sent on to further processing.

In the new system, trays of eggs are sent directly to the automatic candling system, which is programmed to determine viability for further processing through standardized recognition software using parameter sets based on flock age and egg size. These improvements resulted in a repeatable candling process, as well as a large reduction in the incidence of error due to subjective operator decisions. The team also developed a first in the industry data collection system under ISPE GAMP® guidance, which categorizes the rejected eggs based on pre-determined characteristics, positioning the system for sustainability and continuous improvement.

The new system increased throughput from 2,500 eggs per hour to 10,000 eggs per hour, while reducing the need for operator decision from 100% to 10%. In addition, manual handling was reduced from 5,850 events per batch to 4 events per batch.

IPA Spray

In the existing process, IPA was manually sprayed by operators over each tray of eggs prior to harvest. This resulted in increased operator exposure to IPA and inconsistent and uneven distribution of IPA from tray to tray and from operator to operator.

To reduce manual handling and bioburden, automatic tray sensing and spraying was installed. To improve repeatability, consistency, and distribution, the team changed the standard single spray to a multi-sequence spray with each phase independently adjustable. To reduce operator exposure to IPA, an advanced Hazardous Area Classification assessment was per-

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Bio on demand

The dynamic development of the biotech sector has resulted in an increased number of biotech projects and customers worldwide during the last few years, in particular in the emerging markets. Many small, more flexible biotech facilities based on single-use technology are seeing the light of day, especially in China.

To address these new requirements, NNE Pharmaplan has established a standard biotech facility concept called Bio on demand™, which can be built on site in the traditional way or off site as a modular facility. Standardised process and utility modules are combined in various ways to accommodate all the different functions in a modern biotech facility and the

need for flexibility and adaption to local building and GMP regulations and practices.

The Bio on demand™ concept includes the engineering and supply of a facility as well as related quality systems, standard operation procedures (SOPs) and the organisation of necessary quality tests.

NNE Pharmaplan is currently applying the standard Bio on demand™ concept in the design of a number of new biotech facilities.

[Read more on nnepharmaplan.com](http://nnepharmaplan.com)

CHINA. Shanghai Henlius Biotech is building a new state-of-the-art facility for production of MAb-based therapeutics for treatment of malignant tumours.

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Decapped egg inspection.

formed, leading to implementation of a robust safety and local extract ventilation system.

Decap Inspection

In the existing process, a team of operators manually decapped each egg using a hand held pneumatic popper. Once cut, the operator manually removed the individual caps using a scalpel and pushed the embryo aside with a spatula to enable harvesting. The operator then performed a subjective assessment of suitability for harvest. This step required the operator to physically handle each and every egg (36 eggs took 15 minutes) and introduced the risk of bioburden to each egg. The results of manual inspection were subjective, and not scientifically repeatable.

Why Our Project Should Win

The following is an excerpt from MedImmune's submission, stating in their own words, the top reasons why their project should win the 2013 Facility of the Year Award:

- **We revolutionized the egg-based bulk vaccine industry.**

We used our extensive experience with both the detailed manufacturing process for creation of LAIV and our expertise in automation and machine design to develop and deploy the first-in-the-industry, integrated system for inspection, inoculation, and harvest of eggs for the vaccine industry.

- **We pushed the technological envelope without changing the process.**

We improved our manufacturing capabilities, while not changing our regulatory approved process. We redesigned each discrete, manual upstream manufacturing step to a completely automated process, and integrated all discrete steps into a fully automated production train, using the formulas and processes which have proven successful in the production of LAIV. Our redesign of the egg-based bulk vaccine manufacturing process resulted in a significant increase in harvesting yield, while significantly reducing bioburden. In total, we implemented more than 20 significant innovations to egg-based bulk vaccine manufacturing systems. Our team used state of the art equipment and technology and integrated them in a way that pushed the technological envelope, while not changing the underlying science and process.

- **We mirrored Defense Advanced Research Projects Agency (DARPA), Department of Defense (DOD), and US National Aeronautics and Space Administration (NASA) system engineering methodology.**

Our core engineering team developed creative approaches to the specific challenges presented in this project, and produced a state

of the art, first-in-the-industry egg-based bulk vaccine processing system using DARPA, DOD, and NASA system engineering techniques. We started with a Solution-Neutral Statement (SNS) then developed both the system design and the project execution strategy to support the SNS.

- **We created a virtual company by deploying our SMEs at suppliers' facilities.**

We embedded our SMEs at our equipment suppliers' facilities, effectively as employees of the suppliers, creating a new "virtual company" to ensure all equipment designs would be optimized for our process requirements. The structure compelled a real-time, iterative design process, which allowed the team to quickly identify areas which required review or redesign, and led to significant innovations. Not only did we meet the needs of our process, we raised the standards by which the suppliers will continue to serve the biopharmaceutical industry.

- **We inserted disruptive innovations into our existing production process.**

We built a fully-functional Temporary Manufacturing Building (TMB) which replicated our existing process to test the effect our disruptive innovations had on that process, including wetware (human intellectual assets). We co-located the TMB on MedImmune's Manufacturing Site, allowing easy, daily access to the automation systems prior to actual system go-live. The TMB also allowed for development of a new standard of manufacturing training programs and work instructions, incorporating Operational Excellence best practice principles including photos, visual cues, and EHS and quality-risk call outs. This allowed shakedown of the equipment, and performance tuning of operations using actual production staff prior to installation in our GMP space. We achieved all this while maintaining continuity of product supply to market throughout the duration of the project.

In the new system, after the eggs are sprayed with IPA, they are sent via a trolley system to the decapping station, which decaps a single tray of 36 eggs in less than a second. The decapped eggs are presented to a single pattern recognition camera, which repeatedly and objectively inspects and categorizes the eggs for suitability of harvest in less than 2 seconds per 36 eggs.

Individual Harvesting and Isolation

In the existing manual process, the operator manually harvested by moving the embryo aside using a small spatula and aspirating the allantoic fluid using a pipette. Once the fluid was in the pipette, the operator would visually inspect and decide subjectively prior to dispensing the fluid into an aliquot, if deemed acceptable, or to waste if unacceptable. If unacceptable, the pipette tip would be disposed of before continuing to the next egg. This process was repeated for each and every egg in the process. A 36 egg tray took approximately 15 minutes to harvest.

The industry standard harvest system provided a robust platform, but fell short of specific requirements for the following unique challenges:

- Harvest all eggs into a single collection vessel



Harvest inspection.

- No inspection prior to pooling
- No ability to flush lines or nozzles if exposed to bad egg fluid
- No use of disposable technology and required Clean Out of Place (COP)

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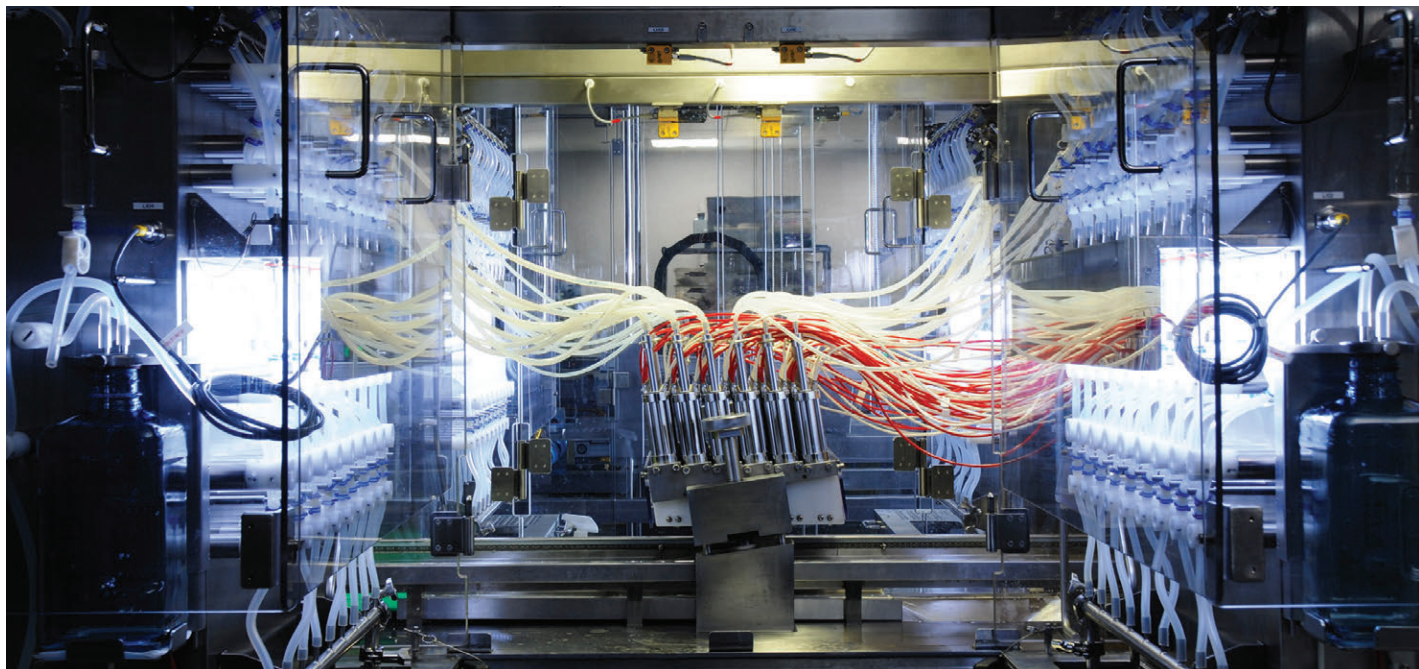
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Harvest system.

MedImmune SMEs worked with suppliers to answer each of the challenges by using advanced technology in innovative ways, as well as improving operating efficiency:

- Individual egg harvest and automated vision inspection system
- Reject and flush sequences of individual lines and nozzles prior to pooling
- External flush of nozzle surfaces using a custom-designed nozzle block
- Employ disposable technology where possible and Clean-In-Place functionality where not possible

Key Project Participants

Designer/Architect/Engineer: WSP CEL, Coventry, UK *(See ad on page 25)*

Construction Manager, Main/General Contractor: PM Group, Birmingham, UK *(See ad on page 52)*

Piping Subcontractor: Mercury Engineering, Glasgow, UK

HVAC Subcontractor: E Poppleton & Son, Conway Bay, UK


Automation and Control Supplier: BAS, Cheshire, UK

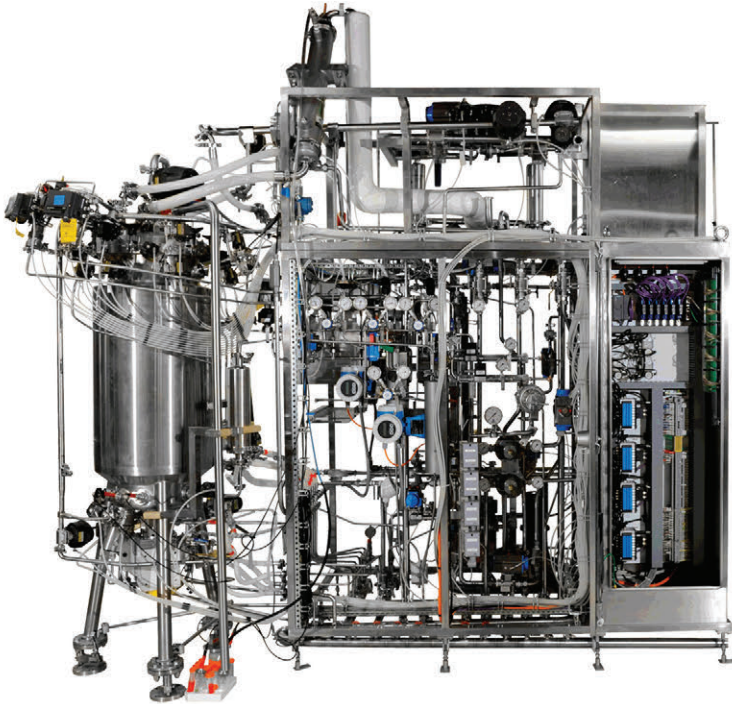
Major Equipment Supplier(s)/Contractor(s):

- Ramé-Hart Inc., Randolph, New Jersey, USA
- Control & Power Systems, Fairfield, New Jersey, USA *(See ad on page 31)*

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, and manufacturers.* ”

Conclusion

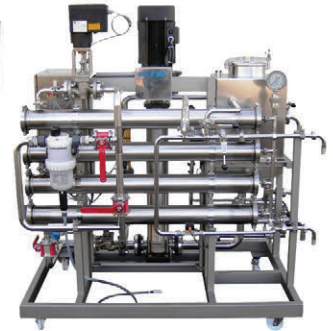
In completely redesigning the egg-based bulk vaccine process from a series of manual steps to a fully automated system, the MedImmune team pushed the limits of technology without changing the manufacturing process. At the same time, they created a more sustainable, repeatable, and scalable platform that is prepared to respond to any influenza pandemic. The new, integrated, automated process stream provides a harvest yield increase of approximately 15% per egg, a reduction in incidence of rejection of high bioburden harvest fluid by 8%, and a 25% reduction in seasonal labor. 



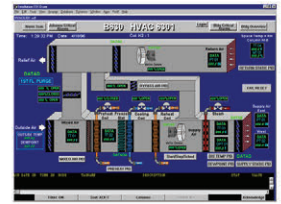
Fermenter - Bioreactor - Single Use



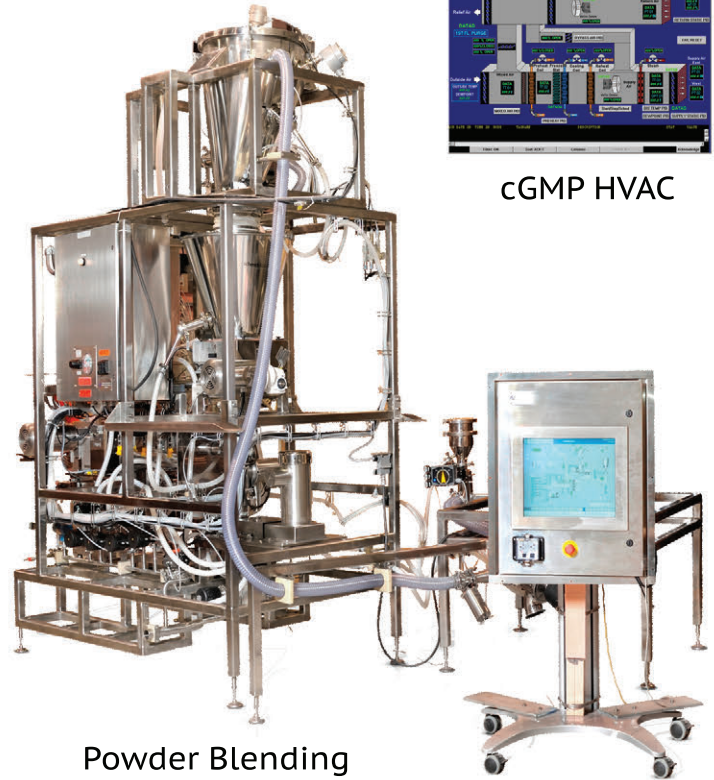
Centrifuge



Filtration / Purification



CGMP HVAC



Powder Blending

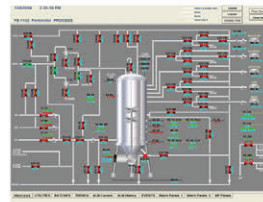
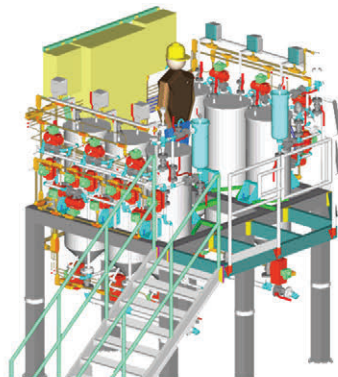
Congratulations MedImmune

CPS is proud to be the systems integrator of the PLC, HMI, Motion and Vision systems for MedImmune's bulk vaccine manufacturing process.

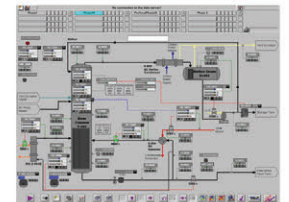
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Merck & Co., Inc.

Building a Lean Structure for High Performance

Introduction

Merck needed to make a strategic investment in its manufacturing network to support its long range biologics and vaccine pipeline.

They made this investment in the **Vaccine and Biologics Sterile Facility (VBSF)** project in Carlow, Ireland.

The project was Merck's first green-field sterile processing facility built outside the US and from the beginning, the project team committed to employing a Lean Six Sigma philosophy. The team followed Lean Six Sigma methodology during the design of the syringe filler, eBeam reliability, and media/buffer suite simplification, as well as during project execution.

These achievements were completed with an inclusive project team culture that served as the foundation for a high performing, sustaining site operational culture, prompting



Operating interface for filling line.

judges to select the VBSF project as winner of the **2013 Facility of the Year Award for Operational Excellence**.

Merck & Co., Inc.

Category Winner – Operational Excellence

Project: Vaccine and Biologics Sterile Facility (VBSF)

Location: Carlow, Ireland

Project Mission: To deliver a world class new vaccine, biologics and manufacturing facility as a strategic investment in Merck's manufacturing network to support the long range product pipeline.

Size: 200,000 sq. ft. (18,581 sq. m.)

Duration of Construction: 19 months

Project Overview

The VBSF project delivered a site with vial and syringe formulation and filling capability for both inline and pipeline products with a schedule driver to support launches for new vaccine and biologics products.

The site features simultaneous manufacturing of two separate products on individual filling lines with shared infrastructure and support systems. Specifically, the 200,000-square-foot sterile production facility includes the following functional elements:

- Process building: 77,000-square-foot modular facility housing a high speed syringe filling line (600 spm), high flexibility vial filling line (200 vpm), adjuvant manufacturing, buffer preparation, and sterile supply

- Materials and maintenance support facility: 95,000-square-foot stick-built building containing warehousing, maintenance workshops, and environmental control and tech ops laboratories
- Energy Center: 11,000-square-foot building with steam boilers, chillers, clean utilities, and waste treatment
- Administration building: 17,000-square-foot fit-out of an existing building shell

Lean Design

The VBSF project was the first major Merck project of this magnitude to formally start with establishing Lean Six Sigma principles and practices as an integral part of the design process, according to Merck representatives.

Challenged with the question, “How will a Merck sterile fill facility of the future be run?” the team built on past successes using Sigma methodologies to drive scope decisions, as well as to challenge existing paradigms of batch operations. The team also reached out for direct support from the Merck Production System and external Toyota Production System Lean Senseis to more deeply explore Lean thinking and create a model Merck Production System operation.

Starting with the Merck Supply Chain, the team developed a Value Stream Map, progressing to the facility flows and detailed



Warehouse facility.

process unit operations of the shop floor. The effort was tied to the “voice of the business” to deliver a reliable, flexible, efficient design which would support the development of a Lean culture.

Process stability and reliability required deep dives into operating design to understand the causes of planned and






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Vial inspection equipment.

unplanned downtimes and design them out. For example, a green belt project commissioned for design of the syringe filler reached into the sterile fill network, resulting in a first in network design – a disposable wetted path integrated into a traditional isolator based design via innovative use of tool canisters and the filling system. This provides all the sterility assurance advantages of an isolator with rapid turnaround for product or lot change overs by eliminating the downtime of CIP/SIP of the wetted path.

Additional Sigma projects included a green belt on eBeam reliability and a black belt on media/buffer suite design simplification. The resulting new buffer preparation paradigm consisted of flexible disposable mixing systems instead of large fixed stainless steel tanks, reducing overall cycle time by 30% and eliminating the need for CIP/SIP and their associated risks. The green belt project saved an estimated \$2.7 million in capital costs and an estimated \$2.1 million in total cost ownership over 10 years.

Why Our Project Should Win

The following is an excerpt from Merck's submission, stating in their own words, the top reasons why their project should win the 2013 Facility of the Year Award:

- **Innovation and Integration – Creating New Benchmarks**
 - Delivered a facility to support Merck's rapidly emerging pipeline in conjunction with developing a lean production system in an outside regulatory climate that was seeing significant changes in the sterile arena.
 - Lean Six Sigma principles were used extensively to manage decisions relating to innovative solutions that in many cases were new to Merck and in some cases new to industry. These resulted in significant cost savings.
 - Accomplishments in process innovations include filling systems designed to conserve product, a highly reliable eBeam system for the introduction of syringe tubs to the isolator, single-use technology applied for the first time at this scale at Merck in formulation and buffer preparation, and a filling wetted path that was removable and largely single-use allowing the lowest possible risk of cross contamination, and a reduction in change over time by 80% over historical benchmarks.
- **Outstanding Project Execution**
 - The execution strategy was built around an integrated schedule that provided line-of-sight from Front End Loading (FEL) through licensing and included a close relationship between the project execution, and the establishment of an operating site.
 - Clear definition, communication, and management of each of the design parties' scopes of work as the team

grew and spread geographically from concept through BOD and detailed design was key to successfully delivering this world class facility.

- **Leadership in Safety**
 - Nurtured the development of a "Generative" Safety Culture on site which focused on behavioral change and leading indicators at all levels rather than "policing" to achieve outstanding safety results.
 - Executed 1.2 million man-hours in construction without a Lost Time Accident (LTA) and a Recordable Incident Rate of 0.64.
- **Collaborative and Sustainable Culture**
 - Met Merck's goal to establish a new site which integrated and aligned the Merck Supply Chain with Carlow. It established the site operational Integrated Project Team (IPT) and Lean philosophies, it grounded the high-performance execution team, and in a sense, founded the sustainability of a new manufacturing entity and culture into the community for all to benefit.
- **Humanitarian Goals**
 - The vaccines and other products that will be formulated in Carlow could ultimately be used by millions of people across the world. Some of the possible therapeutic categories and development products include Asthma, Infectious Diseases, Neurology and Alzheimer's Osteoporosis, Atherosclerosis, Diabetes and Obesity Bone, Respiratory, Immunology and Endocrine and Oncology.

To achieve the ultimate design for a new green-field Lean operating culture, the team had to consider the question, “What does it take to run the fillers at pace?” For the 600 piece per minute syringe filler, the answer seems simple enough: six tubs a minute. However, a true understanding revealed that at that rate, a tub needs to enter the filler every 10 seconds. The team had to step back and think about the operator experience – how they interact with the machine and all the process steps required going from tubs of empty syringes in cartons on a pallet in the warehouse, to tubs of filled syringes on pallets ready to ship to customers.

Outcomes from this early and deep exploration of the material management included U-shaped filling suites versus a traditional linear line, with the filling suite adjacent to the spine to reduce transit length and simplify handling. Syringe and vial pallets never need to enter the core; instead, they can be stripped of packaging in the material transfer zone where the large volumes of waste material can be efficiently handled.

Lean enablers include: liberal use of visual communications between the corridors and suites and suite to suite; use of dedicated airlocks for syringe and vials fed from a common kanban area; vial filler design for rapid turnaround and flexible



Vial inspection carousel.

product mix; a flexible cost-effective design of the formulation suite and solution prep; significant use of disposable technology to eliminate clean up and change over; and a current and future Lean enabled master plan.



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Corridor showing transparency between areas.

Lean Project Execution

Lean Six Sigma also was employed during project execution, where the methodology drove efficiency of decision making and rapid implementation of remediation measures. This resulted in the completion of module setting two months ahead of schedule.

Lean principles encouraged the formation of a “One Team” culture, which improved team interaction, formed cross functional suite based teams early, and integrated organization with Merck partners.

Key Project Participants

Designer/Architect/Engineer/Construction Manager: PM Group, Cork, Ireland (See ad on page 52)

Engineer: Pharmadule, Nacka, Sweden (See ad on page 37)

Main/General Contractor: PJ Hegarty & Sons Ltd., Cork, Ireland

Piping Subcontractor: Radley Engineering Ltd., Waterford, Ireland

HVAC Subcontractor: Dornan Engineering Ltd., Cork, Ireland

Automation and Control Supplier: Sirius Engineering, Cork, Ireland


Major Equipment Supplier(s)/Contractor(s):

- Bausch + Stroebel, Ilshofen, Germany
- Skan, Basel, Switzerland
- Eisai, Allendale, New Jersey, USA
- Stilmas, Milan, Italy
- MECO, New Orleans, Louisiana, USA
- Brian A. Flynn, Limerick, Ireland
- Systecon, West Chester, Ohio, USA
- Jill Flemming, Dublin, Ireland
- ABB, Dublin, Ireland
- Schneider, Kildare, Ireland
- RMI, Bray, Ireland

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.* ”

Merck Sigma toolkits were applied to capital project activities, resulting in disciplined decision making, including the use of structured root cause analysis to quickly resolve issues within the project setting.

Conclusion

A Lean Six Sigma philosophy was the foundation for every part of the VBSF project. The team used Lean Six Sigma to manage the dynamics of the decision process during the early project scoping, design, and integration activities. In addition, many focused Lean projects were done independently and seamlessly integrated back into the larger program, including design of the syringe filler, eBeam reliability, and media/buffer suite simplification. During project execution, Lean Six Sigma drove efficiency of decision making and rapid implementation of remediation measures. This Lean, inclusive culture grounded the high performance execution team and became the cornerstone culture of the new manufacturing entity. 

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Morphotek, Inc.

Winning Commitment to Sustainable Design

Introduction

Morphotek[®], Inc., a subsidiary of Esai Co., Ltd., proved their commitment to sustainable design and environmental stewardship through the building design and construction practices of its Pilot Manufacturing Plant in Exton, Pennsylvania, USA.

Built on a brownfield site, the plant's sustainable features include comprehensive water and energy conservation plans including water recycling, a flexible clean steam generation system, and a roof top solar array for onsite renewable energy; a modular building envelope system with superior insulation; louvered sunshades; and a light shelf to maximize daylight exposure while minimizing interior heat gain.

Strong planning, an integrated team approach, and advanced technology enabled the project team to achieve its sustainability goals without increasing the project budget.

Morphotek, Inc.

Category Winner – Sustainability

Project: Pilot Manufacturing Plant

Location: Exton, Pennsylvania, USA

Project Mission: Provide biological BDS for preclinical and Phase I/II.

Size: 59,910 sq. ft. (5,566 sq. m.)

Duration of Construction: 23 months



Glass-walled viewing corridor exposes production suites (left) and mechanical spaces (right); light tubes bring natural daylight into the corridor from above.

Morphotek's demonstrated commitment to sustainable design earned this project the **2013 Facility of the Year Award for Sustainability**.

Project Overview

Morphotek's pilot plant supports the manufacturing of advanced therapeutic candidates with either cell culture or microbial systems. The facility is designed with state-of-the-art, highly automated, scalable bioreactors, using fixed and disposable technologies associated with downstream purification capability that enable the rapid scale-up and optimization of processes from lab to 1,000 L bioreactor scale. The facility also contains laboratories for technology transfer, release testing, and stability studies.

Commitments to sustainability and LEED certification were goals articulated early and clearly to the entire design team. The project team used Building Information Modeling (BIM) soft-

ware to integrate the best sustainable decisions into the design process.

One of the first sustainable considerations came in site selection. The previously developed brownfield site required demolition of antiquated buildings and contaminated soil was remediated to Pennsylvania Department of Environmental Protection Act 2 Residential Standards, a level exceeding what was required for a commercial site, ensuring a completely clean site for the plant and its employees.

Designing for Water Conservation

As a facility reliant upon water, conservation was critical for both environmental and economic responsibility. A system was put into place to carefully monitor and readily understand water flow into and out of the facility in order to minimize waste.

Every drop of process water that leaves the clean core passes through a waste inactivation system, bringing all wastewater up to sanitation level and adjusting its pH, before distributing it to the sanitary sewer system.

An innovative Water For Injection (WFI) system was part of a comprehensive utility design to help Morphotek save water. Nearly every process in the pilot plant, from upstream to downstream purification requires WFI. The robust approach keeps costs in consideration while offering redundancy so that



Utility access is via the stainless panel within the purification suite; heating hot water pipes color-coded orange appear across the viewing corridor in the mechanical area.

Morphotek staff is guaranteed WFI at all times. Two “trains” for the front-end generation and purification of WFI ensures the facility is able to operate continuously even when automatic maintenance cycles are underway.

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Pilot plant's rooftop includes air-handling units for each production suite; white roofing helps reduce the heat island effect.

All WFI generation occurs in-house. Raw water from the township system is pretreated through the redundant feed water system. The pretreated water is sent to two vapor compression stills, which are also redundant. The water is sent to a central storage tank before circulating throughout the pilot plant. A series of sub-loops go to different production suites. Each sub-loop has independent control, allowing the sub-loop temperature and flow rates to be customized by the production teams on each loop.

In response to Morphotek's concern about utility usage, a water recycling system also was developed. All of the WFI sub-loop waste that might otherwise go down the drain is captured,

Why Our Project Should Win

The following is an excerpt from Morphotek's submission, stating in their own words, the top reasons why their project should win the 2013 Facility of the Year Award:

- Team Integration and Collaboration.** A very small initial team was able to quickly design and execute a project of significant scale relative to the size of the company and experience of the organization. Morphotek's COO was an integral part of the team, contributing to transparency within the organization and immediate decision-making. The project was completed under budget and mechanically complete in 18 months.
- Use of BIM for Advanced Project Management and Efficiency.** The use of Building Information Modeling (BIM) software enabled an advanced level of coordination and project organization. From project conception, all members of the design team used BIM to develop and visualize the pilot plant in three dimensions. BIM was the means for communicating design intent to stakeholders and the construction team, and it was the tool by which construction was verified. BIM not only promoted efficiency within the project, but also did so in a sustainable manner by reducing printed drawings and coordination of travel expenses.
- Strategic Conceptual Planning.** A strong Basis of Design document at the earliest stage of project development established the design direction and budget for the pilot plant and served as a comprehensive reference point for the duration of the project. It became an important tool for internal approvals and fundraising. Early meetings with the FDA ensured the basis of design was sound. When the design process began, no building occupants had been hired. The project team conceptualized the plant, using past experience and judgment to understand requirements and plan accordingly for Morphotek's future needs. The ability to create a plant without the input of end users, with a very small team, on a fast-track schedule can be directly attributed to the strong conceptual planning.
- Innovative Facility Layout and Flexibility.** The pilot plant is highly flexible, with capacity for concurrent processing of multiple products and the ability to produce products from different cell types. Comprehensive water and energy conservation programs – including robust WFI generation system, water recycling, flexible clean-steam generation, and a solar array for on-site renewable energy – offset the significant water and energy needs of the pharmaceutical facility. The innovative layout offers flexibility for product changeover in each of the eight independent production suites, offers dual fixed and disposable technology for choice in manufacturing, and enables Morphotek to bring analysis in-house. Associated cost savings will contribute to Morphotek's ongoing development of treatments for cancer and other diseases, and may extend to development of other previously cost prohibitive pharmaceuticals.
- Sustainable Design – LEED Certification.** The Morphotek pilot plant expects to earn a LEED certification of Silver or higher. Sustainability was woven throughout the design and construction processes and built into the operations and long-term vision of the plant through remediation of a brownfield site to advanced levels of cleanliness, water and energy reducing systems, and on-site solar energy generation. Strong planning, an integrated team approach, and advanced technology enabled sustainability goals to be achieved without increasing project budget. When compared to a standard pharmaceutical facility, Morphotek's pilot plant is 30% more water efficient, 33.2% more energy efficient, and offers a 90% more efficient HVAC system. The rooftop solar array will self-generate electricity to offset Morphotek's usage, (approximately enough annually to power six US homes for one year).

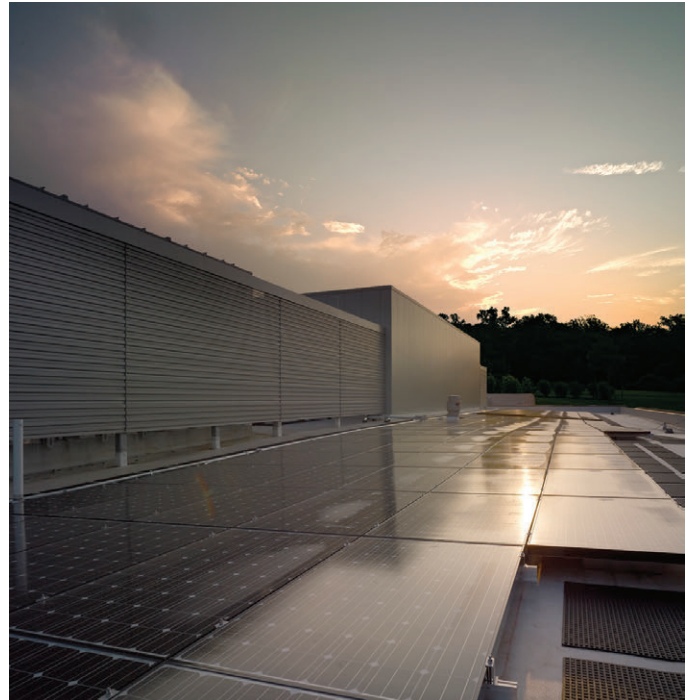
quenched with domestic water and used for cooling tower makeup. Predominately in the summer months, the recycled water will make an impact on the constantly evaporating cooling tower water and limit the amount of potable water needed.

A conservative and flexible clean steam generation system is also in place at the pilot plant. Feed water is sourced from the WFI system. A 1,200-pounds-per-hour clean steam generator produces clean steam predominantly for Sterilization-in-Place (SIP) needs. In addition to meeting stringent pharmaceutical guidelines, the system has EN-285 test elbows to verify steam quality to guarantee effective SIP.

The plant was designed to be 30% more water efficient as per LEED standards; however, when individual building components are examined independently, efficiency increases. For example, the HVAC system is 90% more efficient than standard systems. Process water is not factored into LEED efficiency calculations; Morphotek's water-efficiency measures for process water further enhance the building's water conservation. The net result is just shy of two million gallons of water per year saved.

Capturing and Controlling Energy

Energy conservation was another critical factor in the pilot plant's design. The Morphotek plant is about 33.2% more



Pilot plant's rooftop solar array.



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Completed mechanical room.

efficient than a standard pharmaceutical building with code-minimum systems.

A solar array provides on-site renewable energy. The 9-10 kW photovoltaic system is expected to generate 100,000 kW per year. The 84 kW system includes 330 panels generating 255 watts per panel, roughly enough electricity to power six US houses for one year.

Key Project Participants

Designer/Architect: Arcus Design Group Architects, Inc., Exton, Pennsylvania, USA (See ad on page 41)

Engineer: Precis Engineering, Inc., Ambler, Pennsylvania, USA (See ad on page 43)

Construction Manager and Main/General Contractor: HSC Builders & Construction Managers, Exton, Pennsylvania, USA

Piping and HVAC Subcontractor: Herman Goldner Co., Philadelphia, Pennsylvania, USA

Automation and Control Supplier: Thermo Systems, LLC, East Windsor, New Jersey, USA

Major Equipment Suppliers:

- Sartorius Stedium North America Inc., Biotech Division, Bohemia, New York, USA
- Paul Mueller Company, Springfield, Missouri, USA (See ad on page 39)

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. ”*

The building envelope incorporates prefabricated metal panels, advanced insulation, and architectural elements that control solar gain. A modular exterior wall system clad the lower portion of the building. Panels were fabricated full-height in the manufacturer’s facility with integral insulation built into their cores. The panels were placed into position on-site and attached directly to the building structure. The panels and their installation minimized construction waste and field preparation of materials. The building shell includes energy-efficient spray foam insulation to minimize air infiltration, while maximizing insulation value. In addition to being incorporated into the prefabricated panels, it was site-applied to other areas of the building.

Louvered sunshades and a large light shelf outside the employee café maximize daylight exposure during cooler months, while minimizing interior heat gain.

Conclusion

Sustainability was woven throughout the design and construction processes and built into the operations and long-term vision of the plant, through remediation of a brownfield site to advanced levels of cleanliness, water, and energy reducing systems, and on-site solar energy generation. When compared to a standard pharmaceutical facility, Morphotek’s pilot plant is 33.2% more energy efficient and offers a 90% more efficient HVAC system. The rooftop solar array will self-generate electricity to offset Morphotek’s usage. Strong planning, an integrated team approach, and advanced technology enabled sustainability goals to be achieved without increasing the project budget. 🌱



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Novartis Vaccines and Diagnostics Advancing Vaccine Production for Pandemic Readiness

Introduction

The **United States Flu Cell Culture (USFCC) Facility** in Holly Springs, North Carolina, USA, is home to an innovative cell culture technology that transforms the traditional manufacturing process for flu vaccines into a new, modern platform.

Breaking with the 50-year tradition of utilizing eggs for the method of growing the virus, Novartis Vaccines and Diagnostics developed a process based on robust, deep tank mammalian cell technology, circumventing several issues associated with conventional technology and offering many potential advantages.

Novartis' proprietary technology enables flexible and fast start-up of vaccine manufacturing, offering rapid response to potential pandemic influenza threats and fulfilling the need for seasonal influenza vaccines. Novartis successfully forged a path into a new frontier for vaccine production, earning them the **2013 Facility of the Year Award for Process Innovation**.

Novartis Vaccines and Diagnostics

Category Winner – Process Innovation

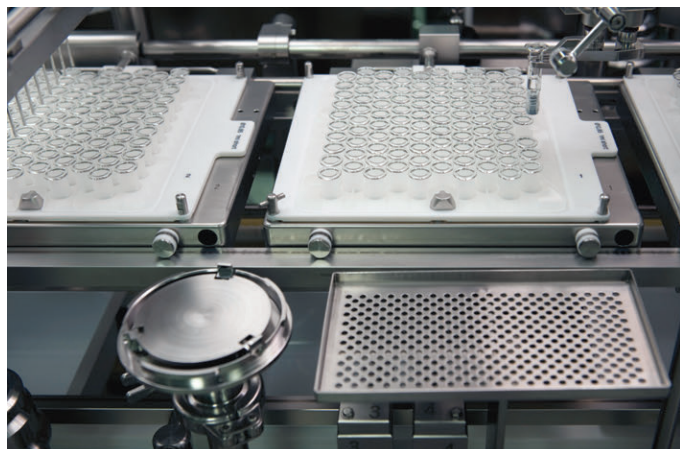
Project: United States Flu Cell Culture Facility

Location: Holly Springs, North Carolina, USA

Project Mission: To design, construct, install, qualify, and operate a U.S. based cell culture vaccine production facility with a seasonal capacity of 50 million trivalent doses. The facility also would produce and fill at least 150 million doses of monovalent influenza vaccine in compliance with FDA and EMEA within 6 months of the declaration of a pandemic.

Size: 490,402 sq. ft. (45,560 sq. m.)

Duration of Construction: 53 months



Syringe filler.

Project Overview

The new greenfield vaccine manufacturing facility is a result of a joint partnership between Novartis and the US Department of Health and Human Services, Biomedical Advanced Research and Development Authority (HHS, BARDA), and the Office of the Assistant Secretary for Preparedness and Response.

The USFCC facility is capable of manufacturing seasonal and pandemic influenza vaccines, including the production of monovalent bulk and antigen sparing adjuvant MF59[®], as well as formulation, aseptic filling, and packaging. The facility has the ability to provide 150 million doses of pandemic monovalent vaccine within six months of a declared pandemic and also can deliver more than 50 million doses of trivalent influenza vaccine on an annual basis when operating in seasonal flu mode.

Egg-Based Vaccine Production

Over the past 50 years, the traditional manufacturing process for flu vaccine has relied upon egg-based vaccine production

technology. This technology, while proven, has disadvantages for both seasonal and pandemic flu strain production. Eggs must be ordered from a limited supply of specialized vendors, 18 months to two years in advance of production needs. This makes rapid response to changing seasonal flu needs – especially a response to a pandemic event – problematic.

Further, in the event of an avian strain pandemic, that same virus the vaccine is trying to control threatens the chickens that produce the eggs traditionally used to propagate the virus, which endangers the supply chain. Also, there are strains of potential flu and pandemic viruses that do not grow well in standard egg-based technology, further aggravating the ability of the industry to respond to pandemic events – a major issue in response to the 2009 H1N1 pandemic.



Production bioreactor.

is propagated in readily available mammalian cell lines, rather than in chicken eggs. The following describes this five-step production process:

Cell Culture Vaccine Production

Cell culture manufacturing offers an approach where the virus



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- **Cell Proliferation** – a large number of cells are required for mass viral production prior to introducing the selected virus. Novartis' proprietary cells have the advantage of grow-

ing in suspension, simplifying vaccine production, during which one vial of frozen cell stock is expanded in culture in several steps. At each stage, the cells are placed in bioreactors that provide the optimal environment for growth, including proper temperature, pH value, and nutrient solution. Cell proliferation is constantly monitored and takes place within a contained bioreactor system inside a Grade D cleanroom.

- **Virus Proliferation** – once the optimal number of cells for production is obtained, the selected virus strain is introduced, taking several days to multiply within the cells. Throughout this process, the virus is released from the cells into the medium.
- **Purification** – the virus-infected medium is separated from the cell debris through a series of purification procedures. The virus is then captured and separated from the medium solution.
- **Inactivation and Splitting** – following purification, a chemical process inactivates the virus. As only fractions of

Why Our Project Should Win

The following is an excerpt from Novartis' submission, stating in their own words, the top reasons why their project should win the 2013 Facility of the Year Award:

- **Innovation in cell culture process for influenza vaccine.** Cell culture manufacturing is the first major innovation for inactivated influenza vaccine manufacturing in more than 50 years, allowing for rapid start-up and response to potential pandemic influenza threats, as well a robust and consistent production of seasonal flu vaccine. Cell culture production allows for the manufacturing of virus strains that cannot be produced in eggs. The fully contained production process allows for operation at lower biosafety levels than traditional manufacturing processes, and the specific mammalian cell line utilized for the process was selected for its reduced risk of exogenous or endogenous adventitious agents.
- **Transformation from seasonal flu to pandemic readiness.** Although the USFCC facility will primarily operate in standard seasonal vaccine mode, the bulk facility and QC laboratories were designed to rapidly transform to operate in pandemic mode, where 150 million doses of pandemic monovalent vaccine could be produced within six months of a declared pandemic. As part of this transformation, the facility can be enhanced to work with strains that require a higher biosafety level.

- **Collaborative environments – facility integration.** The USFCC facility's layout, circulation systems, and physical characteristics inherently encourage interaction and collaboration. The quality assurance, administration, and quality control areas are unified by a central common area that includes a shared front door for the entire facility, reinforcing the message that the entire staff is part of a unified team.
- **Proven adaptability and rapid response.** When the A(H1N1) pandemic of 2009 occurred, the site was in the midst of construction and start-up and responded to the urgent needs of the United States and other governments by deploying approximately 19% of its staff to NVD sister sites in Europe to help produce vaccine. Additionally, during the course of the project, the site re-focused priorities to provide H3N2v monobulk pre-pandemic antigen at the request of HHS. Even with these external factors, the project was still able to deliver H5N1 monobulk pre-pandemic antigen, as contracted by HHS, within four years of breaking ground.
- **Significant contributions – in sustainability.** The USFCC facility incorporated green initiatives not only into the design, but also into operations. While the central plant initiatives result in reduced energy usage, the site incorporated elements that directly impact employees such as the electric vehicle charging station and the eco-friendly cafeteria.

specific viral surface proteins are required for the vaccine, the virus is split and further purified. As the seasonal influenza vaccine contains three viral strains, separate production must be performed for each strain.

- **Blending, Filling, and Release** – once all purification procedures are completed, the pandemic antigen is blended with Novartis' proprietary adjuvant, MF59[®], an oil-in-water emulsion that could boost the immunological response to a vaccine. As this allows antigen to be used per individual dose, it is a major distinguishing factor in how the USFCC facility rapidly produces 150 million doses within six months of a declared pandemic. After filling and packaging, final quality checks are performed and the product is released, prepared for delivery, and made available.

Advantages of Cell Culture Manufacturing

Novartis' new method of vaccine production, which took more than 15 years to develop, provides key advantages:

- **Robustness, Consistency, and Standardized Raw Materials** – virus cultivation utilizing Novartis' proprietary cell line as an exclusive host offers the possibility of more robust virus proliferation. The vaccine is produced in a closed



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bioreactor system with readily available and standardized raw materials. It also offers the possibility for vaccine seed strain development that more closely matches the original “wild” virus. This cell culture technology has the potential to eliminate the need for passage through eggs, where the virus may be forced to adapt in order to replicate.

Key Project Participants

Designer/Architect/Main/General Contractor: Jacobs, Cincinnati, Ohio, USA

Designers/Architects/Planners:

- Flad Architects, Madison, Wisconsin, USA (See ad on page 49)
- CRB Engineering, Cary, North Carolina, USA

Construction Manager: Jacobs, Cincinnati, Ohio, USA

Project Controls: RGD Project Management, Inc., Cary, North Carolina, USA

Main/General Contractors:

- BE&K Building Group, Inc, Raleigh, North Carolina, USA
- CRB Builders, Cary, North Carolina, USA

Piping and HVAC Subcontractor: Gamewell Mechanical, Salisbury, North Carolina, USA

Piping Subcontractors:

- JJ Kirlin, Raleigh, North Carolina, USA
- Kinetic Systems, Inc., Durham, North Carolina, USA
- DSI, Morrisville, North Carolina, USA

HVAC Subcontractor: AC Corporation, Greensboro, North Carolina, USA

Automation and Control Suppliers:

- RoviSys, Aurora, Ohio, USA
- Siemens Industries, Morrisville, North Carolina, USA

Major Equipment Suppliers/Contractors:

- ABEC, Bethlehem, Pennsylvania, USA
- Groninger & Co. GMBH, Crailsheim, Germany (See ad on page 45)
- York Johnson Controls c/o VCS, West Chester, Ohio, USA
- Integrated Process Engineers & Constructors, Inc., Fort Atkinson, Wisconsin, USA
- Stellar Energy Systems, Raleigh, North Carolina, USA

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.* ”

- **Reduces Egg-Based Manufacturing Limitations** – with cell culture technology, Novartis can now produce vaccines for the strains that cannot be produced in eggs.
- **Enables Reduced Biosafety Levels** – as the cell culture process is fully contained in mechanical systems, the living virus is not openly exposed to the work environment, allowing for the facility to maintain a lower biosafety level than egg-based processes. This enhances productivity and reduces operational costs.
- **Reduced Risk of Exogenous or Endogenous Adventitious Agents** – the MDCK cell line was chosen for both inherent and selected characteristics. The cells are broadly and highly permissive for influenza strains, while also restricting growth of non-influenza pathogens that may be present in the viral seed. The cells have been adapted for growth in serum-free media, without animal-derived components.

Conclusion

Novartis Vaccines and Diagnostics developed a process based on robust, deep tank mammalian cell technology, circumventing several issues associated with traditional technology and offering key advantages. The raw materials used in the process are readily available, simplifying production. The cell culture process utilizes closed-system bioreactors, reducing the required biosafety level for the manufacturing space. And, as the facility propagates the virus in mammalian cell lines, the threat of losing the material source due to avian flu infection is significantly reduced.

Novartis’ proprietary technology enables flexible and fast start-up of vaccine manufacturing, offering rapid response to potential pandemic influenza threats and fulfilling the need for seasonal influenza vaccines. 



A Proud Partner

Flad Architects congratulates Novartis on winning
2013 Facility of the Year, Process Innovation.

Novartis Vaccines and Diagnostics

US Flu Cell Culture Facility | Holly Springs, North Carolina, USA

Flad Architects 

It's Your Turn to be Recognized: Now Accepting Submissions for the 2014 Facility of the Year Awards Program

by Scott Ludlum, ISPE's Project Manager for the
Facility of the Year Awards Program

This is really an exciting time of the year! We are celebrating the outstanding accomplishments in new and renovated facility design and construction by the six 2013 Facility of the Year Awards (FOYA) Category Awards Winners.

The award-winning projects were selected from 27 well-qualified submissions from eight different countries around the world. The entire Judges Team – comprising senior level industry executives with extensive experience managing projects worldwide – was truly impressed. The Category Winners represent the caliber of innovation and

the technological ingenuity of projects submitted for the 2013 awards program.

“The six facilities honored by this year’s awards program embody innovation, exemplified by advances in areas including flu vaccine manufacturing, which is very relevant in parts of the world right now where outbreaks have occurred, threatening public health. All of this year’s honorees are to be commended for their important contributions to our industry and, most importantly, to improving people’s lives,” stated Chaz Calitri, Vice President of Network Performance at Pfizer and Chair of the 2013 FOYA Judging Team.

Because the FOYA program is the preeminent global awards program recognizing new or renovated state-of-the-art pharmaceutical and biotechnology projects, a considerable amount of effort and commitment is required in order to compile a submission that meets the program entry requirements. But, the rewards of having a project recognized as a world-class facility by industry colleagues, regulators, and fellow business leaders around the world far outweigh the effort required. “For the entire team, winning the Facility of the Year Award is confirmation of the fact that we have genuinely made a great achievement over the last two years,” stated a FOYA Category Winner in Operational Excellence.

Have you also incorporated outstanding innovation and technological excellence in the construction of a new or renovated pharmaceutical or biotechnology manufacturing facility? If so, now is the time for your hard work and

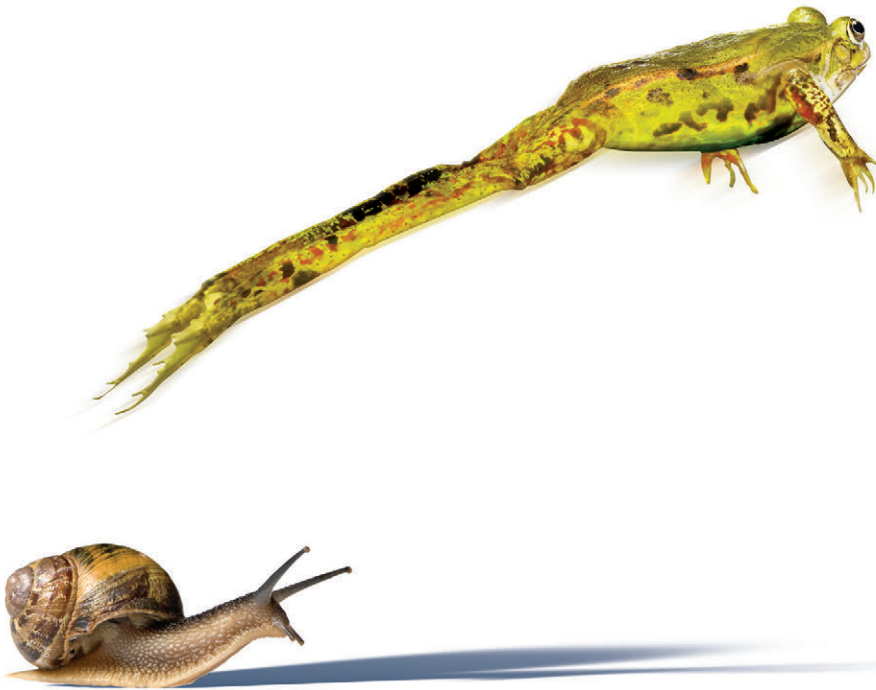
dedication to be recognized. The 2014 Facility of the Year Awards program is now accepting submissions that are due by 18 October 2013. Facilities that meet the following requirements may be submitted:

- Any project that resulted in an interior renovation of an existing facility, facility addition, newly constructed free-standing facility, or substantial improvement to production efficiency may be submitted.
- Facilities must have completed construction and major systems validation between 1 November 2011 and 30 November 2013. As an example, the facility should be occupied and in full operation; or capable of producing product in accordance with an approved product license or under similar operational guidelines.
- For GMP regulated facilities, the facility should have been granted an operating license by an appropriate health authority, or be awaiting such an approval based on an application that has already been made.

If you have completed a new or renovated facility that meets the stated entry requirements, don't wait to submit your project – start compiling your submission now! For more information on eligibility requirements, submission procedures, and past winners, please visit www.FacilityoftheYear.org. You may also contact me, Scott Ludlum, ISPE Director of Member and Industry Initiatives, by telephone at +1.813.739.2284 or by email at sludlum@ispe.org.

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