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Case Study: MedImmune's Frederick Manufacturing Center (FMC) Expansion, Overall Winner, 2011 Facility of the Year Awards

Precision Planning for Innovation

by Rochelle Runas, ISPE Technical Writer

Introduction

Before announcing the Overall Winner of the 2011 Facility of the Year Awards (FOYA) to hundreds gathered at the ISPE 2011 Annual Meeting in Texas, USA, Chaz Calitri, Chairperson of the FOYA Judging Panel, quoted the late Steve Jobs:

"Creativity is just connecting things. When you ask creative people how they did something, they feel a little guilty because they didn't really do it, they just saw something. It seemed obvious to them after awhile. That's because they were able to connect experiences they've just had and synthesize new things."

It's fair to say that those who worked on the Overall Winning project knew exactly what Jobs was talking about, and then took that concept a step further. This article presents the story of how MedImmune used ordinary tools in extraordinary ways to build the MedImmune Frederick Manufacturing Center Expansion, Overall Winner of the 2011 Facility of the Year Awards.

Project Overview

MedImmune, the global biologics arm for AstraZeneca PLC, currently has more than100 products in its research and development portfolio. To enable the future production of products from this robust pipeline, MedImmune chose to expand its Frederick Manufacturing Center (FMC) in Frederick, Maryland, USA. The new facility houses 337,000 square feet of administrative, production, warehouse, laboratory, and utility space. To accommodate future growth, MedImmune designed internal expansion capabilities of an additional 100,000 square feet of production space, creating a flexible, large-scale mammalian cell culture-based production facility.

The facility received licensure in June from the US FDA for the manufacture of Synagis® (palivizumab), a drug to help protect high-risk premature infants from severe Respiratory Syncytial Virus (RSV) disease.

"The licensure of Building 633 represents a prime example of collaboration and flawless execution across a large enterprise. As I look back, there is no single function at MedImmune that I can said did not play an integral role in contributing to the ultimate success of this project," said Greg Liposky, Vice President and General Manager of Operations at FMC.

While there are a number of large-scale mammalian cell culture bulk production facilities in the industry, the ability to accommodate products with a broad titre range and the flexibility built into expansion makes the MedImmune Frederick facility one of the largest single bulk bio production assets in the industry.

The facility and project is notable in several ways:

- They chose to design what MedImmune believes is the first large-scale facility in the industry able to produce a broad base of products with titres ranging up to 7.0 grams per liter.

- They implemented a best-in-class Process Control System (PCS).

- In a short period of time, they transitioned manufacturing operators from a small scale, single product, semi-automated facility to a large scale, multi-product, highly automated facility.

- They provided operators a significant amount of on-the-job training before the start of Process Validation (PV) runs to ensure the validation program was successful.

- Flawless execution of the shakedown and process validation runs resulting in (16) 15K bioreactor batches without a single contamination.

Implementing a Best-in-Class Process Control System (PCS)

The sheer magnitude of the facility dictated the high complexity of the PCS. The team decided that the PCS platform would be based on the Rockwell family of hardware and software. The PCS is a fully integrated, custom installation, designed as a GAMP 5 – Category 4 system. The design of the PCS encompasses the following capabilities:

- Control, monitoring, alarming, and data collection of:
  - 44 production skids
  - all process piping and transfer panels, and holding tanks
  - clean-in-place equipment
  - steam-in-place equipment
  - critical utilities

- Integrated communications with the building management system

- Design to allow:
  - future expansion to implement a second full manufacturing module
  - for ease of transfer to Electronic Batch Record (EBR) methodology

  - for plug and play integration with Manufacturing Execution Systems (MES)

- Use of a common Human-Machine Interface (HMI)

MedImmune faced several typical challenges implementing a system of this type and magnitude, but met them with unique solutions:

Challenge: Plan a solid system integration of all skids from a multitude of vendors.

To integrate 44 skids from more than 12 countries, the team operated under *"a common control system for all"* mission statement. They planned for a modular approach to integration and engaged all equipment skid manufacturers early in the PCS development process. Although they used the S88 model, which is nothing new in itself, the team realized that each vendor played a part in the overall solution. The skidded systems were organized by criticality to the process:

- **Type 1: Process Manufacturing Systems** were the most critical, requiring that these system controllers be programmed using common modules. In keeping with the S88 standard, this approach started with the lowest level of the S88 equipment model – the Program Logic Control (PLC) modules. These modules control, monitor, and alarm devices such as valves, motors, PID loops, and analog alarms.

  The system integrator developed and tested the modules using its pre-existing code library, with specific modifications as required for the project. The PLC modules were then turned over to each critical equipment or skid vendor, and training was provided on how to leverage the modules into the overall application logic for that skid. The Factory Acceptance Test (FAT) for each skid verified the use of the control modules, as well as the integration of the PLC application with the overall PCS HMI/SCADA system, developed for the entire PCS by the system integrator.

- **Type 2: Manufacturing Process Support Systems** were deemed less critical. These equipment vendors were directed to leverage their standard application logic and did not incorporate the project-standard control modules. However, these equipment systems were incorporated into the PCS by utilizing the overall PCS as their HMI/SCADA

Type 1 System	Qty	Type 2 System	Qty	Type 3 System	Qty
Bioreactors	10	Parts Washers	4	Gray Water System	1
Chromatography	2	Autoclaves	3	Carbon Absorption System	1
UF/DF	1			Pure Steam Generators	2
CIP	6			Instrument Air Dryer	1
Centrifuge	2			WFI Generation Stills	2
Viral Filtration	4			Multi Media Filter Skid	1

Skidded systems organized by criticality to the process.

system. This approach allows operators to use one HMI to operate, control, and monitor all systems, drastically reducing the time needed for operators to understand and operate systems.

- **Type 3:** These systems were the least critical equipment systems. These system controls were not incorporated into the PCS; however, the skid vendors were required to "tag" all data and alarm points within their controllers to allow centralized monitoring of all systems. Each vendor provided their standard application logic as well as their standard local Operator Interface Terminal (OIT). This allowed the PCS to capture alarms and data and display the alarms on one common platform.

Challenge: Support simultaneous start-up and debugging of the PCS.

A common issue in automation projects, especially of this size, is interfacing skidded systems with the PCS and with each other. "Traditionally, nothing talks and nothing works and you can spend months upon months trying to solve intersystem communications issues," said Brent Hill, Director of Automation, Global Engineering, MedImmune.

Using a proactive approach to solve this potential issue, the team developed a Factory Acceptance Test Process Automation Core (FATPAC), a portable interface package to support FAT. This package of servers replicated MedImmune's high-level process network and allowed MedImmune to test the equipment in their own environment, at each vendor site.

The FOYA Factor

"This project was a tremendous success and is reflective of the ingenuity, creativity, and commitment shown by the entire project team. They did a masterful job in delivering this challenging and complex project."

– Doug Scott, Vice President, Global Engineering & Facilities, MedImmune

"I can't think of a better way to congratulate all the team members. We worked hard and this is validation for everyone."

– Brent Hill, Director of Automation, Global Engineering, MedImmune

"As an engineer, it's like winning the Oscar, or the closest thing to it. The greatest joy I have is to build a facility and see products go to market that help patients."

– Aaron Vernon, Associate Director of Cost & Schedule Engineering, Global Engineering, MedImmune

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The FATPAC included a domain controller used to preset user access, a PLC, and an HMI client from the PCS system. Communications were set up with the PCS PLC/HMI and used in the FAT for each of the skids. Any problems were identified during FAT, resolved, and retested prior to shipment. "When the skids arrived on site, there was minimal setup required to integrate them into the PCS system," said Hill. "We shaved a good six to seven months of typical delays in start-up, such as commissioning and validation groups waiting on interface issues."

Challenge: Maintain change control over the integrated PCS code during simultaneous start-up of multiple systems.

During automation system start-up in a cGMP environment, it is typical practice to leverage work completed in FATs, installation, and commissioning. More often than not, these activities are limited to hardware IQ checks. Functional OQ test validity is always in question due to lack of code control. Installation and testing of a system this size, with 7,000,000 lines of automation software code and 44 different skids, is a daunting task to manage. In addition, the leveraging strategy dictated by MedImmune added a complexity to start-up activities, which posed a major challenge to the team: how to track, maintain, and control PCS code revisions while simultaneously performing leveraged start-up activities.

To proactively address this problem, the automation group used an off-the-shelf Rockwell configuration management application to manage coding. The tool, which has automatic revision control, requires programmers to "check out" code from a repository. This allows an auditor to go back to any point in time and see what changes were made to code throughout the development and testing process.

"While the tool itself is not unique, we did turn it on relatively early and utilized it right after FATs," said Aaron Vernon, Associate Director of Cost & Schedule Engineering, Global Engineering, MedImmune. The team created a Configuration Management Plan at the onset of planning. This document set the process for managing all application files with the key aspect of the plan being the configuration management tool.

The use of an automated configuration management tool quickly proved valuable during commissioning and start-up, because many changes were identified and implemented during this phase. For example, 15 control engineers were accommodating various change requests to the PCS code.

The process continued through validation with a parallel test system configured as a mirror image of the production system that was being validated. Following validation of each skid or process area, the associated code was versioned again and an automatic schedule for upload and compare was established.

This schedule provided for automatic comparison of the actual code running in the production system to the locked, effective, master version. Any differences between the two

Part of the dedicated training lab.

versions initiated an automatic log and email notice to key team members, said Vernon.

In addition to control of PCS code, this automated configuration management system has been used to control batch file configuration management.

Challenge: Create and deploy operator training to a wide audience with varied levels of experience with automation controls.

MedImmune needed to transition manufacturing operators accustomed to a small-scale, single product, semi-automated facility to a large-scale, multi-product, and highly automated facility. This had to be completed in a short period of time without risking equipment damage to any critical process and support systems or risking loss of product materials due to incorrect use of the PCS.

The solution: a four-tiered, blended learning approach commonly used in the military, but rarely implemented in the biopharmaceutical industry. This approach was developed as a collaborative effort between a number of site and corporate functions, and included:

- **Concept Training** – concept training consisted of interactive Computer Based Training (CBT), which allowed employees to gain a general understanding of how the facility and the process control system would operate. The CBTs, developed according to successful adult learning theories, clearly state the training objectives, and then lead the student from overview and concept understanding to higher-level knowledge of the PCS. The CBTs included detailed checks for understanding after completion of each module. Also included were Printable Quick Reference Guides to be used as job aids while using the PCS HMI. These guides included information on the PCS structure, User Access Rights, a summary of alarm conditions, locations of PCS stations throughout the building, and definitions of terms.

- **Review of Operational SOPs** – this component involved the requirement of students to review the SOPs as preparation prior to attending hands-on training.

- **Hands-On, Instructor-Led Training** – a dedicated training lab was built by creating a pared-down version of the PCS. The lab included a subset of the process control functionality found on the manufacturing floor. The lab allowed operators to train on a "live" system that looked, felt, and behaved like the real PCS. A series of instructor-led sessions which mirrored actual production scenarios were also were created. These sessions allowed operators to use the PCS HMIs to perform tasks, such as media preparation, transfer operations, and cell culture, harvest, and purification operations.

- **On the Job Training with a PCS Simulator** – the project team understood that proficiency on the live system would require additional practice using the PCS. To minimize knowledge loss between operator training and live PCS usage, the project team developed a PCS Simulator for all operators who had completed the instructor-led training in ICQ activities. Use of this simulator helped ensure proper use of equipment through the PCS.

"This robust training developed to assure initial validation run success continues to provide value to the organization. It has become the foundation of our current training program at the site," said Liposky.

The Art of Start-Up: Progressive Shakedown and Process Validation Methodology

The start-up, process shakedown, and process validation schedule was optimized to meet the schedule requirements of the project. More importantly, they utilized an approach to get exposure to the systems as soon as possible for experience
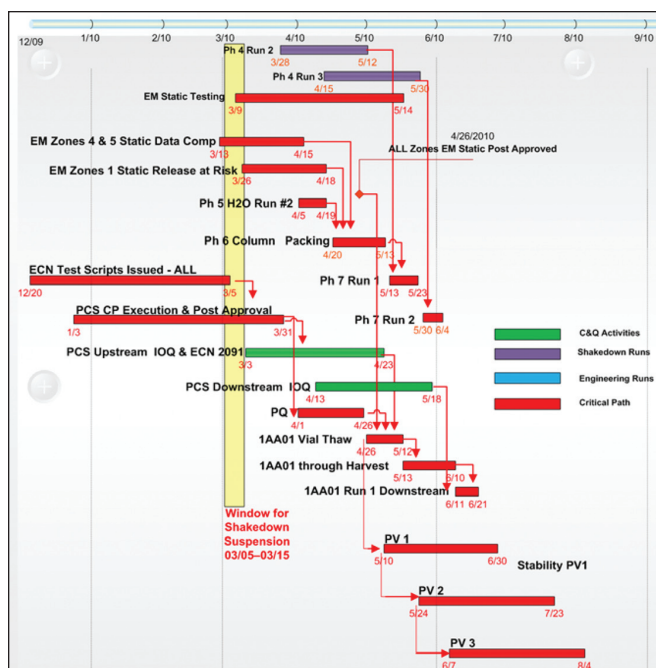
Integrated shakedown methodology.

Facility of the Year Awards

Sponsored by ISPE, INTERPHEX, and *Pharmaceutical Processing* magazine, the Facility of the Year Awards (FOYA) program recognizes state-of-the-art pharmaceutical manufacturing projects that utilize new and innovative technologies to enhance the delivery of a quality project, as well as reduce the cost of producing high-quality medicines. Now in its eighth 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.

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

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2011 Facility of the Year
MedImmune's Frederick Manufacturing Center (FMC) Expansion, category winner for *Project Execution*, was selected as the Overall Winner of the 2011 Facility of the Year Awards among five other Category Winners in 2011. A sixth facility was selected to receive an Honorable Mention. The winning companies and respective award categories are:

- **Merck & Co., Inc.**, winner of the Facility of the Year Award for *Facility Integration* for its Global Clinical Supplies Manufacturing, Packaging and Warehouse expansion project in Summit, New Jersey, USA

- **Novartis Vaccines and Diagnostics GmbH**, winner of the Facility of the Year Award for *Equipment Innovation* for its "MARS Project" (Marburg Site) facility in Marburg, Germany

- **Pfizer Health AB**, winner of the Facility of the Year Award for *Operational Excellence* for its Project Pegasus – Bio 7 Manufacturing facility in Strängnäs, Sweden

- **Pfizer Manufacturing Deutschland GmbH**, winner of the Facility of the Year Award for *Sustainability* for its SPRING and E-MAP (Strategic Plant Restructuring and Energy Master Plan) project in Freiburg, Germany

- **Shire HGT**, Facility of the Year Award *Honorable Mention* for its Project Atlas, Building 400 facility in Lexington, Massachusetts, USA

and knowledge. To meet this challenge, the team planned for successive shakedown runs several years in advance.

Each successive shakedown run phase utilized more equipment than the previous phase and started concurrently with ICQ activities. The shakedown phases separated unit operations to allow for complications, problem-resolution, and gain experience particular to each unit operation.

The approach also maximized operator on the job training, said Vernon. "The shakedowns were as much training for our people as it was testing of equipment."

The project team successfully completed 13 shakedown runs and three PV runs without a single contamination or lost batch. More impressive is that for every batch, MedImmune met all product and process metrics. From the first batch in the production bioreactors, viable cell density, cell growth, and product titer closely matched the average results for more than 200 batches run prior at MedImmune and 20 batches at a contract manufacturing organization.

Offline Integrated Commissioning and Qualification (ICQ)
As shakedown activities took precedence in the schedule, it was necessary for the project team to perform activities related to the commissioning and qualification of the PCS in parallel, without interrupting shakedown runs. Under the strain of limited time on equipment as a result of competing project phases (start-up and debugging of applications, train production operators, and running test batches), the project team developed a separate PCS simulator (in addition to the PCS simulator used for operator training) that allowed them to commission and qualify major aspects of the PCS without having to perform the work on the plant floor. This system, which simulates every Programmable Logic Controller (PLC) in the facility, provided a safe, equivalent environment to perform testing. Today, this simulator is used for qualification and tech transfers, says Hill.

Stellar Safety Record
The project was completed with a safety record of more than 2.3 million man-hours without a lost time incident. "For a complex project of this size and scope, the 2.3 million hours without a lost time incident is an impressive achievement. Worker safety was the highest priority for us, and required extensive collaboration, from the project leadership to the construction workers," said Doug Scott, MedImmune's Vice President of Global Engineering.

Conclusion: Focus on the Front-End
The FOYA Judging Panel was impressed by MedImmune's solid planning, risk management, and creative problem resolution, earning MedImmune earlier in the competition the Category Award for Project Execution. These characteristics of robust project management fueled MedImmune's fast-paced, but efficient execution of implementing its innovative start-up and operator training and unique process for offline validation.