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2011
Facility of the Year Awards
CATEGORY WINNERS

Facility of the Year Awards

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Photos courtesy of MedImmune, LLC, Merck & Co., Inc., Novartis Vaccines and Diagnostics GmbH, Pfizer Manufacturing Deutschland GmbH, Pfizer Health AB, and F. Hoffmann – La Roche Ltd.

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2011 Facility of the Year Awards CATEGORY WINNERS

Articles

2011 Facility of the Year Awards Program:
Best in their Class for the Benefit of Patients

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

"FOYA is a good venue to showcase excellence in engineering and allows companies an opportunity to discuss new and innovative ways to provide these services to our industry, which ultimately benefit our patients and communities," said Jon Reed, Vice President, Engineering, Genentech, for Genentech's ECP-1 Bacterial Manufacturing Facility, Overall Winner of the 2010 Facility of the Year Awards and member of the 2011 Facility of the Year Awards Judging Panel.

"Our organizations all benefit from learning about best in class methods or innovations around process design, sustainability, efficiency, and delivery innovations which drive better quality into our products, higher efficiencies in our production operations, and more cost effective ways to deliver our services."

Six pharmaceutical manufacturing facilities constructed in Germany, Switzerland, Sweden, and the USA were selected as Category Winners in the seventh annual Facility of the Year Awards program sponsored by ISPE, INTERPHEX, and *Pharmaceutical Processing* magazine. A seventh facility was selected to receive an Honorable Mention. The winning companies and respective award categories are:

MedImmune, LLC: centrifuge.

Merck & Co., Inc.: second level fluid bed dryer.

- **MedImmune, LLC**, winner of the Facility of the Year Award for *Project Execution* for its Frederick Manufacturing Center (FMC) Expansion facility in Frederick, Maryland, USA

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

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

- **Pfizer 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

- **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

- **F. Hoffmann – La Roche Ltd**, winner of the Facility of the Year Award for *Process Innovation* for its "MyDose" Clinical Supply facility in Kaiseraugst, Switzerland

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

The Facility of the Year Awards program is truly global, as submissions over the past seven 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, Global Engineering, Pfizer, Inc.

Novartis Vaccines and Diagnostics GmbH: segregation staging of equipment.

Concludes on page 6.

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Pfizer Manufacturing Deutschland GmbH: quantum chilling unit.

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- **Steve Dreamer**
  Head of Global Pharma Engineering and Operational Excellence, Novartis Pharma AG
- **Brian H. Lange, P.E.**
  Director, Quality Services, West Point Quality Operations, Merck & Co. Inc.
- **Geoff Monk**
  Former Vice President, Global Engineering Services, Schering Plough
- **Shinichi Osada**
  General Manager, Biopharm, Industrial and Logistics Systems Division, Hitachi Ltd.
- **Andy Skibo**
  Senior Vice President, Global Engineering and Facilities, MedImmune
- **Ron Trudeau**
  Vice President, Facilities Engineering Services, Baxter Healthcare
- **Jon Reed**
  Vice President, Global Engineering, Genentech
- **Georgia Keresty**
  President, Janssen Alzheimer Immunotherapy, Johnson and Johnson
- **Karen Kinney**
  Director, Sustainable Facilities, LEED AP/Project Management and Engineering, BD

2011 Facility of the Year Events

There will be several opportunities to learn first-hand about the facilities being honored as "best in their class." These events include:

- **INTERPHEX*2011*** – Meet the Category Award Winners from 29 to 31 March at the Facility of the Year Awards Display Area at booth number 1571 in the exhibit hall of the Jacob K. Javits Convention Center in New York City, New York, USA. This is your opportunity to meet personally with representatives from companies of the Category Winners to discuss the success stories associated with these pharmaceutical manufacturing facilities. To register or for more information, visit www.interphex.com.

- **ISPE 2011 Annual Meeting** – Hear presentations from the winning teams and learn first-hand who will win the coveted Overall Facility of the Year Award during ISPE's 2011 Annual Meeting, 6 to 9 November in Grapevine, Texas, USA. For more information, visit www.ISPE.org.

- **Feature Articles** – Comprehensive coverage will appear in *Pharmaceutical Engineering* magazine and *Pharmaceutical Processing* magazine.

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 a Society of 22,000 pharmaceutical professionals in 90 countries who use expert knowledge to create high-quality, cost-effective GMP solutions. ISPE is "Connecting a World of Pharmaceutical Knowledge" by providing Members with opportunities to develop their technical knowledge, exchange practical experience within their community, enhance their professional skills, and collaborate with global regulatory agencies and industry leaders. Founded in 1980, ISPE offers online learning opportunities for a global audience and has its worldwide headquarters in Tampa, Florida, USA; its European office in Brussels, Belgium; an Asia Pacific office in Singapore; and its newest office in Shanghai, China. Visit www.ISPE.org for additional Society news and information.

Pfizer Health AB: buffer hold area.

F. Hoffmann – La Roche Ltd: Vartridge filling and closing unit.

About INTERPHEX

Now in its 32nd year, INTERPHEX is the nexus for FDA regulated drug and drug delivery systems manufacturing for the pharmaceutical, biologic, generic, and contract services professionals. Scheduled for 29 to 31 March at the Jacob K. Javits Convention Center in New York City, New York, USA, the 2011 exhibition will feature more than 650 exhibitors, an expanded conference program, and a high-profile roster of industry professionals and speakers. For information, visit www.interphex.com.

About *Pharmaceutical Processing*

Pharmaceutical Processing magazine is the pharmaceutical industry's leading information provider, reporting on a full range of innovative new products, equipment, technology, and trends for 28,000 engineers and managers responsible for the development, manufacture, validation, and packaging of pharmaceuticals. An official sponsor of INTERPHEX, *Pharmaceutical Processing* distributes critical information to these professionals in a timely manner through a full range of print, electronic and online media. For information, visit www.pharmpro.com.

Fluor Congratulates MedImmune on its 2011 Facility of the Year Award for Project Execution

MedImmune
Frederick Manufacturing Center Expansion
Frederick, Maryland, USA

Award program sponsored by ISPE, INTERPHEX, and Pharmaceutical Processing magazine

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MedImmune, LLC

Implementing Ordinary Tools in Extraordinary Ways

Introduction

To enable production of forthcoming products, MedImmune built the **Frederick Manufacturing Center (FMC) Expansion** facility, winner of the **2011 Facility of the Year Award for Project Execution**. Located in Frederick, Maryland, USA, this complex and challenging project was delivered in an aggressive timeline with an outstanding safety record resulting in a facility capable of handling a wide range of product titers supported by a fully integrated Process Control System (PCS).

MedImmune implemented innovative strategies to assure project success. The project team used a military-inspired, four-tiered training methodology to help transition the workforce to the new facility. The team supplemented the training program with a comprehensive shakedown schedule that maximized practice runs prior to process validation. The team also developed a simulator that enabled them to execute commissioning and qualification of the PCS offline, freeing up physical equipment for shakedown runs. Despite an aggressive project schedule, the team successfully completed more than 13 shakedown runs and three process validation runs – without a single contamination or lost batch – concurrent to on-going construction work and Integrated Commissioning and Qualification (ICQ) efforts.

Project Overview

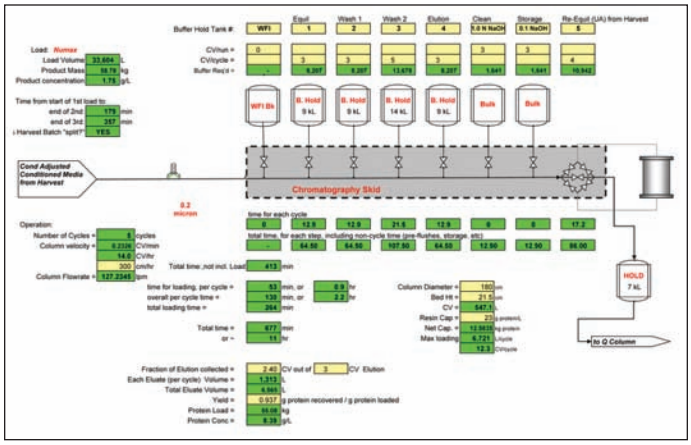
MedImmune currently has more than 100 biologics in research and development. The challenge of having a robust product pipeline is the operational capability and flexibility required to manufacture a diverse group of products with a wide range of titers.

To enable production of forthcoming products, MedImmune chose to build and license a flexible, large-scale mammalian cell culture-based production facility adjacent to MedImmune's existing Frederick Manufacturing Center (FMC), Building 636. The decision allowed the company to leverage the expertise and systems already in place at FMC, which had been used to successfully produce Synagis® (palivizumab) for the past 12 years.

Exterior view.

The new facility, the FMC Expansion, Building 633, houses 337,000 square feet of administrative, production, warehouse, laboratory, and utility space. To accommodate future growth, MedImmune designed internal expansion capabilities of 100,000 square feet of production space. The new facility will be licensed for the manufacture of Synagis® by the US FDA.

MedImmune senior management set forth an aggressive project schedule with a forecasted timeline reduced by overlapping successive project phases. This approach increased the risk of impacting start-up activities, as delays in any one phase would cause a stacking effect of critical activities. Despite the aggressive schedule, the project was completed with an outstanding safety record of more than 2.3 million man-hours without a lost time incident.



Process model.

Continued on page 10.

MedImmune, LLC

Category Winner – Project Execution

Project: Frederick Manufacturing Center (FMC) Expansion facility
Location: Frederick, Maryland, USA
Project Mission: To build and license a large scale, mammalian cell culture-based manufacturing facility to support MedImmune's pipeline
Size: 337,000 sq. ft. (31,308 sq. m.)
Total Project Cost: $588,389,000
Duration of Construction: 39 months

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2011 FOYA Winner
for Project Execution

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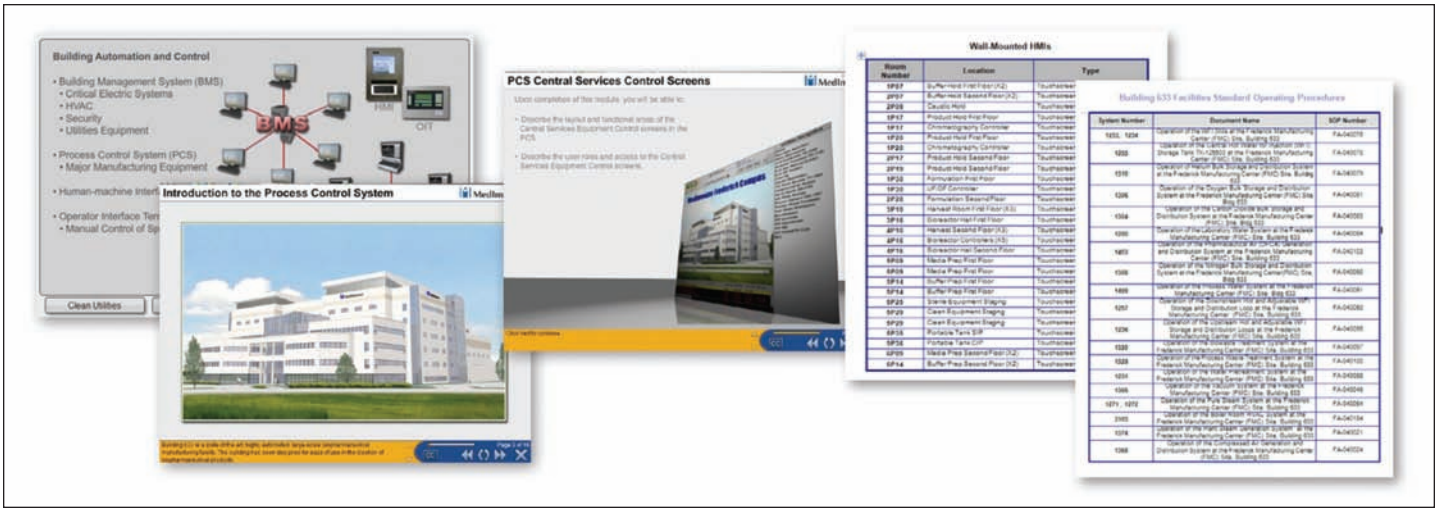


Concept training to gain a general understanding of how the facility and PCS would operate.

Military Training Methodology for Operations Training

The implementation of the automation system posed a complex challenge to the staff of the FMC Expansion, Building 633: by automating the manufacturing process, all procedures used to manufacture product would rely heavily on the PCS. This was a fundamental change from the manufacturing processes in the former production facility.

An audience analysis identified more than 100 staff members and an anticipated 100 additional manufacturing operators who would need detailed training on the use of this system, specific to their job function. The strongest requirement for training these audiences was to change their daily behavior from operation of a small-scale, semi-automatic manufacturing facility to a fully-automated, multi-product facility with a scaled up production volume, 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 MedImmune team designed a four-tiered, blended learning approach, commonly used in military training, but rarely implemented in the biopharmaceutical industry. This training continuum was based upon theories of adult learning and created to allow self-paced, discovery-based knowledge transfer to existing staff and new-hires. Components of this continuum included concept training; review of operational SOPs; hands-on, instructor-led training; and a comprehensive, plant-wide controls simulator for ICQ and operator training.

Concept Training

Concept training consisted of interactive computer based training, which allowed employees to gain a general understanding of how the facility and the Process Control System (PCS) would operate, followed by review of Standard Operating Procedures (SOPs), specific to their job function.

Review of Operational SOPs

The second module in this training continuum involved the requirement of students to obtain operational SOPs from MedImmune's electronic Document Management System and review the SOPs as preparation prior to attending hands-on training.

Part of the dedicated training lab.

Notes from the Judging Panel – What Impressed Them

- *Excellent safety record: 2,300,000 man-hours without a lost time incident.*
- *The focused and thoughtful effort to help the workforce transition related to project execution was impressive.*
- *Overall, it was a complex and challenging project that was delivered in an aggressive timeline and with an outstanding safety record.*
- *The need to achieve flexibility in process at such a scale required MedImmune to overlap project phases, greatly increasing risk to the project.*
- *Use of Military Training Methodology that resulted in the successful shakedown runs and process validation runs performed concurrent to on-going construction and ICQ activities*

Award Category – Project Execution

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

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 control functionality 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

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 2011 Facility of the Year Award:

Exceptional Product Titer Range Capability of 7.0g/L (14x)

- To accommodate the manufacture of future products, we designed Building 633 as a flexible facility with a product titer range of 0.5 to 7.0 grams per liter. Though a 10x process range has been achieved in practice before, we believe that Building 633 is the first large-scale facility in the industry able to produce a 14x process range up to 7.0 grams per liter.

Extraordinary Methods to Implement one of the Largest Process Control Systems in the Industry

- We planned for a modular approach to integration and engaged all equipment skid manufacturers early in the PCS development process. We distributed the S88 model to the skid manufacturers to ensure development of common equipment and control modules. To verify that these skids would flawlessly integrate into our PCS infrastructure, we developed a FATPAC. The FATPAC is a portable package of servers that replicated our high-level process network and allowed us to test the equipment in our environment, at each vendor site.

Complete Replication of Process Control System for Offline ICQ and Operator Training

- We developed a complete, isolated replica of the Process Control System to allow validation activities to be performed at the same time as equipment validation and shakedown, to reduce risk. Replication of the manufacturing equipment operation, using PLC controllers in a virtual environment, proved to be an efficient and effective method for PCS validation.

Military Training Methodology for Successful Operational Training

- Our blended, four-tiered approach to development and delivery of PCS training enabled manufacturing operators to successfully use the automated Process Control System. By focusing on real-world training scenarios, state of the art simulators, and a hands-on approach, we quickly transferred critical knowledge to key personnel to support start-up activities.

Unique, Progressive, and Successful Shakedown and Process Validation Methodology

- We planned for successive shakedown runs several years before the start of qualification and planned other activities with support of shakedown as a top goal. Shakedown activities, which commenced during commissioning and qualification, were planned early on and took precedence in the project schedule. This approach maximized operator on the job training, as well as opportunities to identify issues. The shakedown phases were designed to progressively use equipment through the manufacturing process. We successfully ran 13 shakedown runs and three PV runs without a single contamination or lost batch.

Concludes on page 12.

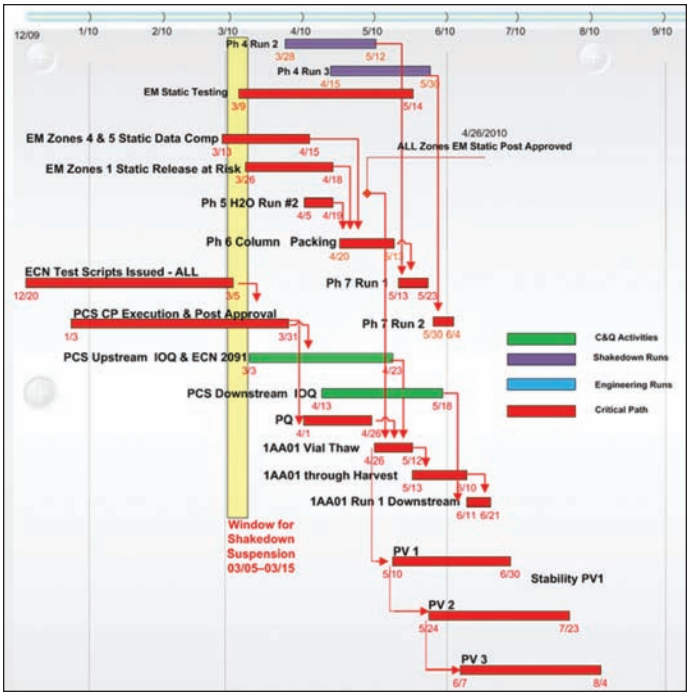
mirrored actual production scenarios also were created. These sessions allowed operators to use the PCS Human-Machine Interfaces (HMIs) to perform tasks, such as media preparation, transfer operations, and cell culture, harvest, and purification operations. Operators were provided the opportunity to learn in a safe environment where they could not harm themselves, others, or equipment.

Comprehensive, Plant-Wide Controls Simulator for ICQ and Operator Training

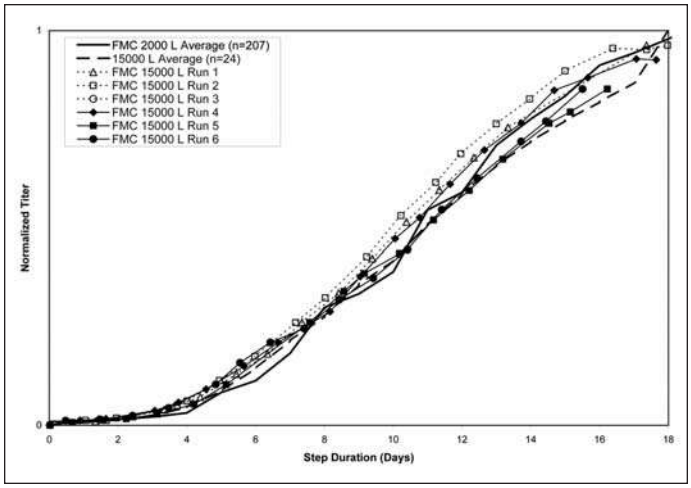
The project team understood that proficiency on the live system would require additional practice using the PCS. In order to not risk the loss of knowledge between the times the operators trained and when they used the live PCS and to assist in ICQ activities, the project team developed a PCS simulator 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.

Shakedown and Process Validation Methodology

The project team needed to allow operators a significant amount of on-the-job training before the start of Process Validation (PV) runs to ensure the effectiveness of the training strategy. In addition, the team needed a great deal of experience running the processes within the facility to find potential issues.



Integrated shakedown methodology.



Process data from shakedown runs.

To meet these challenges, the team ran progressive shakedown runs within the facility over an extended period of time to discover potential operational difficulties. Each 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 lost batches, and gain experience particular to each unit operation.

As the 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. The PCS simulator allowed the project team to commission and qualify major aspects of the PCS without having to perform work on the plant floor. The system, which simulated every Programmable Logic Controller (PLC) in the facility, provided a safe, equivalent environment to perform testing.

Conclusion

The project team achieved its goals by implementing ordinary tools in extraordinary ways. Its innovative approach to startup and operator training, its process for offline validation, and robust project management processes allowed it to overcome many potential problems.

The project team completed more than 13 shakedown runs and three PV runs and did so concurrent to on-going construction work and intense commissioning and qualification efforts. The final three shakedown runs were complete runs that were fully representative of the process. From the start of manufacturing in the facility, the product met all established process benchmarks at both medium and large scale without a single contamination or lost batch.

In the end, solid planning, innovative problem resolution, and fast-paced but efficient execution allowed MedImmune to build and validate a world-class, flexible manufacturing facility with a state of the art automation system.

Key Project Participants

Engineer: Parsons Commercial Technology Group (Boston, Massachusetts, USA)

Construction Managers:

- Fluor Enterprises Inc (Greenville, South Carolina, USA) *(See ad on page 7)*
- Parsons Commercial Technology Group (Boston, Massachusetts, USA)

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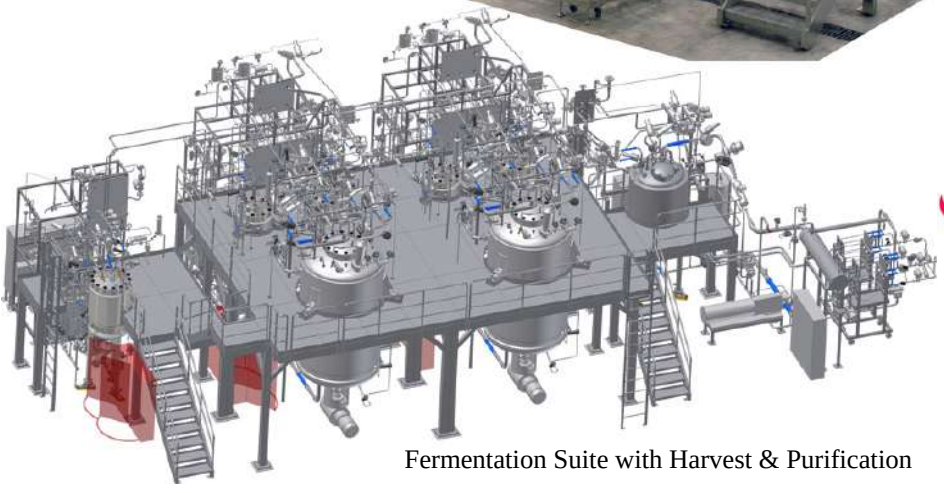
Congratulates MedImmune, LLC in their outstanding achievement.



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2011
Facility of the Year Awards
CATEGORY WINNER
Project Execution • Supplier

Merck & Co., Inc.

Maximizing Existing Infrastructure Expands Clinical Supplies Capability

Introduction

Merck & Co., Inc. was on a mission to expand, enhance, and integrate its core drug product development, manufacturing, and packaging capabilities. Part of that mission was to meet a strategic need to increase productivity, efficiently manage a significant increase in clinical trial patient demand, and create a facility capable of supporting both conventional and potent compounds.

To accomplish these goals, Merck & Co., Inc. embarked on the **Global Clinical Supplies Manufacturing, Packaging and Warehouse Expansion** project, which consolidated several cGMP clinical manufacturing, packaging, and warehouse areas within a single state of the art facility in Summit, New Jersey, USA. Deemed by the judging panel as truly representative of its category, the project is winner of the **2011 Facility of the Year Award for Facility Integration**.

The project team employed a parallel, three-phased "hybrid-build" approach, integrating greenfield, modular, and stick-built construction. The team used an existing decommissioned production building, partially demolishing, renovating, and adapting the structure for improved clinical manufacturing and development.

Merck & Co., Inc.

Category Winner – Facility Integration

Project: Global Clinical Supplies Manufacturing, Packaging, and Warehouse Expansion
Location: Summit, New Jersey, USA
Project Mission: To expand and improve core drug development capabilities, meet the strategic need to increase productivity, and efficiently manage a significant increase in clinical trial patient demand. Create a facility with the ability to achieve 10ug/m3 over an 8-hour time weighed average, thus introducing engineering controls to limit possible exposure and reducing reliance on personal protective equipment.
Size: 240,666 sq. ft. (22,359 sq. m.)
Total Project Cost: $216,000,000
Duration of Construction: 24 months

Exterior view.

Response to a Business Plan

Merck & Co., Inc. needed to support their growing product development pipeline. Their Global Clinical Supplies units were operating in several locations in New Jersey with limited space, equipment capability, and scale. Third party organizations were being utilized for portions of the clinical manufacturing process. Due to these limitations, meeting the growing pipeline needs was difficult. In addition, the mix of potential compounds in the pipeline indicated a need for a flexible, multi-product solution to manufacture and distribute clinical supplies.

An existing building was selected to support drug development in the stage between discovery and commercialization where products for clinical trials are manufactured along with the new technologies developed for transfer to commercial production facilities.

The most cost effective solution was to renovate and expand the selected site into a single, state of the art facility capable of producing all types of dosage forms, including tablets, capsules, non-sterile liquids, and inhalation products.

Exterior of clinical manufacturing operations.

Continued on page 16.

Congratulations, Merck & Co., Inc.

Facility of the Year - Facility Integration

Facility of the Year 2011

Global Clinical Supplies Manufacturing, Packaging and Warehouse Expansion

Summit, NJ

IPS Booth #1579

Facility of the Year Display Area #1571

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Project Overview

The project consolidated clinical manufacturing, packaging, and warehouse areas within 240,666 square feet of state of the art facilities at the Summit, New Jersey site. A successful three-phased "hybrid-build" approach was employed, including utilization of modular construction for primary manufacturing operations; adaptive reuse of a former pharmaceutical warehouse; new construction of an Operations Support Building; and a parallel site utility project and solar install. Upon completion, the team met aggressive deadlines with minimal site and environmental disruption and maximized utilization of existing infrastructure.

The clinical manufacturing facility was constructed by Pharmadule modular fabrication in Sweden. Related equipment and utilities were installed during fabrication and integrated into each module, thereby reducing time and enabling concurrent engineering project completion in Sweden. At the same time in New Jersey, demolition, excavation, and foundation work was

Module fit-out in Sweden.

Why Our Project Should Win

The following is an excerpt from Merck & Co., Inc.'s submission, stating in their own words, the top reasons why their project should win the 2011 Facility of the Year Award:

Factors for winning revolved around the fact that diverse and complex technical user requirements involving the design of GMP clinical supply and development facility to support existing and future manufacturing technologies supports an existing and projected new chemical entity development portfolio over the next 15+ years.

- **State of the art, flexible GMP facility** was designed and constructed for present/future growth to meet the strategic need for increased capacity, capability, productivity, and efficiency.
- **Outstanding project execution, integrated, multi-phased "hybrid-build"** design/construction approach:
  - partial demolition of a decommissioned commercial production facility
  - adaptive reuse of former pharmaceutical warehouse as part of overall facility
  - utilization of modular fabrication/construction for primary manufacturing functions
  - "stick-built" three-floor Operations Support Building (OSB)
- Integrated, well coordinated, and collaborative **project management** approach utilizing **complex front-end planning, outstanding integration** of several **high performance** project teams, including communication and collaboration, was key for successful on time, on budget project completion. An EU inspection team provided input throughout the design and construction phases. **Multiple safety teams** were an integral part of all project teams from project inception.
- Co-located (three sites in Sweden/four sites in the US) project teams utilized a customized, **web-based Project Information Management System (PIMS)** to develop, review, monitor, control, document, and archive **key aspects** of the design, construction, qualification, schedule, and costs.
- **Innovative integration** of overall manufacturing strategy with scalable design to support development of a **variety of products**, including oral solid dosage, liquid, and inhalation products – for early and late stage clinical manufacturing – packaging and process development.
- Ability to achieve 10ug/m3 over an 8-hour time weighed average, thus introducing engineering controls to **reduce possible exposure** and **reducing reliance** on personal protective equipment.
- **Integrated functionality** supporting material and personnel flow from raw material storage and dispensing through manufacture and clinical packaging, including drug product GMP ICH guideline stability storage and staging
- Process technology platforms included a **combination** of **portable** and **fixed process equipment**.
- Incorporates **innovative technologies** and facility controls for solid oral and potent compound containment to promote **safety, quality, and compliance**.
- **Innovative redesign** solution of modular building support piers originally to be cast in place prior to setting the modules. By pre-casting the piers, a smaller, 300-ton crane was able to move throughout the modular building footprint enabling the pre-cast piers to be moved into place and bolted down as needed. Installation of the building modules continued **uninterrupted** and in a **very cost effective** approach.
- **Cutting edge data gathering** system incorporating both building management and process control capabilities within the **same platform**, while utilizing non-proprietary commercially available software allowing for ease of modification.
- Multiple integrated risk assessment and HAZOP reviews to **promote safety** and enabled the team to **engineer out known issues**.

Notes from the Judging Panel – What Impressed Them

- *The project was very well done from a facility integration perspective as the project is truly representative of the category definition for Facility Integration.*
- *Good integration of greenfield, modular, and renovated facilities to satisfy the project requirements.*
- *Good utilization of a "hybrid" construction approach that enabled Merck & Co., Inc. to achieve an aggressive timeline while making use of existing facilities, resulting in a facility that is flexible with integrated functionality.*
- *The "hybrid" approach was more cost effective compared to conventional options and enabled Merck & Co., Inc. to maximize reuse of the existing infrastructure.*

Award Category – Facility Integration

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

ongoing. When the modules arrived, they were set, assembled, and "hooked" up.

Parallel, Three-Phased "Hybrid-build" Approach

As part of a three-phased "hybrid-build" approach designed to accelerate the timeline, the project team was dispersed geographically on three concurrent multi-project phases guided by a Merck & Co., Inc.-driven master schedule. Key to this approach was well-coordinated project management with a high level of front-end planning and constant communication.

To further complicate matters, an existing adjacent Solutions Distributions Center had to remain fully operational during all phases of the project and required extensive pre-planning, automation and sensitivity testing, simulation vibration and measuring impact. In addition, the existing Summit campus is an active site with high levels of site traffic; this continued during all three phases of the project. Careful consideration and a high level of pre-planning from all project teams was given to the people and material flow plans along with extensive planning of the transportation of the modules from Sweden and the setting of the modules in the city of Summit, New Jersey.

Site preparation included the demolition of portions of the former pharmaceutical manufacturing and warehouse structure, clearing, grading, and site utility upgrades. Work also included modification and tie-in to existing underground utilities and coordination with site utility projects (chiller and solar installation) to support the new operations.

A very significant element of the site preparation was the construction of the modular building process and manufactur-

Modular site unique foundation and piers.

Module fabrication.

Concludes on page 18.

Stick-built mechanical mezzanine.

ing foundations. These were constructed to a +2 mm tolerance in preparation for receipt of the modules. A portion of the foundation piers also were designed to be removable in order to allow a more efficient and lower cost rigging approach. As the modules were rigged into place, the crane worked its way out of the foundation area and removable piers were set for the balance of module setting.

Modular Fabrication and Assembly (50,000 sq. ft./ 4,647 sq. m.)

This phase included fabrication of 82 modules in Sweden; transport to the Summit site; and installation and assembly of the modular process and manufacturing building, including all related process equipment, clean utilities, HVAC, and building equipment. The facility, equipment, and utilities were commissioned and validated. Utilizing a portion of an existing structure and fabrication construction, the completed two-story structure now contains clinical scale manufacturing and processing operations, including oral solid and non-sterile liquids and inhalation products production.

Key Project Participants

Architect: Jacobs/Wyper Architects, LLP (Philadelphia, Pennsylvania, USA)
Design Manager/Engineer: Integrated Project Services (IPS) (Somerset, New Jersey, USA) *(See ad on page 15)*
Construction Manager: Skanska USA Building Inc. (Parsippany, New Jersey, USA) *(See ad on page 19)*
Modular Design/Fabrication: Pharmadule, Inc. (Bedminster, New Jersey, USA)

Stick-Built Renovation (80,000 sq. ft./7,432 sq. m.)

The remaining areas of the existing building were renovated back to the basic structure with roof membrane and insulation removal and replacement. This phase included retrofit of the existing building to accommodate shipping and receiving, warehousing, primary and secondary clinical packaging, dispensing, stability, locker rooms, laboratories, calibration, process equipment maintenance, utility, mechanical and support areas. Electrical substations and other building utilities were designed and installed to support the renovation, modular manufacturing, and the Operations Support Building. Construction was completed for a new structural mezzanine within the existing warehouse to house mechanical and electrical equipment and to provide access to the second floor of the modular building. The facility, equipment, and utilities were commissioned and validated.

Greenfield Construction (90,000 sq. ft./8,736 sq. m.)

This phase included construction of the new Operations Support Building (OSB), a three-story building connected to manufacturing operations via an enclosed walkway. Approximately 40% of the OSB third floor was left as a shell for future expansion. The facility and utilities were commissioned and validated.

Conclusion

Utilizing the "hybrid-build" approach enabled Merck & Co., Inc. to achieve an aggressive timeline while making use of existing facilities and minimizing site disruptions. The outcome was a facility that is flexible with integrated functionality. The approach also proved to be cost-effective compared to more conventional options, as Merck & Co., Inc. was able to maximize reuse of existing infrastructure.

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Novartis Vaccines and Diagnostics GmbH

Innovative Equipment Design Increases Productivity

Introduction

The Novartis Vaccines' **MARburg Site (MARS)**, located in Marburg, Germany is intended to satisfy future potential growth in vaccine production volumes driven by healthcare and market demands, current and future GMP and regulatory requirements, requirements for state of the art facilities, and efficiency and productivity improvements.

Winner of the **2011 Facility of the Year Award for Equipment Innovation**, the facility produces vaccines for Rabies and Tick Borne Encephalitis (TBE). The project impressed the judges in several respects, most notably the facility's Laser Egg Opener or LEO, a system capable of handling 3,000 eggs per hour. The system eliminates the potential for cross contamination compared with traditional contact methods and increases process throughput, resulting in a tenfold productivity increase for Novartis.

Project Overview

The MARS project integrates onto one site the manufacture of existing vaccine concentrates and the production of media, buffer, and adjuvant products. It also integrates support function, for example, by centralizing the equipment cleaning and sterilization facilities for the Marburg site and beyond. The MARS project also provides a new state of the art Quality Control Building that consolidates the analytical and other QC functions.

The production facility is capable of manufacturing 20 million doses of Rabies vaccine or 40 million doses of TBE vaccine or any combination utilizing two interchangeable production lines. The media, adjuvants, and buffers production supports all of the 20 vaccines (registered in more than 80 countries worldwide) within the Novartis portfolio.

The QC facility typically performs 35,000 to 40,000 analytical tests and more than 100,000 environmental and utility monitoring samples per annum.

Novartis Vaccines and Diagnostics GmbH

Category Winner – Equipment Innovation

Project: MARburg Site (MARS)
Location: Marburg, Germany
Project Mission: A strategic investment to satisfy future potential growth volumes and current and future GMP and regulatory requirements
Size: 257,042 sq. ft. (23,880 sq. m.)
Total Project Cost: $242,000,000
Duration of Construction: 18 months

Aerial view.

The warehouse is an integral part of the production facility, ensuring lean raw material and final product movement via a connecting spine. It has a capacity of 4,000 pallet spaces with chilled and ambient temperature storage.

The power plant and utilities ensure that the facility is independently supplied with utilities.

A New Process Flow

The design leverages the revised requirements for live vaccine processing issued by the US FDA in October 2007 and made effective in July 2008. The unique facility design and operating concept allows concurrent manufacturing of two different live vaccines on two segregated manufacturing lines in the same production area. The changeover procedure allows the switch of manufacturing from one vaccine to another. In other words, there is full flexibility to manufacture two vaccines either con-

QC facility.

Notes from the Judging Panel – What Impressed Them

- *Fast-track execution in only 26 months.*
- *Excellent safety record: 1.7 million man-hours with no LTI.*
- *Flexibility allowed for concurrent production of two live viruses.*
- *The Laser Egg Opener is capable of 3,000 eggs per hour and the system eliminates cross contamination and increases process throughput that resulted in a 10-fold productivity increase.*

currently or in campaign. This inherent flexibility allows the facility to respond fast to public health and market needs and reduce the cost of running dedicated facilities.

Cell Preparation

The upstream of the process is based on the infection of a suspension of chicken embryos fibroblasts with live virus. The cells and the viruses are incubated at controlled temperature for five days in single use cell factories and the virus suspension is harvested into a fixed stainless steel vessel.

Virus Propagation

The harvest is filtered in a second vessel in which the inactivation agent is added to the harvest and mixed. To complete the inactivation, a maturation step takes place in a third vessel.

Inactivation

A purification/concentration step by ultracentrifugation on sucrose gradients completes the process. The transfer between vessels to the ultracentrifuges is with stainless steel lines. From the harvest vessel to the ultracentrifuge, the biosafety and sterility of the product is ensured by a closed system. All transfers are driven by the automation system. Transfer lines and vessels

Fixed mixing inactivation and maturation vessels.

Continued on page 22.

Facility hallway.

are sterilized with clean steam (SIP), cleaning in place (CIP) by units dedicated to each of the two manufacturing lines.

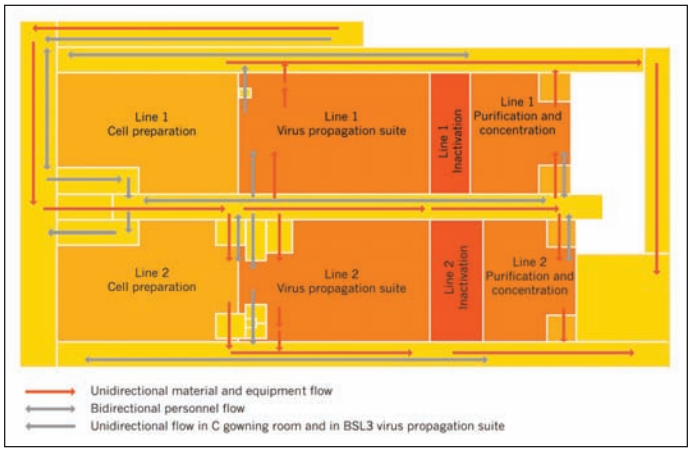
Lean and Clean Layout

The layout of the process flow is not only LEAN, but also accommodates the manufacturing of sterile inactivated virus suspension concentrate and a production suite ensuring biosafety Level 3 containment for the upstream steps of the virus production.

To avoid potential conflicts between GMP and biosafety, the cleanroom classification and air pressure regimes ensure that the correct air quality and airflow direction maintains the overall integrity of the facility. At the same time, biosafety Level 3 is achieved and cross contamination avoided, accommodating GMP and biosafety requirements. To efficiently manage the risk of personnel carrying virus particles in the surrounding corridor, an airshower has been installed between the sink airlock within the biosafety boundary and the bubble airlock in the surrounding corridor. The airshower acts as a containment cabin with interlocked airtight doors in which HEPA filtered air is circulated at high speed. This device is typically used to access cleanrooms from unclassified areas. In this design, it is used as a measure to avoid potential cross contamination.

The manufacturing suites are completely independent from each other with process step segregation for each stage of manufacturing. The lines are composed of a cell preparation suite, a virus propagation suite, an inactivation maturation suite, and an ultracentrifugation suite.

The central clean corridor separates the two manufacturing lines ensuring no cross contamination. This corridor allows movement of clean/sterile materials, consumables, and reagents to the manufacturing suites through unidirectional material airlocks. The airlocks prevent process cross contaminant in the corridor and ensures no impact on the batches manufactured on the second line.



Manufacturing suite layout.

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 2011 Facility of the Year Award:

- The facility uniquely combines from original concept design the concurrent production of two live viruses to produce inactivated vaccine concentrates. This inherent flexibility allows the facility to respond fast to public health and market needs and reduce the cost of running dedicated facilities.
- The design of the production facility is based on the full integration of the raw material, receipt flow into the manufacturing area through to the warehouse in a single controlled environment (via connecting spine). The incorporation of lean process flow enables the optimization of manufacturing costs and increased throughput contribution to a 10-fold improvement. Scale up and integration of the new centralized washing facility is a true example of equipment innovation within the facility. The QC facility is planned with high flexibility of space to suit the rapidly changing needs of the vaccine business. Its unique features rely on its potential to realize fast adaptation. This is achieved while maintaining the Bio-Safety Level 2 and 3 integrity essential to performing viral safety testing.
- In the MARS facility, the process of opening eggs is performed using an industrial scale laser process to eliminate cross contamination. This equipment is one of the largest applications of this type of technology and represents the combination of accurate manipulation, laminar flow control (aseptic conditions), and laser cutting to achieve 3,000 eggs opened per hour.
- The unique application of "PENTA-GEN" technology is a smart mix between conventional and state of the art generation providing five energies: electrical power, emergency power, hot water, steam, and chilled water. This combination achieves the highest efficiency representing a 12.755/year reduction of CO_2 (60% reduction compared to industrial park supply).
- The project execution truly achieved a balance of highest quality, optimum cost within a schedule compared with the best of fast track examples. During its project execution, the business and team in Marburg also responded positively to a public healthcare challenge caused by the 2009 H1N1 pandemic.

Concludes on page 24.

Eggs opened using an industrial scale laser process.

Award Category – Equipment Innovation

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

Laser Egg Opening: Eliminating Cross Contamination

The production of Rabies and TBE vaccines consists of three major production steps: 1) preparation of the cell suspension, 2) virus propagation, and 3) concentration of the inactivated virus.

In the first step of production, eggs are used to produce cells for the next steps in the production flow. In the new MARS facility, the process of opening eggs is performed using an industrial scale laser process under strict cleanroom conditions. The Laser Egg Opener (LEO) automatically opens eggs in parallel while maintaining aseptic conditions.

Within the new LEO handling system in the MARS facility, the pre-disinfected eggs are handled on trays with capacity for 84 eggs with potential to accommodate 3,000 eggs/hour. The trays are manipulated by the operator at the front end of the laser egg opener within a laminar flow tent. Transportation of the eggs through the egg opener is by means of a conveyor belt system controlled by optical sensors. These can detect tray position and occupation. This ensures that the laser is only distributed to the eggs present and not to the empty spaces. The layout of the trays and the conveyor system allows the opening of four eggs in parallel using four individual laser beams.

In the past, the opening of the eggs was performed manually with the help of an "egg puncher" device, which operated pneumatically. The operator had to manually open every single egg with this device. This method, carried out under cleanroom classification C, increased the risk of cross contamination due to the contact and damage to the eggs.

The LEO system eliminates the potential for cross contamination and increases process throughput, resulting in a tenfold productivity increase for Novartis.

Conclusion

The MARS facilities are the pillars of the Center of Excellence for modern vaccines production at Novartis in Germany. As demonstrated by the LEO system, the project represents Novartis' strategic investment in its global vaccines manufacturing capabilities, providing an opportunity to: enhance LEAN manufacturing techniques, innovate processes, improve efficiency and productivity, and reduce the costs of producing high-quality medicines.

Key Project Participants

Engineers:

- Production: M+W Process Industries (Stuttgart, Germany) *(See ad on page 21)*
- Warehouse: Miebach Consulting GmbH (Frankfurt, Germany)
- Quality Control: Labotech Planungs GmbH (Griesheim, Germany)
- Power Plant: Pöyry GWK GmbH (Erfurt, Germany)

Laser egg opener.

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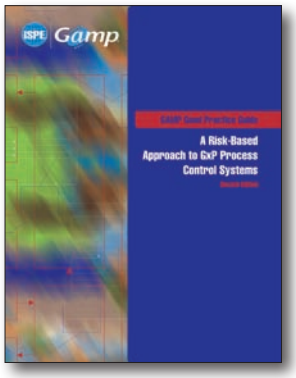

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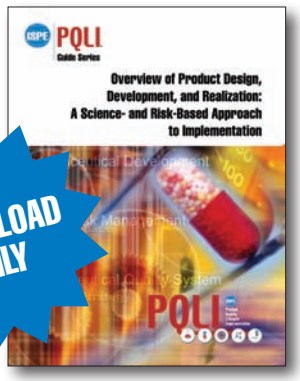

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Pfizer Manufacturing Deutschland GmbH

Engineering a Long Term Sustainability Program

Introduction

According to the judging panel, **Pfizer Manufacturing Deutschland GmbH's Strategic Plant Restructuring and Energy Master Plan (SPRING and E-MAP)** project, winner of the **2011 Facility of the Year Award for Sustainability**, encompassed the engineering of a long-term sustainability program that is unparalleled in pharmaceutical manufacturing.

Located in Freiburg, Germany, the project consisted of five major projects and a series of 200 minor projects that collectively enable the facility to operate with 91% renewable energy sources, reduce its production costs by 15%, and realize a 30% energy savings.

Commitment to the Environment

The Pfizer Freiburg site, located in Germany's Black Forest region, is Pfizer's largest European facility. The plant is one of Germany's most modern production and packaging facilities for tablets and capsules. More than 230 million packs of drugs leave the Freiburg plant each year and 1,000 employees develop and produce pharmaceuticals for treating pain, cardiovascular diseases, and epilepsy.

Pfizer's environmental management credo is taken seriously at this facility. The Site Leadership Team considers the increase of automation and reduction of energy consumption and carbon footprint as an important strategic part of the facility's long-term vision.

Cost was also a major driver for Pfizer Freiburg's interest in energy efficiency. It was the increasing cost focus of the pharmaceutical industry resulting from the global economic downtown that brought renewed interest in Pfizer Freiburg to the questions of energy efficiency.

Main entrance.

Project Overview

A key task for Pfizer Freiburg is to identify projects that make sense from both a Green-energy and CO_2 reduction perspective. This effort resulted in the Strategic Plant Restructuring and Energy Master Plan (SPRING and E-MAP) project.

SPRING and E-MAP is a plan to optimize the manufacturing and packaging operations on site which contains five major projects and more than 200 smaller projects all aimed to implement cost- and energy-efficient technologies. Freiburg implemented the following main technologies:

- geothermal heating and cooling of office buildings

Energy tubes area in geothermal field.

Continued on page 28.

Pfizer Manufacturing Deutschland GmbH

Category Winner – Sustainability

Project: Strategic Plant Restructuring and Energy Master Plan (SPRING and EMAP)
Location: Freiburg, Germany
Project Mission: Look for innovative ways where GMP improvements and savings can be made to the benefit of the corporate bottom line, our colleagues, and the planet. Working together for a healthier world.
Size: 173,837 sq. ft. (16,150 sq. m.)
Total Project Cost: $42,300,000
Duration of Construction: 40 months

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Solar panels produced green electricity.

- biomass steam for pharmaceutical manufacturing and packaging
- biomass absorption cooling for pharmaceutical manufacturing and packaging
- adiabatic cooling for laboratories and high efficiency manufacturing areas
- photovoltaic for electricity generation

Two hundred smaller projects, related especially to the implementation of employees' continuous improvement proposals include:

- electric car for the internal transports
- reduced air changes in laboratories and manufacturing area
- stand by operations in various areas
- reuse of waste water from purified water system

SPRING and E-MAP stands on three pillars: using renewables, increasing energy efficiency, and saving energy.

Renewables

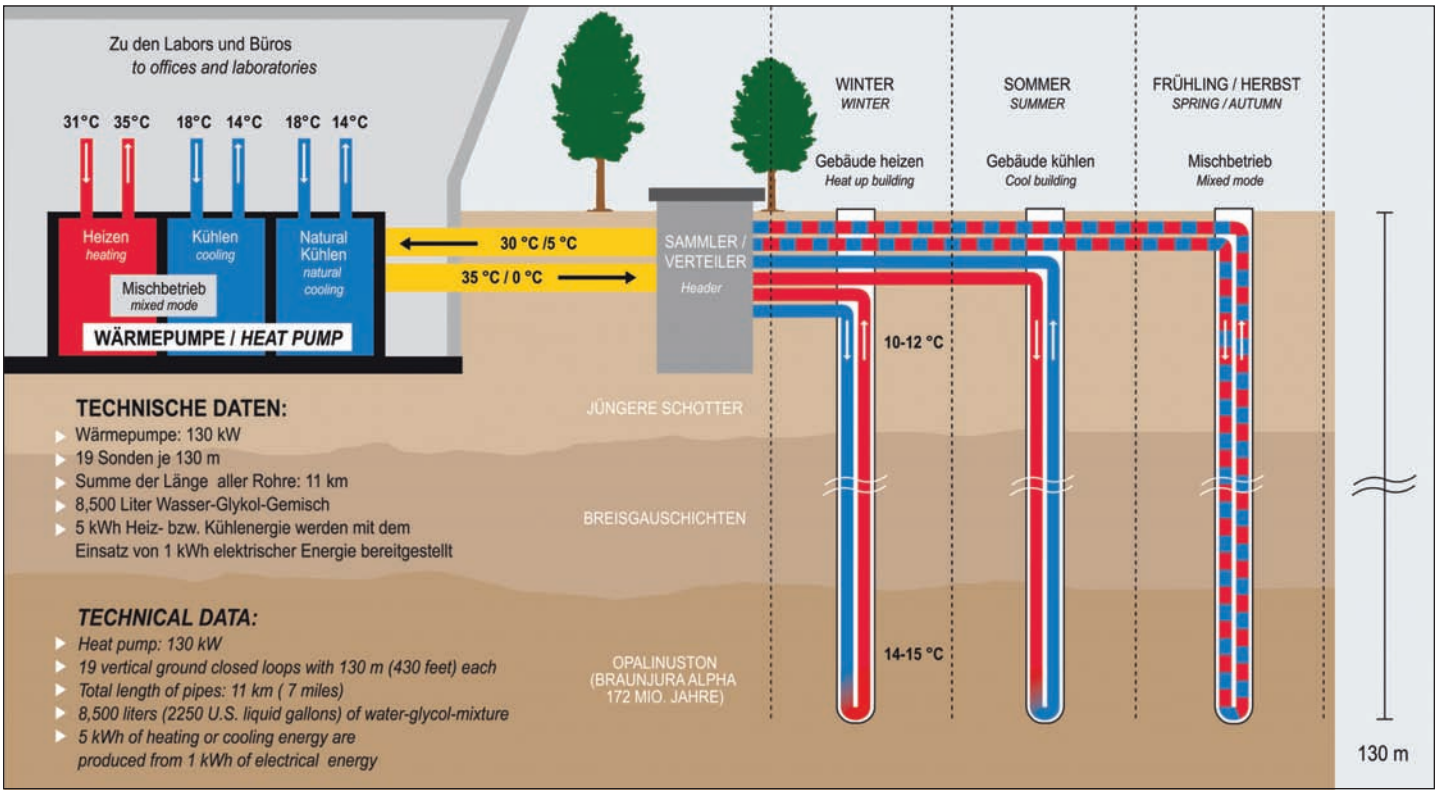
Two key components of the renewables pillar are geothermal energy and changing to biomass as fuel in the heating system.

Geothermal Energy

The first major project undertaken was the installation of the geothermal heating and cooling system for the laboratory and office building. Geothermal energy was chosen because it is one of the most profitable "renewable" energy sources. Due to increasing energy prices, investments in geothermal systems pay off more quickly and it is always available regardless of the season.

A prerequisite for the use of geothermal energy and systems for heating and cooling a building is a building concept that limits the heating and cooling capacity to a minimum. This requires good heat insulation of outside walls, minimal air exchange, and outside sun protection in the summer to minimize heat absorption, thus reducing the necessary cooling capacity. Otherwise, the required heating and cooling capacity would be so high that it could only be achieved with conventional heating and cooling systems.

The system used for geothermal heating and cooling of the office building consists of a borehole heat exchanger field and a compact power station which feeds the heating and cooling



Cross section of the borehole heat exchanger field.

energy to the building services equipment. At the heart of the system is a heat pump with a nominal heat output of 130 kilowatts with an electrical output of 30 kilowatts. R407C is used as a cooling agent.

The borehole heat exchanger field consists of 19 exchangers, two collector and distributor shafts, and the piping to and from the building. Total length of the heat exchangers is 2.47 km, thus total length of the installed heat exchanger tubes is 9.9 km. The boreholes have a diameter of 15.2 cm. If the building requires heating and cooling at the same time, the system will check if there is a net heating requirement or a heat surplus in the building. Depending on the energy balance, the borehole heat exchanger field is either used as a heat source or a heat sink.

This geothermal system reduced the carbon footprint of the facility annual by 750 tons, which equals the emissions of a small city.

Wood Pellet Boiler System

A new wood pellet boiler system was installed, replacing two of four boiler systems. Touted as the Europe's largest pellet boiler, the new system generates heat and process steam almost entirely with wood pellets with a steam output of 5.5 tons per hour.

The pellets are produced from dried, untreated residue wood (sawdust, shavings, residue wood from the forest). They are compressed under high pressure without adding chemical binding agents and have a heat value that corresponds to the energy content of half a liter of heating oil per kilogram.

Wood pellet steam boiler.

Pellets are environmentally friendly, since unlike fossil fuels, they are CO_2 neutral; during combustion, the energy sources only release the same quantity of carbon dioxide that the tree has absorbed while growing. The combustion of pellets releases less sulfur dioxide than conventional wood combustion. Since this gas contributes to the formation of acid rain, the conversion to pellets as a fuel also helps protect local forests.

Why Our Project Should Win

The following is an excerpt from Pfizer Manufacturing Deutschland GmbH's submission, stating in their own words, the top reasons why their project should win the 2011 Facility of the Year Award:

- The vision driven long-term strategy of transforming Pfizer Freiburg into a green facility led to a beacon sustainability concept. Pfizer Freiburg realized a powerful multi-pronged approach. The measures not only include spectacular individual measures, but they also secure the site's impressive high energy standard and considerably reduce its environmental impact at the same time.

- Converting a classical production site to the use of renewable energy sources at an industrial scale is unique. Pfizer Freiburg is the largest packaging site in the Pfizer network. The entire site made a far-reaching change to renewables: 91% of the required primary energy is generated using renewable energy sources. EU provisions for 2020 are thus already today far exceeded. The findings on the payback cycles (three years only) and cost-effectiveness (30% energy cost reduction) in industrial applications are groundbreaking for the entire pharmaceutical field.

- Outstanding reduction of greenhouse gas emissions: Pfizer slashed carbon dioxide gas emissions by 80% by employing Six Sigma and lean methods. The savings totaled 7,000 tons, which equal the emissions of a small city. The company exceeded EU provisions targeted for 2020 and can be considered to be very well prepared for the future challenges in the field of energy self-sufficiency and energy supply security. In 2011, Freiburg could reduce the overall CO_2 emissions below 650 tons CO_2 (in 2005, it was 13,500 tons CO_2).

- Pfizer Freiburg's SPRING and E-MAP revealed the enormous potential the move to renewable and energy efficiency contained for the pharmaceutical industry. Increasing cost pressure has been answered with product cost-savings of 15% by combining the economic advantages with environmental benefits. Additionally, we promote all the green achievements proactively as a "lighthouse as guide to a healthier world" to increase the acceptance within Pfizer and the industry.

- The pioneering spirit of the employees considerably drives the company's power. Pfizer employees create a more desirable workplace and Pfizer becomes the best place to work. The participative approach of SPRING and E-MAP which was core to the plan increased employees motivation in facility engineering management regarding environmental issues and raised the company's credibility in dealing with local authorities and external stakeholders.

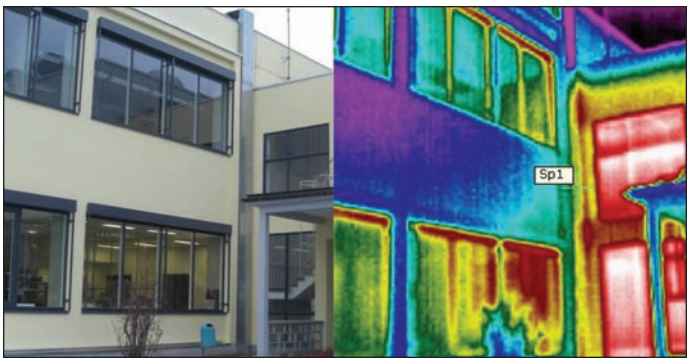
Concludes on page 30.

Notes from the Judging Panel – What Impressed Them

- *Overall it was an excellent project.*
- *The project exemplifies what Sustainability is all about. The implementation of the SPRING and E-MAP to optimize operations generated impressive results for this pharmaceutical manufacturing plant.*
- *The innovative and forward thinking plan consisting of five major projects and a series of 200 minor projects collectively enabled the facility to operate with 91% renewable energy sources. Additionally, there was an energy savings of 30%.*
- *Most impressive to the judges was how Freiburg engineered a long term sustainability program that is unparalleled in pharmaceutical manufacturing.*

Award Category – Sustainability

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



Thermo graphic inspection shows heat loss.

While crude oil and natural gas are becoming scarcer and more expensive, the production of pellets is increasing steadily. Wood is available locally. According to Pfizer, in times of global crises and long transportation distances, local fuels are a stabilizing element. Due to sustainable, natural forest management, wood as a fuel will continue to be available in the long term.

According to Pfizer, the new biomass fuel system saves the environment 5,500 tons of carbon dioxide annually as well as six-figure heating costs for the company and in the future, will provide around 85% of the heat and steam required at Freiburg.

Key Project Participants

Designer/Architect: Architekturbüro Frey (Bingen am Rhein, Germany)

Main/General Contractor: Siemans Axiva (Frankfurt am Main, Germany)

Innovation Support: The Freiburg team is collaborating with The University of Freiburg and Offenburg PMD Germany and ZEE-REM (Green Universities of the City of Freiburg in a collaboration of other universities under the umbrella of the ZEE Centre for Renewable Energy) http://www.studium.uni-freiburg.de/.

Efficiency

Many achievements were accomplished by fine tuning detailed tasks, together having an enormous effect on the site's energy balance. Technicians optimized the many ways building management systems were controlled. A broad range of projects were initiated, including: reducing the number of circuits using frequency converters in the neutralization process or in the generation of compressed air, increasing the service life of drives and reducing energy consumption; cooling laboratories and office buildings with evaporating water (adiabatic cooling) as an alternative to using compressors which require a great deal of energy; and employing heating and cooling ceilings, which use less energy than conventional radiators.

Saving Energy

Pfizer Freiburg improved the insulation of outer walls, invested in high thermal insulated windows, and reduced the cooling energy requirements in the summer by using an automatic sun shading system. An intelligent lighting system ensures that energy is only used where it is actually needed. The air exchange rate of the ventilation system is easily adjusted to the actual requirements in different GMP rooms at the touch of a button.

Conclusion

SPRING and E-MAP's energy framework is filled with numerous, carefully targeted individual measures to increase energy efficiency or save energy. The end result is not a fixed point, rather a manufacturing plant that can be just as dynamically adjusted to changes as the company itself. Pfizer's ambitious goal is to be open-minded toward the future and to prepare future developments today. The investments made in environmental and climate protection are paying off. The facility is operating with 91% renewable energy sources, reduced its production costs by 15%, and realized a 30% energy savings.

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Pfizer Health AB

An Operation of Great Ingenuity

Introduction

Pfizer Health AB's Bio 7 Manufacturing Facility, a new microbial drug substance production facility at Pfizer's production site in Strängnäs, Sweden, was designed and constructed primarily to manufacture two legacy Pfizer products that have opposite effects on the human physiology, yet are similar molecules. Pfizer scientists explored this similarity to develop an innovative manufacturing process with virtually identical unit operations that could be utilized for both products.

Project Pegasus – Bio 7 Manufacturing Facility was named winner of the **2011 Facility of the Year Award for Operational Excellence** for Pfizer's ability to bring a new facility online with added capacity without additional headcount or extended shift patterns. This was achieved by incorporating a high degree of flexibility into the facility design and developing and implementing key design and process enhancements.

Project Drivers

Genotropin®, which has been on the market for 24 years, is a recombinant Human Growth Hormone (rHGH) used for the treatment of growth hormone deficiency. Somavert®, which has been on the market for 13 years, is a growth hormone antagonist used for the treatment of acromegaly (over-production of growth hormone). Genotropin was and still is partly manufactured in an existing facility at the Strängnäs site, while Somervert DS was sourced from a contract manufacturer.

The drivers for constructing a new facility were several fold, including bringing Somavert manufacture in house, thus reducing the cost of goods; introducing improved processes designed to increase yield; eliminating capacity constraints in the existing facility; eliminating animal derived products; and reducing cycle time. Other fundamental criteria were the need to maintain existing head count and limit the operations schedule to a two shift pattern with no night shift.

Exterior view.

Project Overview

Bio 7 is a two story facility with interstitial space between floors. Total floor space is 54,465 sq. ft. (5,060 sq. m.). An additional 5,380 sq. ft. (500 sq. m.) in an existing building was retrofitted to facilitate installation of a buffer and media preparation facility including filtration room. The Strängnäs site was chosen for this new facility due to the manufacturing know how on site, presence of existing utilities with sufficient capacity to simultaneously serve the existing and new facility, and available space for the new facility plus any future expansion.

Bio 7 under construction.

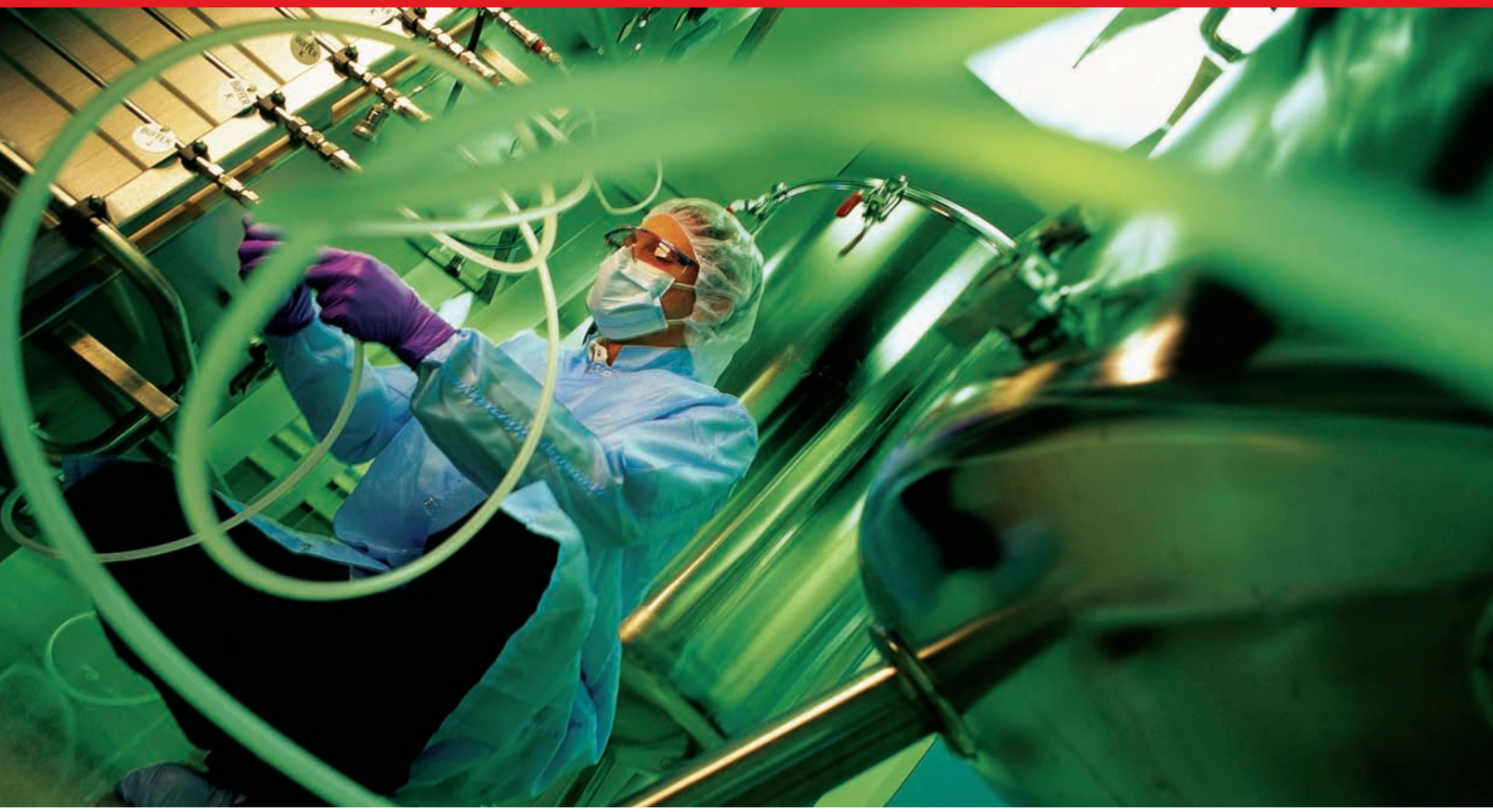
Continued on page 34.

Pfizer Health AB

Category Winner – Operational Excellence

Project: Pegasus – Bio 7 Manufacturing Facility
Location: Strängnäs, Sweden
Project Mission: Establish a strategic facility of technical and quality excellence for Genotropin and Somavert drug substance and future microbial cell products; realize cost benefits from more efficient processes and in-house manufacturing of Somavert; change to animal free media for supply assurance; assure long term capacity for both products
Size: 54,465 sq. ft. (5,060 sq. m.)
Total Project Cost: $188,700,000
Duration of Construction: 25 months

Our Award-Winning Expertise ...to Benefit *Your* Microbial Products



Operational Excellence in Microbial Manufacturing

Pfizer CentreSource delivers innovative, high quality services that leverage Pfizer's award-winning leadership in biologics development and manufacturing across microbial platforms. And with Pfizer's advanced facilities, regulatory track record, and highly experienced bio-therapeutics professionals, we can apply Operational Excellence to manufacturing therapeutic proteins in a way that benefits your product, and your bottom line.

Among the capabilities available to Pfizer CentreSource customers are:

- **Industry-leading protein expression technologies**
- **Expertise in biological product characterization**
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- **Biologics manufacturing and supply chain experience**
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2011
Facility of the Year Awards
CATEGORY WINNER
Operational Excellence

Pfizer's Project Pegasus - Bio 7 Manufacturing Facility in Strängnäs, Sweden, is a 2011 Facility of the Year Award (FOYA) winner for Operational Excellence.

PfizerCentreSource
Partnering with our customers for a Healthier World™

Pfizer

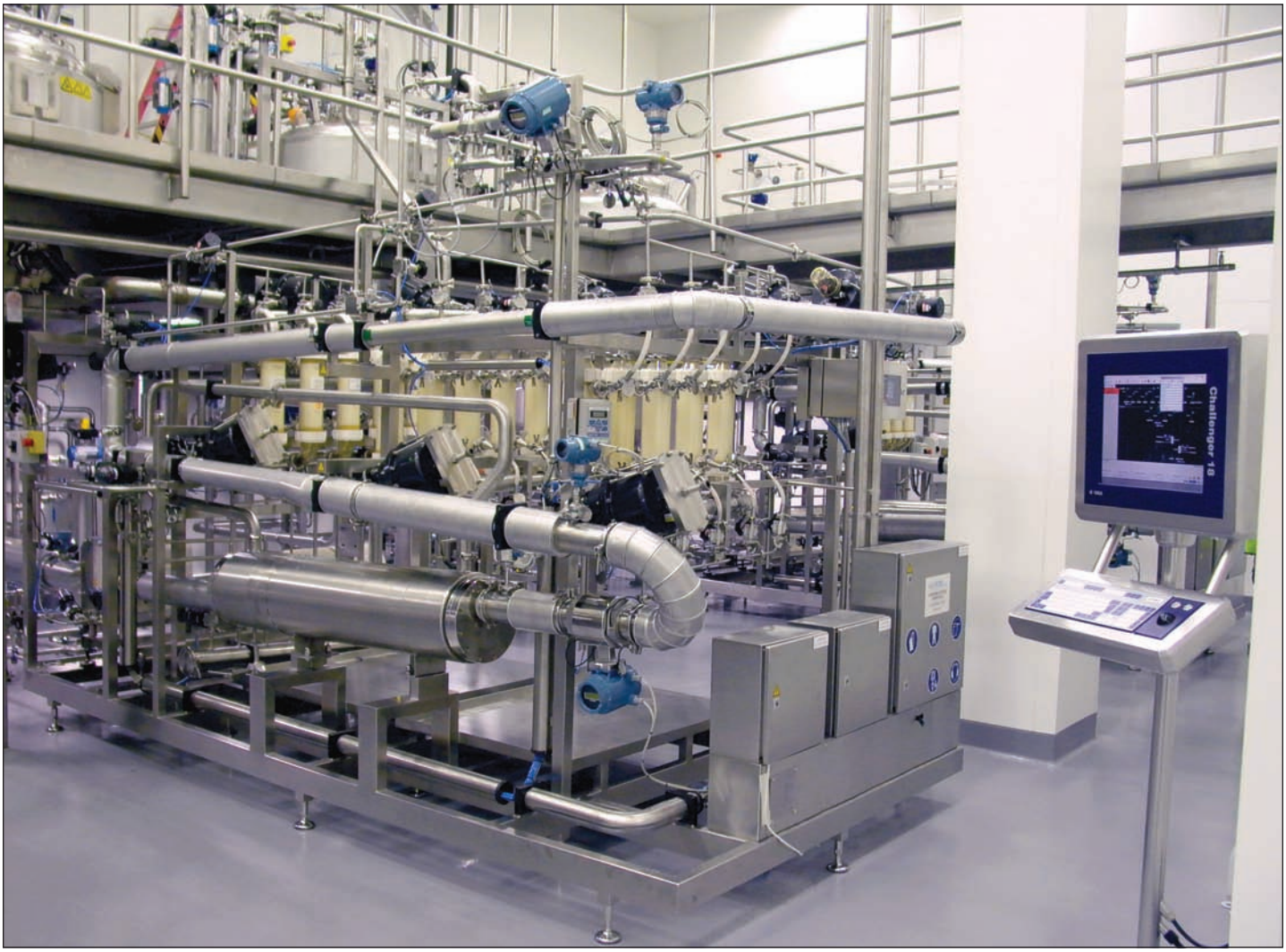
The facility design was based on closed processing utilizing stainless steel equipment which minimized cleanroom requirements. The facility contains two independent fermenter trains, each configured with a 300 L seed fermenter, 3,000 L main fermenter and two support vessels. This is followed by one process equipment train from harvest and product recovery, downstream purification, to formulation and bulk filling. The facility is highly automated utilizing a control system and a limited number of packages utilizing PLCs, e.g., autoclaves, washers, centrifuge, etc.

Streamlining for Efficiency

While Genotropin and Somavert have opposite effects on the human physiology, they are similar molecules. Pfizer development scientists exploited this similarity to develop an innovative manufacturing process with virtually identical unit operations that could be utilized for both products. The old manufacturing process for these two products are completely different; therefore, the creation of a common manufacturing platform was of enormous benefit to Pfizer in terms of reducing capital investment required for the facility and enhancing operational excellence. In addition to creating a common manufacturing platform, the batch yields have increased significantly.

Fermentor super skid – assembled at vendor workshop prior to FAT.

Minimizing manual interactions in the process was a key feature of the design intent to allow the control system to run seamlessly from one process step to another. This intent



Harvest area – microfiltration skid (cell removal unit operation).

is reflected in several features of the design, including use of automated valves instead of transfer panels, very few inline filters, TFF skids with automated integrity testing capability, and vessel vent filter configuration.

Another key feature of the facility is the control system recipes, which when activated, run through the entire process from buffer preparation to CIP post bulk filling.

Minimizing equipment cleaning times was identified very early in the project as a critical goal to ensure maximum facility efficiency. The elimination of SIP functionality in the downstream processing area was another key decision in the drive to achieving a highly efficient facility.

Why Our Project Should Win

The following is an excerpt from Pfizer Health AB's submission, stating in their own words, the top reasons why their project should win the 2011 Facility of the Year Award:

Operational Excellence

- Pfizer has realized a facility which is extremely efficient and truly fit for purpose. In the current environment where cost is of the utmost importance, the Pfizer Strängnäs Bio 7 Facility is an example of how to create efficiency and significantly reduce cost of goods without incurring excessive capital investment cost.
- The goal of Project Pegasus was not just to deliver a functional facility, but also a facility which would operate in a lean fashion without requiring an extended shift pattern or additional head count.
- Excellent efficiency creates additional capacity in the facility which, when taken up with new products, reduces capital depreciation effect on cost of goods. While the original requirement was to allow for processing of two batches per week, the facility can process an estimated 3.5 batches per week and this can be further increased with minor optimizations.

Project Execution

- The early creation of a highly competent and experienced Pfizer team, which was in place for the duration of the project, greatly assisted the goal of meeting budget and schedule while delivering a facility which is fit for purpose, efficient, and ergonomic. The wealth of experience and operational know-how in the Pfizer team provided enormous added value to the facility design and reduced overall project risk. Completing the C&Q execution within six months was a major achievement for Pfizer and was due in no small part to the expert knowledge provided by the Pfizer team during the design phase.
- Despite the very complex nature of many aspects of the manufacturing process, the commissioning effort was completed ahead of schedule and the facility is now operating in a very robust manner. There has only been one instance of microbial contamination for a total of 32 batches completed in the facility, which is excellent for a start-up of this size.
- An exceptional value engineering exercise was undertaken, which not only significantly reduced capital investment cost, but also contributed to facility efficiency by optimizing overall facility ergonomics and reducing maintenance requirements.

User Friendly – Ergonomic

- While delivering a functional facility within budget and on schedule is the standard measure of a project's success or failure, the Pegasus management team gave equal weight to facility operability. From an operations perspective, the new Bio 7 facility is extremely user friendly and ergonomically smart. This is based on feedback from operators and maintenance personnel, many of whom have worked in several different facilities. This is a vindication of the continuous involvement of Pfizer mechanical, process, operations, E&I and EHS personnel in the 3D model review of the facility.
- This also contributes to the efficiency of a facility as it allows for faster turn-around and maintenance of equipment.

Innovation and Flexibility

- Creating a cost effective facility of exceptional efficiency required the application of innovative design and processing techniques in several areas of the manufacturing process. The successful use of in-line dilution in combination with gradient generation on chromatography unit operations is one example. Concurrently running multiple unit operations in the harvest area is an example of utilizing innovative processing techniques to reduce processing time and save on capital investment. Reconfiguring the primary WFI loop to a self contained recirculation loop also displayed innovative thinking to resolve a challenging problem.
- While the Bio 7 Facility makes limited use of disposable technology, the equipment configuration allows the manufacturing platform to be easily configured for new microbial based fermentation products.

Reduction in Cost of Goods

- The significantly higher fermentation titers, higher step yields, reduced number of unit operations, and introduction of "batch oneness" has significantly reduced batch release time and overall cost of goods. While the previous Genotropin process required a total of 18 batches to create one final batch, the new process takes a single batch from fermentation to bulk fill. This greatly reduces batch release time and simplifies investigations as traceability is straightforward.

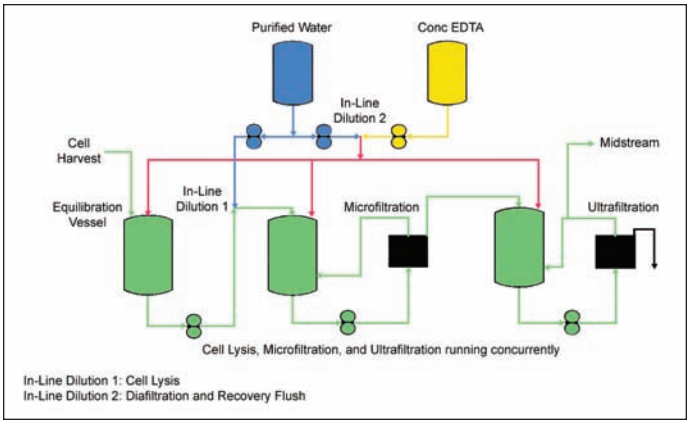
Concludes on page 36.

Notes from the Judging Panel – What Impressed Them

- *Nice job of optimizing existing processes, good risk management, and a good job on allowing for reuse of buffer filters*
- *Due to incorporating a high degree of flexibility into the facility design process, Project Pegasus was able to bring a new facility online with added capacity without the addition of any headcount or extended shift patterns.*
- *The project team did a good job of minimizing manual interactions in the process, enabling seamless movement through process steps.*
- *Key design elements, including the minimization of equipment cleaning time and elimination of SIP in downstream processing enhanced efficiency.*
- *As a result of the focus by the Pfizer team on Operational Excellence, the facility has an estimated capacity of 3.5 batches per week as opposed to the original target of two.*

Award Category – Operational Excellence

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



Integrated harvest unit operations.

Process enhancements such as membrane flushes, integrated harvest operations, multi batch buffers, and positioning of liquid filter housings are additional examples of the team's focus on operational excellence.

While the new manufacturing processes were well developed, there were a number of unknowns and additional optimization which the development group worked on during the facility design. A Pfizer team of experienced process engineers with extensive hands-on commissioning, process optimization, and debottlenecking experience were key to realizing an efficient facility.

Key Project Participants

Designer/Architect: Jacobs UK Ltd. (London, UK)/Sweco (Stockholm, Sweden)
Construction Manager: Pfizer
Main/General Contractor: Skanska (Solna, Sweden) *(See ad on page 19)*

Conclusion

Project Pegasus was able to bring online the Bio 7 Manufacturing facility with added capacity without the addition of any headcount or extended shift patterns. This was achieved by incorporating a high degree of flexibility into the facility design. The project team also had to minimize manual interactions in the process, enabling seamless movement through process steps. Control system recipes were developed that run from the buffer preparation through CIP. Minimizing equipment cleaning time and elimination of SIP in downstream processing were also key design elements that enhanced the efficiency of this biotech operation. Process enhancements demonstrated the team's focus on operational excellence. Targeted output of the facility was two batches per week, but as a result of the team's focus on operational excellence, the facility has the capacity for up to 3.5 batches per week.

Downstream processing area – chromatography skid and column.

Rockwell Automation would like to congratulate Pfizer Health AB on winning the FOYA category in Operational Excellence for the Pegasus Project in Stragnas, Sweden.

LISTEN.
THINK.
SOLVE.®

The Rockwell Automation EMEA Life Sciences team are delighted to have been involved in delivering a component of a successful FOYA category winner for a third consecutive year. If you require an Automation/MES/ Process Technology partner or are looking for further information on how we could assist you in delivering an award winning facility please visit our website:

www.rockwellautomation.com/industries/lifesciences

2011
Facility of the Year Awards
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F. Hoffmann – La Roche Ltd

Innovative Process Ensures Innovative Drug Delivery to Patients

Introduction

The Roche Global Engineering Department received its instructions from the Roche Board: design and construct a facility capable of producing a device with completely new technology in a small space and extremely aggressive time frame.

The device, called MyDose, is a single-use infusion device which is a new platform for automatic drug delivery of high volume drugs to patients. The device consists of 83 individual components and requires 40 production steps to manufacture.

Thirteen months later, the first MyDose devices were produced in the **MyDose Clinical Supply** facility in Kaiseraugst, Switzerland. Deemed by the judging panel as a project that demonstrated excellent innovation in the industry, the facility is the winner of the **2011 Facility of the Year Award for Process Innovation**.

To meet this project's unique requirements, Roche employed a combination of existing, proven technology and specific customizations. In some cases, entirely new applications served as a basis for the manufacturing process layout. Assembly and welding of the fluid path components of the MyDose device is the most complex step and required the installation of a laser welding process in a cleanroom environment. The process design and development were critical success factors of Roche's new delivery platform.

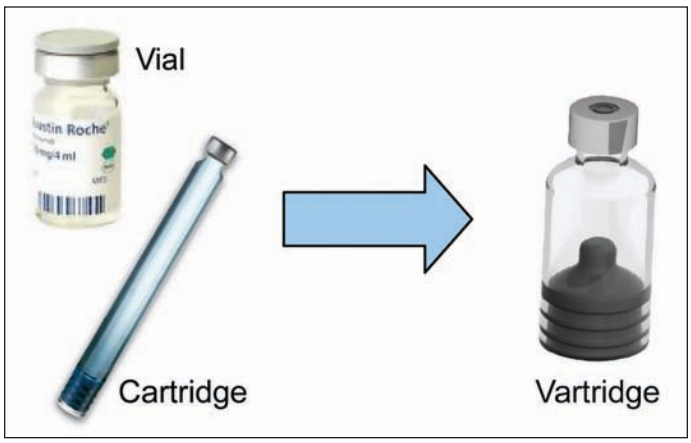
The MyDose Device

MyDose is the trade name for a single use infusion device that enables the subcutaneous administration of large quantities (up to 15 ml) of liquid medicine. The medicine is a new formulation of drugs which allows various monoclonal antibodies to be delivered. MyDose's main functional component is a Vartridge (hybrid between a vial and a cartridge), housed in the fluid path container and set in motion by a motorized drive.

Exterior view of facility.

Vials and cartridges are glass containers for drugs with a closure. The vial is similar to a bottle with a bottom. The cartridge is a slim glass tube (diameter between 6 to 9 mm) equipped with a piston to close the container at the bottom. The patented Vartridge is a hybrid between both. The design of the piston is unique as well. The conic form of the piston ensures that the Vartridge will be completely emptied when the piston is pressed down.

Administration of the MyDose Device is simple. The patient puts the device on the stomach. An adhesive patch attached to

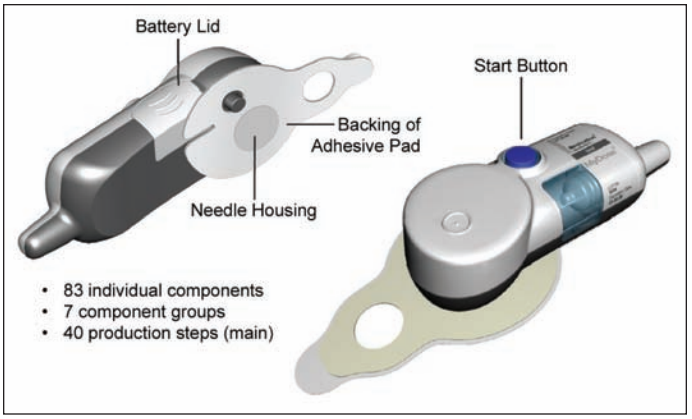


The Vartridge is a hybrid between a vial and a cartridge.

F. Hoffmann – La Roche Ltd

Category Winner – Process Innovation

Project: MyDose Clinical Supply facility
Location: Kaiseraugst, Switzerland
Project Mission: A new production facility with state of the art process modules tailored specifically to the production of innovative MyDose device.
Size: 3,444 sq. ft. (320 sq. m.)
Total Project Cost: $11,891,102
Duration of Construction: 7 months



MyDose device.

the device keeps the device in place. The mechanism is activated by pressing the start button. A sterile needle penetrates the abdominal wall. The battery driven motor depresses the piston down. The drug is injected subcutaneously.

The MyDose Facility

The MyDose Clinical Supply facility is situated at Roche's Kaiseraugst site, which has become a thriving center for galenical manufacturing and hosts the largest and most up to date packaging and logistics facilities for Roche. The Kaiseraugst facility supplies 120 million packages of medicine each year to 130 countries.

The device components and medicine are sourced globally, containing drug substance requiring application volumes from 3 to 15 ml, with pre-assembly of components (base, cover, fluid path) in Ireland; API production in Penzberg, Germany; plastic component manufacture in Asia; and compounding in Basel, Switzerland.

Sterile filling, welding, final assembly, and packaging take place at the MyDose Clinical Supply facility on the Kaiseraugst site in Building 231. The new production area was installed in existing space on the second floor. It encompassed 3,444 sq. ft. (320 sq. m.) separated into five cleanroom classes. Zone Grad G (controlled, not classified) accommodates the technical area providing the infrastructure for the production. All production rooms follow cGMP zone classification standards.

Process Overview

The production process for the MyDose device is unique as no other product in galenical manufacturing demands so many state of the art (off the shelf) production steps. The challenges associated with developing and designing the device were vastly outweighed by the challenges of producing the correct, optimized manufacturing process layout in a relatively small existing space and under enormous time pressure.

Due to time pressures, existing technology was adopted as

Continued on page 40.

Vartridge filling and closing unit.

the basis for the manufacturing process layout. Where necessary, the proven technology was supplemented by either specific customization or entirely new applications, specifically:

- Multiple production steps resulted in extreme space restrictions and additional equipment to be qualified and validated.
- New liquid Vartridge required the modification of standard machines for production steps such as washing, siliconization, and filling.
- Strict temperature control was required during the whole production process as the innovative enzyme is extremely sensitive to temperature changes.
- The zoning concepts were extremely strict. The product requires Zone Grade C (ISO 8) with Grade A (ISO 5) air supply for the filled Vartridge from inspection until welding process.
- The unique integration of a laser welding process under cleanroom conditions [Zone Grade C (ISO 8) with Grade A (ISO 5) air supply] produced a bottleneck in production, which had to be designed out of this process.
- Production of the device involves many more steps and components than a normal auto injector device. This in turn

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 2011 Facility of the Year Award:

A major advance in ensuring supply of an innovative oncology drug to patients

- This allows substances usually administered intravenously to be given via subcutaneous injection. The LifeCycle Leader for this product confirms the benefits for the patient: "The subcutaneous formulation and the associated new administration device will greatly simplify patients' lives. There is also hope that patients will experience fewer infusion reactions through slower absorption after subcutaneous administration."

Exemplary project management and leadership, excellence in project procurement, expediting, and quality control

- Project execution within 13 months from kick-off
- Empowering and integrating the whole project team of service providers, suppliers, trade contractors, designers, engineers, and Roche
- Great team spirit and participation and with an outstanding focus on the key project goals
- Outstanding performance in product and process innovation
- Implementation of innovative design and execution strategies with high degree of flexibility and adaptability during all project phases

Milestone in Product Innovation with regard to the concept, materialization of functional requirements, and integration with technological advances

- The creation of a new platform for "automatic" drug-delivery of high volume drugs to patients was only possible after the project team integrated several major technological advances.
- New enzyme which allows substances usually administered intravenously to be given via subcutaneous injection. When administered subcutaneously, technology temporarily opens a small cavity in the tissue, which allows painless injection.
- A hybrid vial/cartridge which would provide the necessary volume on the one hand and ability to inject on the other, named "Vartridge."

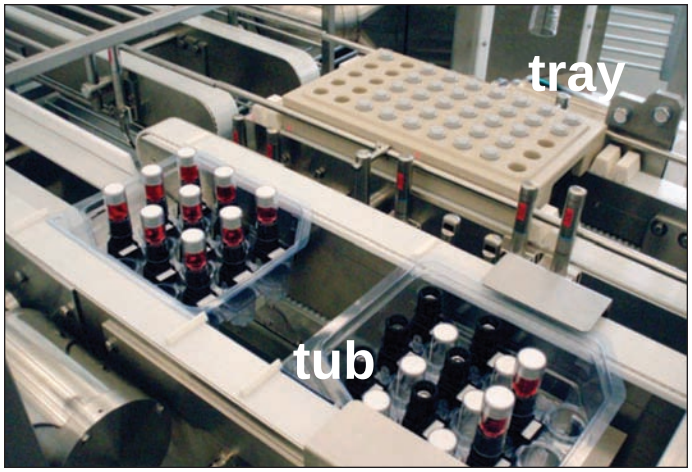
Excellence in Process Innovation and integration of several state of the art technologies

- Introducing laser welding process under cleanroom conditions (ISO 5)
- Temperature limits and restrictions of cooling free time due to the nature of the innovative enzyme which requires rigorous controlled process operation time with optimized material flows and limited idle time
- Embedding and integrating welding as a complex process in a conventional process of filling and finishing sterile drugs
- Filling and closing of a high volume (5 ml, 10 ml, 15 ml) vial/cartridge hybrid called "Vartridge"

Value Stream Map and a unique approach to derive facility and business benefit

- Utilization of production planning tools enabled to identify bottleneck areas.
- Material flow was analyzed in-depth and helped establish the most efficient arrangement of material, equipment, and human resources to streamline the production process.
- Pallet storage space was evaluated and incorporated into the layout.

Vartridge with piston in filing machine.



Part of the assembling and welding process.

produces more interaction between incoming goods and Work in Progress goods as well as the problem of storing the necessary inventory in an already confined facility space.

The value-adding steps in the production of the MyDose Device can be grouped into the following four major segments:

1. Vartridges delivered to the production line in trays followed by careful washing, silinconizing, depyrogenization, sterile filling, and closing of the Vartridge to provide for the core characteristic of the product
2. Manual quality inspection
3. Assembly and welding of the fluid path components (Vartridge, cartridge holder, and transfer unit) to produce the finished fluid path
4. Further assembly including base plat, housing, fluid path, and plaster before country specific labeling and packaging

Step three was the most complex. The biggest challenge was to install the assembling and welding process under cleanroom con-

Concludes on page 42.

Notes from the Judging Panel – What Impressed Them

- *Overall, the project excelled, especially in Process Innovation.*
- *The project demonstrates excellent innovation in the industry.*
- *The complex design and development components of the project were critical success factors in enabling Roche to create a new delivery platform for automatic drug delivery of high volume drugs to patients.*

Award Category – 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.

Assembing and welding machine robot.

Robot picks a filled Vartridge.

ditions [Zone Grade C (ISO 8) with Grade A (ISO 5) air supply]. After filling, closing, and inspection of each Vartridge transport is enabled by using special designed trays. The transfer unit and cartridge holder arrives sterilized in tubs. Trays and tubs are delivered manually to the assembly and welding machine.

A cleanroom validated robot picks the three components (transfer unit, filled Vartridge, and cartridge holder) one after another and assembles them. The laser welding process under controlled conditions follows to seal the transfer unit with the cartridge holder. This new component is called a fluid path. It must be air tight to guarantee sterility.

Key Project Participants

Architect/Design Manager/Engineer/Construction Manager: Roche (Basel, Switzerland)

HVAC Subcontractor: M+W Group GmbH (Stuttgart, Germany) *(See ad on page 21)*

Major Equipment Suppliers/Contractors:

- OPTIMA Packaging Group GmbH (Schwäbisch Hall, Germany)
- Insys Industriesysteme AG (Münsingen, Switzerland)

The production process underwent several major changes during the project as the design of the devices developed and the full implications of the production process were understood. For example, some of the crucial production steps, such as laser welding of fluid path components under cleanroom conditions, proved to be difficult to achieve in the time frame available.

Conclusion

The MyDose project was delivered as an ultra fast track project to meet the clinical supply milestone thus ensuring the delivery of an innovative oncology drug to patients. In order to achieve the very demanding time lines, the project team had to innovate process design and development of new machine technologies, which were the critical success factors in this project.

The Roche Global Engineering team surpassed its project goals. Handover of the facility – with complete functionality of the building, process equipment, and process automation – to the development department was accomplished within 13 months after kick-off. Performance lots had been successfully produced ahead of the original fast track schedule scenario and without any technical problems. All this was achieved as a result of the meticulous care invested in every planning and execution phase.

CONGRATULATIONS SHIRE

2011 Facility of the Year Awards Honorable Mention

CRB, KlingStubbins and Bovis Lend Lease would like to congratulate Shire for the recognition of Project Atlas as Honorable Mention in the 2011 Facility of the Year Awards program. Project Atlas' entire upstream process line utilizes single-use technology and is the first plant to use a single-use sterile train at the 2,000 liter scale, which required a number of custom modifications. Atlas also employs a number of single-use technologies in the downstream processing, such as buffer hold and centrifugal filtration. This technology along with the overall design led to a facility smaller in size with diminished utility requirements and more than a quarter fewer carbon emissions than a comparable stainless facility.

While the use of cutting-edge technology makes Atlas stand out among its stainless steel contemporaries, perhaps even more impressive was the execution of the project. Atlas utilized an integrated design and construction approach, integrated commissioning and validation, and a fully working mock-up of the Atlas facility's sterile train, dubbed Sandbox. Teamwork and agility were the defining characteristics for the Atlas team, and both were critical for delivering the project—ahead of schedule and under budget—amidst a remarkable series of challenges introduced by market forces and opportunities.

Congratulations Shire! Thanks for allowing us to be a part of your team.

Shire Human Genetic Therapies (HGT)

Brave as the People they Help

Shire pursues opportunities on behalf of patients and families facing such rare conditions as Fabry disease, Hunter syndrome, Gaucher disease, hereditary antioedema, and metachromatic leukodystrophy – patients whose lives often hinge on the discovery and delivery of extraordinary medicines. Shire Human Genetic Therapies (HGT), a business unit of Shire, is dedicated to the study of rare genetic diseases, many of which are treated by the enzyme replacement therapies produced in their new facility, Building 400, in Lexington, Massachusetts, USA.

Project Atlas, Building 400, winner of the **2011 Facility of the Year Award Honorable Mention**, pushed the envelope with its extensive deployment of single use technologies at commercial scale and its implementation of fully single-use upstream process technology at 2,000 liter scale.

Project Atlas, Building 400, is the company's third cell culture facility, intended to support the manufacture of Replagal®, which helps treat Fabry disease, and VPRIV®, a medication for type 1 Gaucher disease, as well as a robust product pipeline for future programs. The building features cell culture suites, purification suites, support services, and a large administrative space.

Speed to market was the primary driver for the facility's design; Shire faced unmet demand for their present therapies. A feasibility study on the use of single-use technology versus stainless steel discovered a number of benefits in favor of disposable or single-use technology, including: 1) reduced build time/time to market, 2) decreased contamination risk, 3) reduced cost of goods, 4) increased flexibility, and 5) reduced environmental impact. Additional benefits included decreased cycling time, decreased system complexity, and increased throughput.

The study also compared a standard hypothetical stainless steel facility to a comparable single-use facility, revealing that a single-use facility would result in a:

- 34% reduction in total facility size
- 40% reduction in initial capital costs

Aerial view of Project Atlas with trailers.

- 10% to 20% reduction in cost of goods
- 70% to 95% reduction in water use
- 50% to 75% energy savings
- 40% to 50% shorter project schedule

Despite the benefits, the design team was concerned with proceeding with fully single-use upstream process technology. Single-use technology had yet to be proven at the 2,000 liter scale, and the fledgling single-use system industry posed some considerable supply chain uncertainties as new suppliers overcame barriers to entry and other struggled to sustain growth. However, the benefits to single-use technology were too significant to overlook, and Shire and its partners felt that as a team, they could achieve their goals by leveraging their collective expertise and that of their suppliers to develop the technology both time- and cost-effectively.

Project Atlas' entire upstream process line utilizes single-use

A full working mock-up of the sterile train located offsite.

Shire HGT

Honorable Mention

Project: Atlas, Building 400
Location: Lexington, Massachusetts, USA
Project Mission: We enable people with life altering conditions to lead better lives.
Size: 200,000 sq. ft. (18,581 sq. m.)
Total Project Cost: $230,000,000
Duration of Construction: 24 months

Mid volume buffer tote for UF operation.

technology: media hold, inoculum preparation, seed and production bioreactors, centrifugal clarification, and harvest filtration and hold. According to Shire HGT, Atlas is the first plant to use a single-use sterile train at the 2,000 liter scale. They also employ a number of single-use technologies in downstream processing, such as buffer hold and centrifugal filtration.

To do this, they had to overcome numerous challenges and technical adaptations such as bioreactor agitation and single-use product contact surfaces in centrifuges. Shire and its project partners made a number of novel modifications to existing technology, and designed cutting-edge control software from scratch. They tackled the particularly complex problem of solution agitation in 2,000 liter single-use bioreactor bags so successfully that the bag vendor has made the team's modifications standard for all customers.

Key Project Participants

Designer/Architect: KlingStubbins (Philadelphia, Pennsylvania, USA) *(See ad on page 43)*

Engineer: Clark, Richardson, and Biskup (CRB) (Plymouth Meeting, Pennsylvania, USA) *(See ad on page 43)*

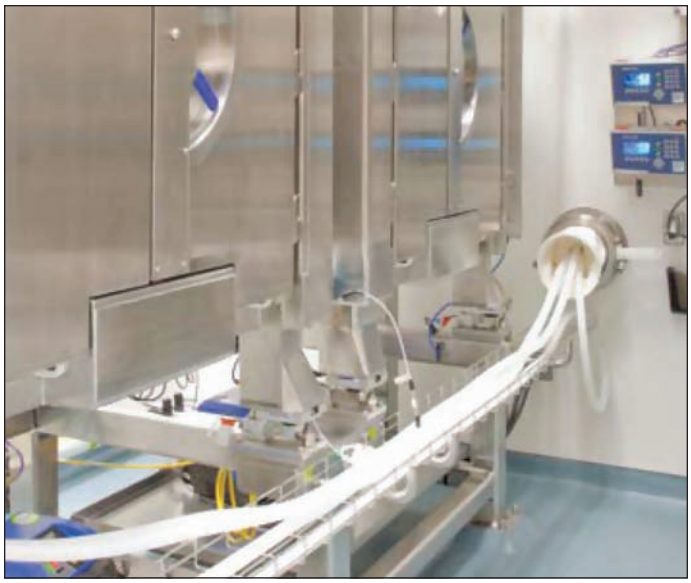
Construction Manager: Bovis Lend Lease (Boston, Massachusetts, USA) *(See ad on page 43)*

Notes from the Judging Panel – What Impressed Them

- *Project Atlas, Building 400 pushed the envelope by its extensive deployment of single-use technologies at commercial scale.*
- *Project Atlas was designed and delivered with the corporate philosophy in mind of being as brave as the people they help.*
- *Shire overcame numerous challenges and technical adaptations to implement fully single-use upstream process technology at a 2,000 liter scale. As a result, the facility was delivered faster with reduced investment that is also similar in size and lower in utility requirements.*

Single-use technology along with the overall design led to a facility smaller in size with diminished utility requirements and more than a quarter fewer carbon emission than a comparable stainless steel facility. While the use of cutting-edge technology makes Atlas stand out among its stainless steel contemporaries, also impressive was the execution of the project. Atlas utilized an integrated design and construction approach, integrated commissioning and validation, and a fully working mock-up of the Atlas facility's sterile train, dubbed Sandbox. Teamwork and agility were the defining characteristics for the Atlas team, and both were critical for delivering the project – ahead of schedule and under budget – amidst a remarkable series challenges introduced by market forces and opportunities.

The Atlas facility stands as an example for other life science companies who wish to increase consistency, product safety, and speed to market; decrease campaign turnover time, initial capital cost, and ongoing operation costs; and enjoy flexibility and scalability.



Harvest hold bag stations with iris valve.

Interview with Chaz Calitri, 2011 FOYA Judging Panel Chair

Q You have been the Facility of the Year Awards (FOYA) Judging Panel Chair for several years now and you have volunteered as a judge since the beginning of the program. What significance does the program have to you personally and why do you continue to be involved?

A First of all, it is a privilege to be a judge for ISPE's Facility of the Year Awards Program. This program is the premier recognition program for pharmaceutical engineering. I personally enjoy helping to encourage pharmaceutical companies to compete for more innovative ways to design and deliver projects that make products that help people. We work in a noble industry, in spite of the poor reputation that is portrayed in the media. As an engineering leader at a pharmaceutical company, I feel part of my responsibility is to engage across the industry to help us move pharmaceutical engineering forward. In 2007 I judged a project that won Facility of the Year. Only one year later I would learn that this facility made a new product that was used for my wife's breast cancer therapy. I would also comment that our judging panel is a team of highly skilled and experienced professionals, who are fun to work with and I learn a great deal from them and from the projects that I review. So all in all, I love being part of this great program.

Q The judging process involves carefully reviewing each submission received and then attending a meeting with all judges present to choose the Category Winners and overall Facility of the Year Award Winner. Can you explain how the judging process works and how such difficult decisions are made in just one day?

A We have a robust process for judging that has been matured over the years. The judges are all well versed in that process. Our process has been reviewed and approved by the FOYA Committee, which oversees the entire program. We also have a continuous improvement process that we run through every year after we make our selections. As for how we can complete the process in a single day, it's simple: we spend a great deal of time preparing and we use our structured process with templates to help judge the projects. We are also calibrated as a team – the benefit of having a core group of us who have worked together for a few years. That said, we do get into open and candid debates. Judges are encouraged to challenge each other. That's how we get to the best decisions. Last year we added two judges and it was amazing how efficiently our process worked even with two new members – a testimony to our process and the caliber of professionals we have on our judging team.

Q In considering how many times a big pharma project has won the overall Facility of the Year Award and how many big pharma projects have been recognized as Category Winners, the perception might be that only big pharma companies should enter and/or can win. Can you explain why this is not the case and can you explain why it is beneficial to small and mid size companies to enter the program?

A This program is all about innovation and helping to move our industry forward – not project or company size. Let me cite several recent examples of non-big pharma winners. Two years ago, Orchid Pharmaceuticals based in Aurangabad, India was a Category Winner, along with Aseptic Technologies based in Gembloux, Belgium. Last year, Mannkind Corporation (a non-profit) won TWO categories; that was an unprecedented achievement. In the 2011 program, we recently announced that Shire HGT received an Honorable Mention. So you see, it is all about engineering innovation and excellence. The reason we moved to Category Winners a few years back was to recognize projects with attributes that merit recognition, regardless of size, geography or affiliation. In fact, if you read the category definitions, you will understand what the judges are looking to reward. We also look for "capital efficiency" on projects – that is, how much was invested versus what was achieved. I can also give examples of multi-hundred million dollar investments by big pharma companies which we did not recognize as Category Winners because in our experience they spent much more money than was warranted to achieve their result. As our industry looks to contain cost, it is encouraging to see projects that are smaller in investment from companies who are innovative, and very impactful in terms of what they have achieved and contributed to our industry.

Q Based on your extensive experience as an industry professional and on your years of experience as a judge, can you describe how the Facility of the Year

"My challenge to our industry is to continue to find ways to make our products more affordable to more people. We have to enable that process. It's all about people – they are the true beneficiaries of what we do. We have to remember that always."

Awards program is truly accomplishing its goal of recognizing innovation and creativity utilized by manufacturing facilities serving the regulated healthcare industry? Can you provide some examples?

A That's easy. We have created a platform to enable companies to compete in categories which we believe are crucial for successful projects. By design, this helps drive engineering teams to innovate and raise the bar. **Here is a brief recap of our categories:**

- **Process Innovation:** 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.
- **Project Execution:** 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.
- **Equipment Innovation:** Novel application of commercially available and custom developed process manufacturing and facility management tools, which yielded superior results, advanced processing understanding and improved competitive position. Includes imaginative collaboration with vendors/suppliers/manufacturers.
- **Facility Integration:** 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.
- **Sustainability:** Application of novel approaches, tools, and techniques intended to improve the effective use of energy, minimize waste, and reduce carbon footprints, incorporate green manufacturing techniques, reduce environmental impact, that results in more efficient processing, utilities support, and business advantage.
- **Operational Excellence:** 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.

Using sustainability as a case in point, only a few years ago we were asking the question as to whether sustainability even applied to pharma manufacturing. We created this category and I recall the first year we did not see any submittals that merited this category award. Since then we have seen tremendous progress in sustainable design and operations for pharma manufacturing. Our Category Winner this year not only won ISPE's award, it was also selected by its host country to represent it at the China Expo. That's impact!

Q What are some of the notable technological and innovative advances taking place in facility design and construction? How are these advances changing the way facilities are built and pharmaceuticals are produced?

A That's easy. Let me cite a few recent examples to illustrate why we believe our program is achieving innovation and excellence. In 2010, Mannkind's project developed the first-ever solid-dosage pharmaceutical adaptation of a cryopelletizer. In 2011, Roche created a new platform for automatic drug delivery of high volume drugs to patients. A hybrid vial/cartridge was developed and named "Vartridge." The patented Vartridge has 83 individual components and requires 40 production steps to manufacture. In the area of project delivery, we have seen novel models to accelerate project delivery including hybrid models that we would not have envisioned a few years back. In Operational Excellence we have also moved the needle and had recent Category Winners that achieved huge increases in output with little added inputs. This is the case with all of our categories.

Q Do you have any advice for companies that are considering submitting an entry for the 2012 Facility of the Year Awards program?

A Don't try to impress the judges with elaborate submittals. It's all about content. Focus on WHY you feel your facility is innovative and achieved excellence that makes it a compelling story for our judges. Be specific and give us the results that were achieved.

Q Do you have any final comments about your experiences with the FOYA program?

A I love being part of this program – it's driving innovation and excellence in pharmaceutical engineering. It's helping all of us learn and grow. My challenge to our industry is to continue to find ways to make our products more affordable to more people. We have to enable that process. It's all about people – they are the true beneficiaries of what we do. We have to remember that always.

The day Larry found himself buried in his plant's work processes.

Feel familiar?

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[1]Larry is a fictional character and any resemblance to you or any of your plant personnel is purely coincidental.

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Labeling Pharma "Green"

by Dana Buker and Jamie Kaushik

This article presents arguments for the implementation of an electronic labeling system in the life science industries. These systems are capable of generating significant Return on Investment (ROI), while at the same time reducing waste, improving efficiency, and delivering on regulatory compliance requirements.

Introduction

Sustainable manufacturing issues have come to the forefront of current news with the idea of "green" driving many new initiatives. There are many ways to reduce a company's carbon footprint and function in a more environmentally friendly way. These "green" issues, such as recycling, energy and cost reduction, and increased efficiency are not only concerns in industries, such as automobile manufacturing and power plants, but in all industries, pharmaceuticals included.

In pharmaceutical manufacturing, there are many processes that produce large amounts of waste, expend excess energy, increase costs, are inefficient, and can introduce a greater level of risk than necessary. While many processes can become more environmentally responsible and economical, one process that could be improved with minor changes to operating methods is the design, approval, control, printing, and application of product labels. Implementing an Electronic Label Management System (ELMS) can deliver significant improvements that can make a company more "green." Other areas may require significant investment in new facilities, equipment, and systems, but labeling can translate with little relative cost and effort.

It once was true that a regulatory compliant third-party ELMS solution was not available as a Commercial Off-The-Shelf (COTS) product. That is no longer the case and today a pharmaceutical company's IT organization need not develop and maintain compliance add-ons because today the required functionality is built into the product.

Implementation of an ELMS affords many benefits including: waste reduction, cost reduction, decreased risks, and increased efficiency, all of which make a company more productive, sustainable, and "green."

Common Existing Practices versus ELMS

Manual System Summary

The following describes a simplified typical scenario where there is no ELMS in place:

In many if not most pharmaceutical manufacturing facilities today, the typical process begins with a label template being developed within a label design software application. The template creation process normally requires printing many hard-copy examples before the objective appearance is achieved. Once this point has been reached, the label is routed through a manual approval process for review and red-lining. This may take several weeks to complete depending on the circumstances. Finally, a template for the label is approved for printing and application to products - *Figure 1.*

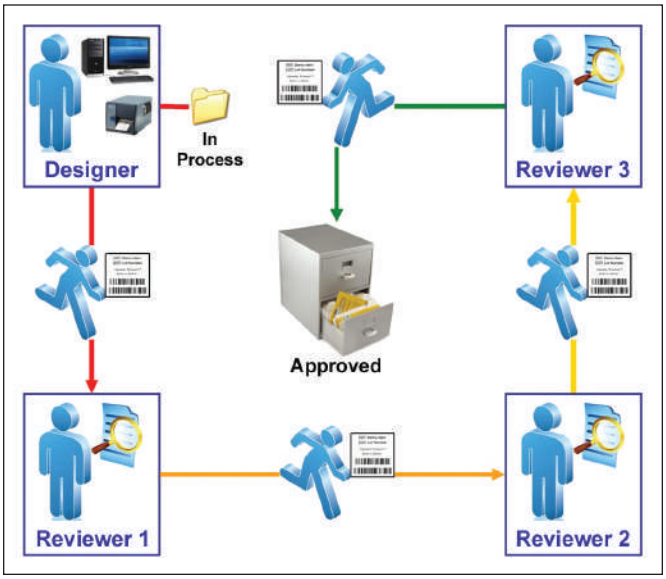

Figure 1. Typical process flow in a manual label review/approval routing process.

When it is time to print, the approved template is merged with variable lot/product data. This is normally a manual process that takes place in advance of the packaging operation in a label printing room, and so requires management,

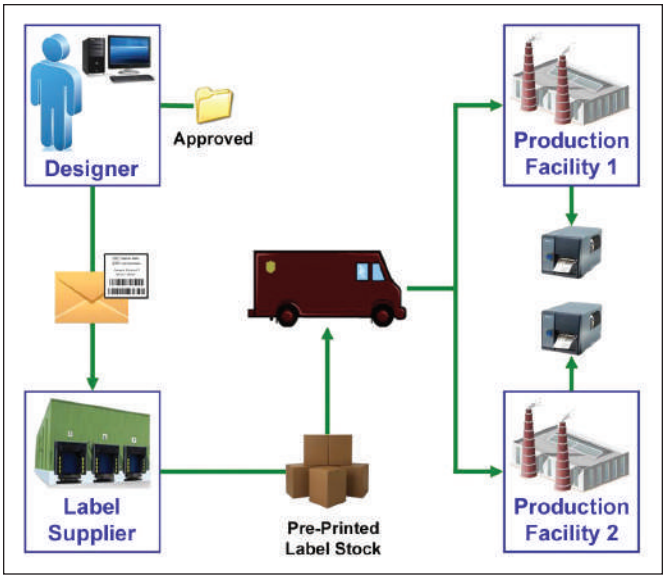

Figure 2. Traditional flow of labels in the pharmaceutical manufacturing supply chain with labels from third party suppliers.

storage, movement, and control of the labels.

At packaging time, the pre-printed labels must be picked and moved to the packaging line. Once at the line, the labels must be verified prior to use. Samples are applied to the batch record and the line is approved for the packaging operation to begin. In many cases, labels are pre-printed by third-party suppliers adding yet another layer of complexity with its associated time, cost, quality, and control considerations - *Figure 2.*

Electronic Label Management System Summary

By contrast, when there is a validated ELMS in place, once a label has been designed, the approval process sends the image as an attachment through a workflow simultaneously to all reviewers - *Figure 3.*

The system architecture can allow for a global approval process. In this case, the company's Wide Area Network (WAN) is used to facilitate communication among the reviewers who can share comments and document feedback electronically in real-time in order to dramatically improve the overall label template approval process - *Figure 4.*

Once the approval workflow is complete, the label template version is approved with its effective begin and end dates. The template may then be assigned to product(s) lot(s) at the time of packaging.

The approved label image is then ready to accept variable lot data. The ELMS may have been interfaced with a validated ERP or other database(s) so that the variable information such as lot number and expiration date are available for merging into the template at print time. Labels are then printed on demand and applied to containers, cartons, shippers, bundles, and pallets during the packaging process for a fully automated print-and-apply process. The need for pre-printing and all of the related costs, lead times, and controls have been eliminated.

Benefits of an ELMS

Regulatory Compliance

Are there significant efficiency improvements and waste reduction benefits from implementing an ELMS? Yes, definitely. However, in today's regulatory environment, for many companies, the primary driver for implementing an ELMS is compliance. According to one source, heavily regulated industries are now spending more than 40% of their IT budget on compliance.[1]

Many companies might have recognized the benefits of automation and jumped to implement electronic systems for labeling, perhaps a bit too soon. Most systems available until only recently were not developed with regulatory compliance in mind. So, somewhat ironically, replacing a manual system with a more efficient electronic system might have been a perceived hurdle that many companies did not care to jump

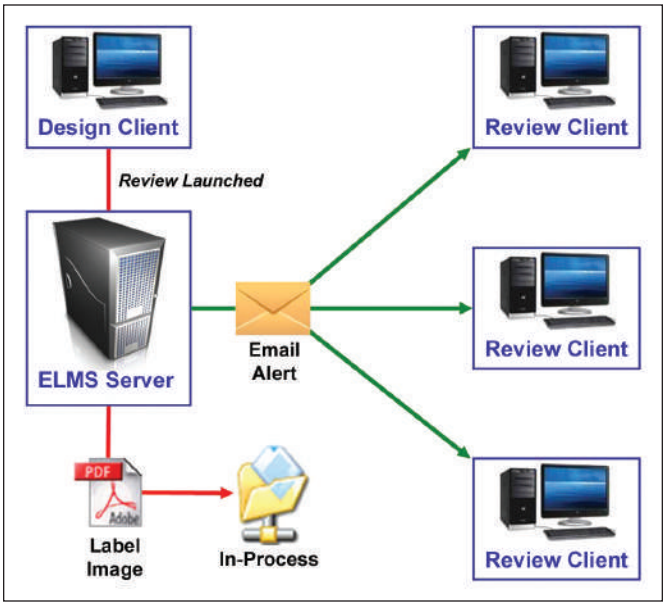

Figure 3. New or updated label review notification process via email using an Electronic Label Management System (ELMS).

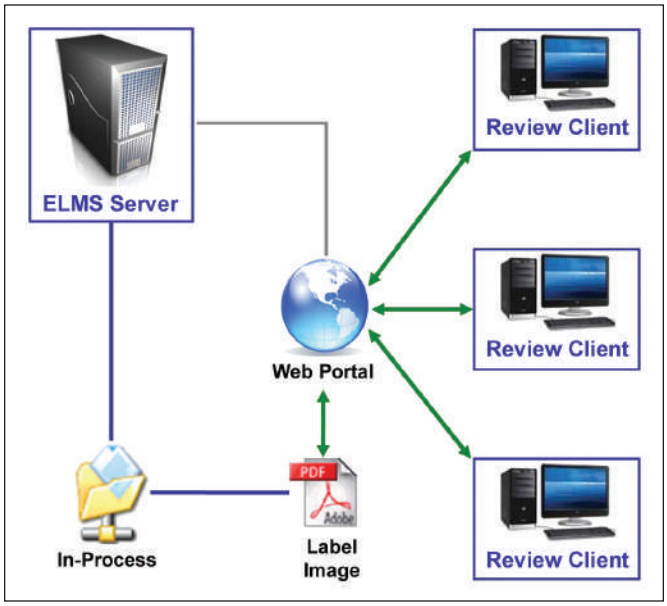

Figure 4. New or updated label design review via the internet in an Electronic Label Management System (ELMS).

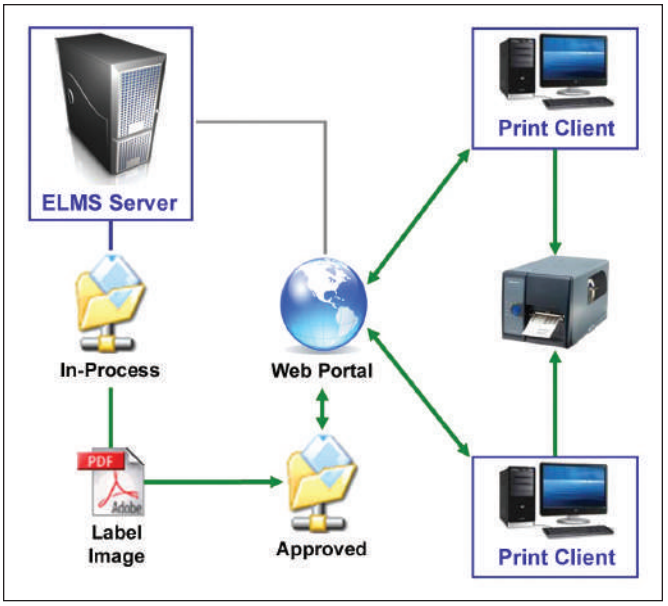

Figure 5. Printing process via Web client print portal in an Electronic Label Management System (ELMS).

over until it was seen as an absolute need. That is no longer the case, because today compliant ELMS solutions are readily available in the marketplace.

FDA's regulation 21 CFR Part 11 section 11.1 paragraph (e) states "Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA inspection." As computer systems have become more prevalent in industry, electronic labeling has evolved and is now being developed around the specific needs of pharmaceutical companies and the regulations that guide them. ELMS capable of complying with 21 CFR Part 11, Annex 11, and other regulations are now available.

Many of the regulations and requirements of the industry have changed to include specifics about electronic data and record keeping. With a more concrete picture of what is required, manufacturers as well as solution providers have been enabled to shift from manual to electronic systems within the manufacturing environment because the requirements no longer fall into a grey area. Provided that these specific guidelines and regulations are met, many companies have been able to realize the benefits of moving into an electronic labeling process.

Risk management also plays a large role in the sustainability of a given manufacturing plant. High risk processes and procedures can lead to costly losses. A regulatory compliant ELMS can assist companies in label management matters that are considered high risk.

Without an ELMS, paper files and paper documentation are kept in order to satisfy, among other things, audit requirements enforced by various regulatory agencies and internal audit groups. These requirements force companies into keeping traceable records of each label, from design to printing and all of the steps in between. When providing this information in paper form, the ability to quickly and accurately retrieve and present the data can be a daunting task. Loss of any paperwork through the shuffling of hard copy documents is a real risk and can negatively impact a company's audit trail. This in turn can create major problems with the agencies if and when requested documents cannot be produced. If all label-related documents can be kept in electronic form, there is never a question of whether the data can be produced. An ELMS keeps files from being misplaced or shuffled into stacks of papers. The risk of losing important audit information is minimal with an ELMS. Also, the speed at which data can be located is typically much faster than with a manual paper system.

"If all label related documents can be kept in electronic form, there is never a question of whether the data can be produced."

No matter what process a company uses, there is always risk when creating, approving, and maintaining labels. In a process that is paper-driven, there is risk to loss of data simply by the required movement of documents in the label approval process. There is risk to missing pieces of an audit trail and there are risks surrounding a formal audit when all required documents are in hard copy paper form.

That's not to say there aren't risks involved in electronic labeling. Often, a lack of understanding and preparedness surrounding computer systems creates anxiety about having a paperless system. Computer malfunction is a concern, but with disaster recovery plans and sufficient backup policies and procedures in place, loss of data is a non-issue relative to an electronic labeling system. To ensure that data loss does not occur, it's important to have a backup system in place. Generally, backing up the database and associated label folders, i.e., image folders and approval documentation folders to a place other than the main server once daily will keep data safe. Many manufacturing sites will choose to backup more frequently if possible, and some may additionally send copies of their databases to an offsite third-party in case of system failure within the network.

In order to be efficient, a plant needs to be able to print around the clock. There is risk in an electronic system that connectivity may be lost and/or the network may become inaccessible due to power outages or other unforeseen circumstances. In this case, it's important to have another point of access to all data in the form of a cache or database backup on workstations. In the event of connectivity issues, a cache file may allow a plant to continue the manufacturing process as normal. Having another database copy on an off-site server also may provide a second layer of access should a site's internal network become inaccessible. This process may or may not be desirable, but is certainly an option with today's technology. Pharmaceutical Information Technology and manufacturing organizations are now very familiar with the requirements for business resumption and disaster recovery. It is probably safe to say that all companies in the life sciences industry now have formal methods and procedures in place and that they are tested routinely.

Another concern surrounding a fully electronic ELMS is data corruption. Should the network or a workstation

become exposed to malware or other viruses, or should an outage happen during a process that causes a saved file to be corrupted or inaccessible, backups can restore the database and subsequent label printing system back to its most recent uncorrupted state.

Although it does not represent the level of concern it once did, system validation is still a major undertaking and should not be considered lightly. Today, using a risk-based approach, the burden of validation and computer system life cycle (CSLC) maintenance is well understood and more reasonably addressed than in the past. An application that is assessed to be in the COTS 4 category (configurable software) can be "validated" with much less effort than in the past using a practical approach and leveraging the supplier's documentation and compliance awareness.

Environmental Benefits of an ELMS

Eliminating Waste

Electronic labeling makes the pharmaceutical labeling process more environmentally friendly and proficient. When creating labels electronically, there is less waste due to:

- fewer printed approval documents
- fewer printed audit documents
- fewer required test prints

Typically, a pharmaceutical manufacturing company will generate significant paper waste in the labeling process. Much of this is from test labels and other forms of paper. A good method of reducing paper waste is by turning much of the paper into electronic form – both of sample labels as well as approval and audit documentation. Many forms of waste can and should be recycled; however, creating less waste in the first place has an even more significant environmental impact. With an ELMS, paper waste can be significantly reduced.

When creating a label, the look and feel of the label is a high priority. Often, to be sure that a label looks the way it is supposed to look, a test label will be printed multiple times to ensure that the data prints correctly. Changes are made frequently based on the outcome of test prints, and then the updated labels are again tested to ensure quality, readability, and alignment. With an ELMS, the need for this paper waste is significantly reduced, because a user is able to design a label and preview it in the system, using data from any item entry in the database. A program that can construct a label's exact size and color will be able to give a nearly 100% accurate representation of what will physically print. If a data object does not fit properly, is the wrong size, or wrong font, it can be caught through an onscreen preview reducing the number of printed samples.

Waste is also reduced when the label approval process is made electronic. An average approval cycle for a label creates a large paper file containing various types of documentation for an audit trail. Often, there is a printed label sample, along with supporting documentation breaking down the label layout and design. These documents are placed in a file folder which is then routed amongst the various departments required to sign off on the approval. Within the file, more documentation is added as the label sample moves from department to department. Documents containing reviewer comments, approval forms, and other supporting materials may be added along the way. Electronic label approval can remove the paper from each step of the process. There is no need to print a label sample to be routed; instead, a preview image can be created in the electronic labeling system, and routed as an electronic image. To get this image to the correct reviewers in the various departments, electronic routing makes the image and all additional documentation available to the correct departments all at the same time.

"Electronic label approval can remove the paper from each step of the process."

PROCESS	Manual System	ELMS	Comment
Label Design	Design Errors	Chance of error reduced up to 80%	Labels are designed as templates and not one for one. The likelihood of errors in a manual system is increased due to the added volume.
Label Approval	Approval Errors	Chance of error reduced up to 80%	Same as above.
Storage and Control	Control Errors	None	Management of physical inventory inherently introduces known error rates for accuracy.
Printing	Data Entry Errors. 6∂ Study shows .5% of all batches impacted.	None assuming integration with validated systems.	Manual keying of data introduces known error rates.

Table A. Opportunities for error reduction from Electronic Label Management System (ELMS).

Reducing Space and Equipment Requirements

Paper label control systems can require significant in-house storage space as well as increased supply costs due to high volumes of printed label documentation.

Manufacturers in the pharmaceutical industry also must keep many years of audit material on hand. With a paper system, more space and equipment is required to store records. The cost for storage of important paper files is exacerbated by the need for fire-proof and climate-controlled conditions. Access and other administrative controls and procedures also must be in place to accommodate a paper/manual method. An electronic file system saves time, facilities, equipment, and supplies. With an ELMS, these considerations have already been built into the required architectural design for computer systems management.

With documentation in electronic form, storage is consolidated onto file servers. This saves money on the cabinets and required facility floor space and manual filing and control activities. In this regard, the ELMS can have a positive impact throughout the enterprise because an electronic labeling sys-

tem will allow access to the stored data across sites without having to keep multiple copies of documents in geographically separate locations. Also, if the ELMS can be centralized, rather than purchasing separate servers for each manufacturing location, all sites can share data on one server environment. If the ELMS is internet-capable (i.e., available through a web browser) it helps contain costs because the requirement for a separate software license for each machine that will be used for printing or designing labels may be reduced. Instead, perhaps only one license purchase is needed and all connected workstations can work off the application server.

Other Cost and Efficiency Benefits of an ELMS

Simplification of the Review and Approval Process

With different departments working concurrently rather than in an ordered line, employees are more efficient and the elapsed time to complete the routing process can be significantly reduced. An electronic review and approval process not only reduces paper and office supply costs by omitting the need for paper and hard copy files, but it also simplifies and speeds up the process while reducing the chance of errors and omissions.

When everything was documented in files and on paper, the original file could only be in the possession of one business group or one person at a time. With an electronic label routing system, a copy of the label and its documentation can be available concurrently to all involved departments. A process that was once linear now becomes parallel through electronic routing. This saves time by eliminating the need to move a physical file from place to place, and it makes the process more efficient by allowing all parties to view the documents and make comments without having to leave their desks or wait for another department to complete their work.

"A process that was once linear now becomes parallel through electronic routing. This saves time by eliminating the need to move a physical file from place to place…"

Risk and Error Reduction

The ability to reduce or remove human intervention from a process invariably reduces risk by improving accuracy. Think of all the places in the process where human intervention takes place where errors can be introduced. Table A shows how replacing manual with electronic methods in the labeling process can result in error reduction.

Determining ROI for ELMS

The primary driver for ELMS is usually to meet compliance needs. However, Return On Investment (ROI) can and should always be factored into any significant investment.

Table B is a tool that may be used to help identify the value of an ELMS investment.

A Case Study of an ELMS

This section presents a case study of a recent implementation of an ELMS. The project was intended to replace a semi-

Item	Current System	ELMS	Benefit	Calculated Saving
Design	One-to-One Label	One-to-Many	Stored approved templates reduced by up to 80%	
Approval	File Transportation	Electronic Process	Movement of paper from place to place	
Printing				
Pre-package Handling	SOPs, storage, and inventory control costs	N/A	Electronic system requires no inventory management and related costs	
Pre-package Control	SOPs, Planning/Scheduling	N/A	No inventory means no need to plan and schedule	
Pre-package Movement	SOPs, material handling operations	N/A	No need to move pre-printed labels from storage to the packaging area at time of packaging	
Pre-package Approval	SOPs, QA Review and Release	N/A	Use of validated systems precludes the need for active approval at of labels at time of packaging	
Other Add other items as they apply. Do not overlook the fact that there may be multiple sites benefitting				
Cost of Non-Compliance				
Cost of current and future systems(s) – Total cost of Ownership (TCO)				
Opportunity Costs				
TOTAL				

Table B. Quantifying potential return on investment from an Electronic Label Management System (ELMS).

electronic label design and approval system to improve the label development process from design to print.

The original label management system allowed for label design work to be done electronically, specifically on a one to one basis. Electronic sampling was in use in the original system with test prints being done for all labels for the review and approval process. Once the label was designed and printed, it was sent around to the necessary departments in a linear flow. On average, four to five employees were part of the label approval process and the movement of the paperwork from one to the next required that the first person's approval be given before the file was sent to the next person.

While lost documentation wasn't a major issue at any time, frequently paper files would end up in a pile of other documents and forgotten until the due date approached, causing the process of approval to lag. Documents were then scanned into electronic files to be stored. The paper files also were maintained and stored.

In implementing the fully electronic label management system, there were improvements seen in many areas of the label design and approval process. The approval procedure saw the greatest improvement with parallel routing allowing for each of the four or five employees in the approval process to review and approve or reject labels at the same time without delay. Instant notification alerted each individual to the need for label approval and expedited action on that approval.

Another benefit was the ability to create templates for use with multiple products. There was about an 80% reduction in the number of labels requiring control since templates could be approved for use with a number of products.

Not only were label approvals being routed, but the label routing system was also put to use to route other label-related items; image updates, new requirements documentation, etc. This also created a decrease in waste and paper usage by making the majority of label-related tasks paperless.

Perhaps the most obvious improvement from the ELMS is the ability to address rush items. With a one hundred percent electronic system, expedited items can get through the entire routing and approval system within hours due to the ability to access the system from anywhere at any time. This elevated efficiency and cut down on costs since a courier was no longer needed to transport paper files across various sites. Overall, high priority items are taken care of quickly and man hours are reduced in getting things through the approval process. All documents are automatically placed in the proper electronic folders when finished without employees needing to worry about placing them there.

Part 11 compliance was also important. The original system was not compliant with the regulations; therefore, many changes were made to procedures to ensure compliance. The electronic system with routing capabilities also allows for complete audit control, making the system compliant with all regulatory requirements. The ELMS has been in place for almost four years now and auditors are happy with the system's compliance features and no system-related citations have been issued to date. Audit trails are intact and compliance is ensured.

Conclusion

Electronic label management systems capable of meeting challenging regulatory requirements using current technology standards are available to pharmaceutical companies today. Although not typically viewed as a high-impact cost-reduction opportunity, the hidden costs of staying the course with older technologies incapable of complying with regulations such as 21CFR Part 11, Annex 11, and others may be viewed as prohibitive or unwise. We know that labeling has traditionally been a hot button item for auditors and that labeling errors have historically been the most common cause of product recalls. Today, there are commercially available systems that offer compliance, cost, and "green" advantages that had not been available only a few short years ago and they should be considered by companies looking to improve in the label design, approval, control, and print areas.

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About the Authors

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Increasing Central Plant Efficiency via a Water to Water Heat Pump

by Jim Heemer, Alexander Mitrovic, and Michael Scheer

This article presents annual energy savings of more than $600,000 per year and an annual reduction in carbon dioxide emissions of 4,438 tons per year via a water to water heat pump installed at the Novartis Flu Vaccine Facility.

Pharmaceutical central utility plants often generate chilled water and steam year round to handle both process and HVAC loads. In addition, simultaneous heating and cooling are often required to maintain both humidity and space temperature set points in Good Manufacturing Practices (GMP) spaces driving utility demands higher. Power requirements can be substantial. Typical plant design includes both chillers and boilers running year round to meet demand. A heat pump (heat recovery chiller) may be installed to allow for recovery of the waste heat off the chiller condenser water to generate heating hot water for plant heating in addition to generating useful Chilled Water (CW). This will allow for the reduction of loading on the chillers, steam boilers, cooling tower fans, and cooling tower water makeup. The installation of a heat pump was considered and implemented as part of the original plant design at the Novartis Flu Vaccine Facility in Holly Springs, North Carolina.

Some of the challenges faced by the team and calculations required included:

- conveying a clear understanding of the basic concept and the potential energy savings
- basic system configuration to minimize/eliminate impact on plant reliability
- overcoming the perception that heating hot water needs to be delivered at 180°F (82°C) to the HVAC heating coils
- determining energy savings
- determining economic feasibility
- reviewing environmental benefits
- ensuring all design issues were addressed to maximize plant success

Basic Concept and Potential Energy Savings

A heat pump is nothing more than a chiller. The difference is that a chiller typically operates with a condenser water supply temperature to the chiller of 55°F (13°C) to 85°F (29°C) and a condenser leaving water temperature of 60°F (16°C) to 95°F (35°). This leaving water temperature is too low to be utilized effectively as a heating source for process or HVAC loads. However, a heat pump can be utilized to generate Chilled Water (CW) and work at higher condenser water temperature up to 170°F (77°C), which makes for ideal use as a heating hot water source in HVAC systems.

The basic simplified economics of the heat pump comes down to comparing energy input and output of the heat pump to a natural gas fired boiler and chiller system. The heat pump can have a Coefficient of Performance (COP) – "useful energy out/energy in" of 6.3 versus a COP that may be below 0.8 for a steam boiler, steam to Heating Hot Water (HHW) converter combination. The simple payback calculation for the heat pump is shown in Figure 1 which shows the energy input required to generate the same heat output as a steam boiler plus the additional benefit of the chilled water generated. With the projects boiler and heat exchanger combination, one unit of energy is input to get 0.82 units of useful energy out of the system. This includes a gas fired steam boiler efficiency of 83.5% with an assumed additional 1.5% loss in the steam to hot water converter. Even though the unit cost of electricity for the site is $21.97 per decatherm (Dth) (1,055 MJ) versus $6.75 per Dth (1,055 MJ) for natural gas, the greater COP of the heat pump overcomes the higher unit power cost of electricity over natural gas.

Basic System Configuration

For installation in a pharmaceutical plant, chilled water and heating hot water flows and supply temperatures can be critical to plant operation and product viability. To this end, the best approach is to install the heat pump in side

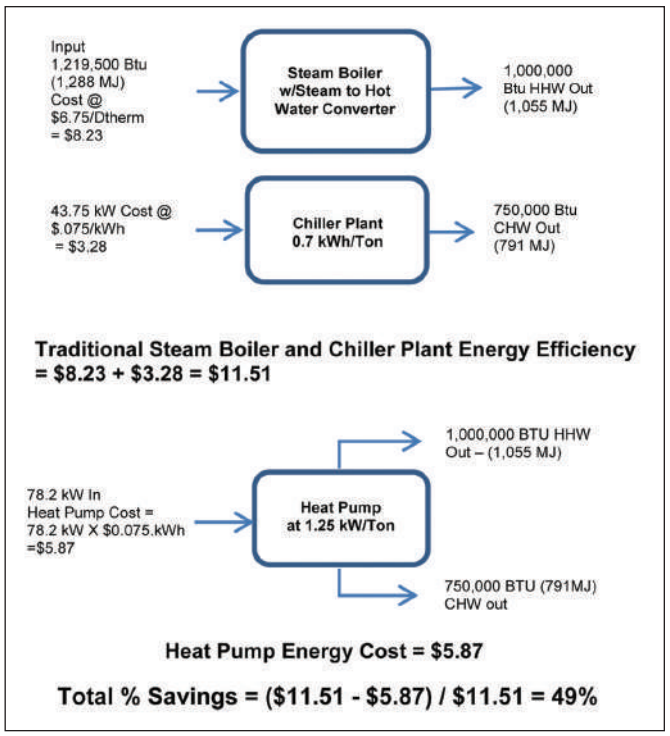

Figure 1. Basic concept.

car arrangement as shown in Figure 2. This approach serves several purposes: 1. it allows for independent control of the main chillers and heating plant, 2. it allows for less complex control, and 3. it protects the plant from out of range chilled water and/or heating hot water temperatures if the heat pump should fail.

Installing the heat pump in side car arrangement allows both the main chillers and heating hot water plant to run independently of the heat pump for the most part. The chillers run as needed to maintain critical discharge temperature to both process and HVAC loads regardless of heat pump operation.

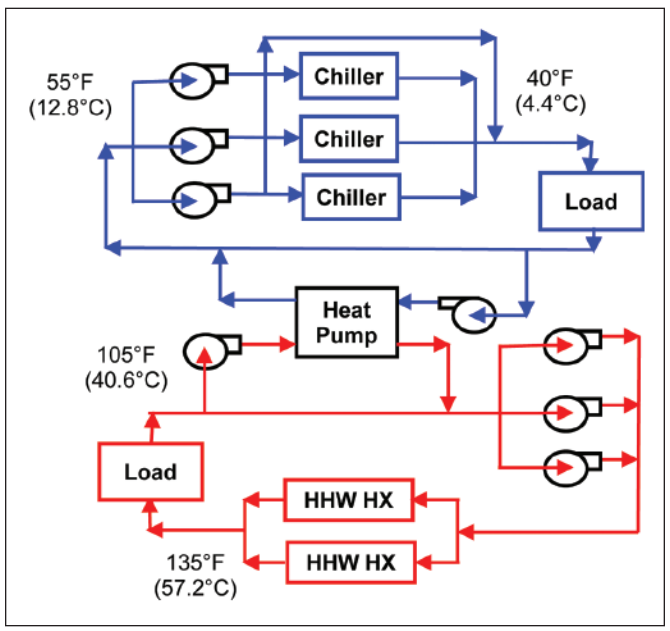

Figure 2. Flow diagram.

The load on the main chillers will vary as a function of plant loading and heat pump operation, but handles both via its own independent control system. The same goes for the heating hot water side of the plant.

Since the control of the heat pump does not need to be tied in with the other equipment, control logic becomes simpler and troubleshooting control issues easier. One caveat is control during low load. The plant personnel may not want to have the main chillers shutdown if the heat pump should be able to cover the entire load, so sequences can be set up to ensure the heat pump capacity is reduced to maintain at least one main chiller running at low load. If the load is too low to allow for the heat pump and the main chiller to both run, the heat pump can automatically shut off.

The chilled water system services both HVAC and process loads. Some of the process loads are critical, thus making the chilled water a qualified system requiring tight temperature control. With the main chillers delivering set point chilled water to the plant downstream of the heat pump, the delivered chilled water temperature to the load is not impacted by heat pump operation. If the heat pump should fail, the chillers and the steam to heating hot water heat exchanger will continue to control to leaving water temperature, so failure of the heat pump should have no impact on supply temperatures to the plant. For redundancy, the main chillers and heating hot water heat exchanger should be sized as a minimum to handle the entire load if the heat pump should fail.

Lowering Heating Water Temperature

Typical HVAC heating hot water temperatures for pharmaceutical plants is 180°F (82°C) supply and 160°F (71°C) return. At these temperatures, it is difficult to find a heat pump that will be effective from both a capital cost and operating cost standpoint. The lower the heating hot water temperature, the more applicable a heat pump is, due to increasing efficiencies as heating hot water temperature drops. However, as temperature of the hot water and air temperature approach one another, the more heating hot water coil surface is required to meet design conditions. Larger surface areas equates to higher first cost. In addition, the larger coil translates to higher pressure drop on both the airside and waterside of the coil. The additional power required must be compared to the power savings obtained from the heat pump, due to lower heating hot water temperature. Consideration also needs to be given to ASHRAE 90.1-2007 (American Society of Heating, Refrigeration, and Air-Conditioning Engineers – Energy Standard for Buildings Except Low-Rise Residential Buildings) allowable fan horsepower with the increasing airside pressure drop through the coil.[1]

The design team looked at the increased pump and fan power, due to the increased heating hot water coil pressure drop on both airside and water side at lower supply heating hot water temperatures along with reduced power consumption of a heat pump. For the plant, temperature from GMP chilled water coils was set at 48°F (9°C) for dehumidification. With high air change rates for GMP spaces, it was found that air delivery temperatures were needed in the 60° F to 66°F (16°C to 19°C) range to maintain room space temperatures

Heating Hot Water		Airside Side Delta-P (1) WC"(cm)	Water Side Delta-P (1) ft (m)	Additional (HP)		Added Pump and Fan Power (kW)	Annual Power Increase (kWh)	100 Ton Heat Pump		Power Savings (kW)
Supply °F (°C)	Return °F (°C)			Fan (HP)	Pump (HP)			Reduced Power (kW/Ton)	Annual Reduction (kWh)	
155 (68)	125 (52)	0.35 (.89)	7.45 (2.27)	-	-	-	-	-	-	-
145 (63)	115 (46)	0.37 (0.94)	7.5 (2..29)	0.20	0.002	0.15	1,320	0.081	70,956	69,636
135 (57)	105 (41)	0.42 (1.07)	7.58 (2.31)	0.72	0.005	0.54	4,736	0.162	141,912	137,176
125 (52)	95 (35)	0.58 (1.47)	11.05 (3.37)	2.35	0.130	1.85	16,200	0.243	212,868	196,668
115 (46)	85 (29)	0.69 (1.75)	11.17 (3.4)	3.48	0.134	2.69	23,608	0.324	283,824	260,216
105 (41)	75 (24)	1.06 (2.69)	18.29 (5.57)	7.26	0.391	5.71	49,979	0.455	398,580	348,601
Assumes 100 ton heat pump delivering 1,600,000 Btuh heat. Lifting air temperature through coils from 55°F to 85°F for 42,318 CFM. Fan Hp = CFM X TP /(6356 X Fan Eff.); Fan Efficiency 65%.						At 30°F delta-T water flow = 107 gpm .7545 kW = 1 HP Pump HP = gpm X Hd (ft) /(3,960 X Pump Eff.); Pump Eff. = 75%				

Table A. Heating water temperature verses system power consumption with heat pump.

from 66°F to 70°F (19°C to 21°C). For some of the office and utility spaces, supply air temperatures were required to be in the low 80's (27°C) for adequate space heating. With this, the analysis of temperature delivery was based on an entering air temperature to the heating hot water preheat coil of 50°F (10°C), assumed 2°F (1°C) rise across the supply fan with a discharge temperature of 85°F (29°C). This assumption would yield conservatively high power consumption through the coil since it is based on the lowest heating hot water coil air to water side temperature differential. A reference temperature of 155°F (68°C) supply with a 30°F (-1°C) delta-T was used as the base case for the heating hot water for the high end supply temperature. Refer to Table A for increased power savings as the temperature is lowered from 155°F (68°C) supply to 105°F (41°C). Table B shows increase in capital cost of the coils verses discharge temperature and net present value. Based on the data, the supply heating hot water temperature of 105°F (41°C) provides the best economics. However, various team members were uncomfortable with using 105°F (41°C) heating hot water supply temperature. They were concerned with freezing outdoor air coils at winter design outdoor air temperature of 13°F (-10°C). Pumped recirculation loops were considered to allow for lower temperature water, but it was agreed that a 135°F (57°C) supply temperature would be used so pump loops would not be needed.

The decision to use a 30°F (17°C) delta-T was based on cutting water flow and associated pump power by 33% while keeping the return water temperature high enough to maintain heat transfer in the coils. Pressure increase on the air side of the coils is minimal having little impact on fan power in relation to ASHRAE 90.1-2007 maximum fan horsepower requirements. Also to be considered is the type of heating system to be used in unison with the heat pump and temperature limitations on the equipment. For example, using a noncondensing boiler is problematic at these low temperatures.

Determining Energy Savings

Typically, the chiller(s) and boiler(s) are sized to match the plant load. In the case of a heat pump, the machine sees a hot water heating load and a chilled water load. The unit matches the smaller of the two loads the machine sees. Roughly one quarter of the energy input into the hot water is electric power input to the heat pump converted to heat. The remaining three quarters of the heat pump energy supplied to the heating hot water is heat transferred from the returning chilled water. Note that this varies depending on machine efficiency and operating temperatures.

Selecting the correct size heat pump is based on determining coincident heating hot water and chilled water loads throughout a typical year. Since both the heating hot water load and chilled water loads are highly dependent on outdoor air temperature, a good approach is to develop a profile relative to outdoor air

HHW Temperatures		Coil Capital Cost		Annual Power Savings		
Supply °F (°C)	Return °F (°C)	42,318 CFM Coil Cost ($)	Additional Coil Cost ($)	Power Reduction (kWh)	Annual Savings ($)	Net Present Value at 15% ROR
155 (68)	125 (52)	$6,705	-	-	-	-
145 (63)	115 (46)	$6,804	$99	69,636	$5,223	$32,592
135 (57)	105 (41)	$7,126	$421	137,176	$10,288	$63,976
125 (52)	95 (35)	$8,954	$2,249	196,602	$17,203	$105,429
115 (46)	85 (29)	$9,515	$2,810	260,216	$19,516	$119,348
105 (41)	75 (24)	$13,828	$7,123	348,536	$26,140	$156,497
Electric cost $0.075 per kWh; Blended rate at the site. NPV at 15% rate of return for 20 years				Cfm basis; (100 tons X 1.33 X 12,000 Btu/Ton)/1.08 X 30°F = 42,318 Coil cost based on 20,000 Cfm coils.[2]		

Table B. NPV at various HHW temperatures for a 100 ton heat pump.

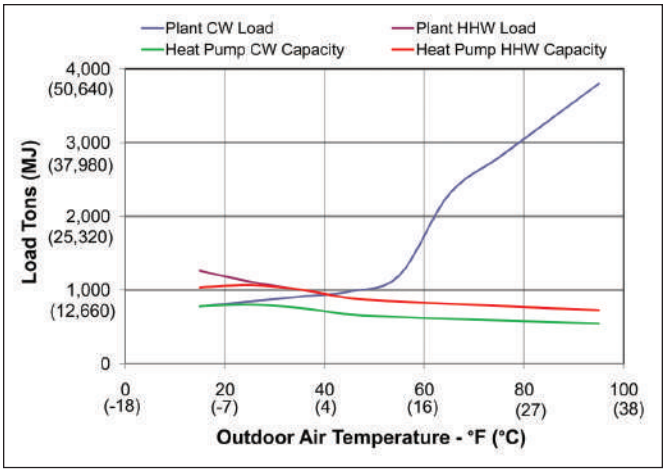

Figure 3. Plant and heat pump loads.

temperature. The more difficult task is determining coinciding process chilled water loads. One solution is to set the process load at its minimum value throughout the entire year to ensure the heat pump is not oversized. Ideally, the heat pump will be sized to handle the peak and minimum coincident loads if load profile allows. Refer to Figure 3 for the overlay of the heating hot water load, chilled water load, and associated heat pump loading for the Project.

For this particular application, the heat pump handles the entire hot water heating load as long as the outdoor temperature is above 28° F (-2°C), which for Raleigh, North Carolina area is 96% of the year. At this outdoor air temperature, the chillers handles both the entire heating hot water and chilled water load. Below this temperature, the heat pump handles the entire chilled water load. With the need for tight pressure control within the GMP spaces, economizers are not used creating the need for year round HVAC cooling, unless air temperature reset is used which may create a compliance risk.

With the exception of peak loading, the heat pump is limited in capacity by whichever load is smaller; the chilled water load or the heating hot water load plus the electric energy input into the heat pump converted to heat in the heating hot water stream. The temperature set point will be satisfied for the smaller of the two loads. For the larger load, the heat transferred will not be enough to hit set point temperature. Therefore, on the load side that is not satisfied, the temperature floats as the transfer of heat allows based on the limiting side load.

The installation increases electrical consumption to drive the heat pump and associated pumps. The additional fan and pump horsepower, due to larger heating hot water coils, needs to be accounted for as discussed previously. Power consumption is reduced to drive the main chillers and the Variable Frequency Drive (VFD) cooling tower fans. The biggest savings come from reduced natural gas consumption when boiler generated heat is replaced with heat from the heat pump. Also to be considered is the cost savings associated for the reduced tower water makeup. Water consumption is reduced by roughly 2 gallons (7.57 L) for every ton-h (12.7 MJ – h). This reduces utility water cost. Chemical treatment is also reduced somewhat, but is not included in this analysis.

Tables C through E provide the operating cost data on the standard chiller plant and the plant with an 800 ton heat pump. The cost of running those items that vary in power consumption, due to the installation of the heat pump, is totaled in the kW/Ton column. These variations include the main chillers operating at reduced load, the condenser water temperature being lowered, possible reduction of the number of condenser water pumps running, and the VFD cooling tower fans running at lower speed depending on the load. The net cost of meeting the annual load with the chilled water plant without the heat pump is $802,042 - *Table C.* For the main chillers with the heat pump, the cost drops to $492,195 annually (Table E), but the cost of running the heat pump and the associated pumps is $526,803 - *Table D.* Total electrical cost for running both the chiller and heat pump to meet the chilled water demand is $1,018,998, so the net increase in electrical operating cost with the heat pump is $216,905 annually.

One other item needs to be factored. When running with the heat pump, every ton-h (12.66 MJ-h) of cooling generated by the heat pump reduces cooling tower water make-up by 2 gallons (7.57 liters). The heat pump replaces 5,558,989 ton-h (70,376,801 MJ-h) annually, so the associated water savings is 11,117,978 gallons (42.32 ML). Water cost at the facility is

Bin Data (Raleigh, NC)			3 - 1,350 Ton VFD Chillers, Condenser Pumps, and Tower Fans					
Hours	DB °F (°C)	WB °F (°C)	Load Tons (MJ)	(1) KW/Ton	Electric (KW)	Mw-Hrs	Annual Cost $	Annual Ton-h (MJ-h)
119	90/99 (32/37)	76 (24)	3,800 (48,108)	0.756	2,872.80	341.9	$25,640	452,200 (5.72 X106)
924	80/89 (27/31)	72 (22)	3,300 (41,778)	0.706	2,329.80	2,152.7	$161,455	3,049,200 (38.60X106)
1,994	70/79 (21/26)	68 (20)	2,800 (35,448)	0.650	1,820.00	3,629.1	$272,181	5,583,200 (70.68X106)
1,809	60/69 (16/20)	59 (15)	2,300 (29,118)	0.599	1,377.70	2,492.3	$186,919	4,160,700 (21.44X106)
1,411	50/59 (10/15)	49 (9)	1,200 (15.192)	0.540	651.60	919.4	$68,956	1,693,200 (21.44X106)
1,246	40/-49 (4/9)	40 (4)	979 (12,394)	0.503	494.40	616.0	$46,202	1,219,834 (15.44X106)
904	30/39 (-1/3)	31 (-1)	912 (11,546)	0.488	445.06	402.3	$30,175	824,488 (10.44X106)
310	20/29 (-7/-2)	22 (-6)	845 (10,698)	0.470	397.15	123.1	$9,234	261,950 (3.32X106)
47	10-19 (-12/-8)	13 (-11)	778 (9,849)	0.467	363.33	17.1	$1,281	36,566 (462,926)
Notes: 1. Includes chiller, condenser water pumps (CS), and VFD cooling tower fans.						**10,694**	**$802,042**	**17,281,298 (219X106)**

Table C. Main VFD chiller energy cost without heat pump.

Bin Data (Raleigh, NC)				Heat Pump Data					
				Load Data			Annual Data		
Hours	DB °F (°C)	WB °F (°C)	Plant CW Tonnage (MJ)	Cooling Tons (MJ)	KW per Ton	Electric (KW)	Electric Energy (MW-Hrs)	Annual Energy Cost	Cooling Load Ton-h (MJ-h)
119	90/99 (32/37)	76 (24)	3,800 (48,108)	546 (6,912)	1.329	726	86.4	$6,480	64,974 (0.82X106)
924	80/89 (27/31)	72 (22)	2,750 (34,815)	566 (7,166)	1.313	743	686.5	$51,490	522,984 (6.62X106)
1,994	70/79 (21/26)	68 (20)	1,700 (21,522)	588 (7,444)	1.297	763	1,521.4	$114,107	1,172,472 (14.84X106)
1,809	60/69 (16/20)	59 (15)	1,373 (17,382)	610 (7,723)	1.281	782	1,414.6	$106,098	1,103,490 (13.97X106)
1,411	50/59 (10/15)	49 (9)	1,046 (13,242)	633 (8,013)	1.266	801	1,130.2	$84,766	893,163 (11.31X106)
1,246	40/-49 (5/9)	40 (4)	979 (12,394)	670 (8,482)	1.242	832	1,036.7	$77,750	834,820 (10.57X106)
904	30/39 (-1/4)	31 (-1)	912 (11,546)	755 (9,558)	1.194	901	814.5	$61,088	682,520 (8.64X106)
310	20/29 (-7/-2)	22 (-6)	845 (10,698)	800 (10,128)	1.171	937	290.5	$21,785	248,000 (3.14X106)
47	10/19 (-12/-8)	13 (-11)	778 (9,849)	778 (9,849)	1,182	919	43.2	$3,239	36,566 (462,926)
							7,024.0	**$526,803**	**5,558,989 (70.38X106)**

Table D. Heat pump energy cost.

$7.35 per 1,000 gallons ($1.94 per 1,000 liters.) Annual water savings is $81,717.

For changes in heating hot water generation costs, refer to Tables F and G. With a gas fired steam boiler and a steam to hot water converter, an 82% total thermal efficiency was estimated. The annual natural gas cost to generate the heating hot water is $740,151.

The natural gas cost is only $4,230 for the system fit out with the heat pump. Reduction in natural gas consumption is significant at $735,921 annually which exceeds a 99% reduction. Note that the electrical cost of generating heating hot water was already factored in when the entire kWh consumption of the heat pump was considered with respect to when looking at the chilled water side.

Total annual utility savings is estimated at gas savings plus water savings minus additional electrical power ($735,921 + $81,717- $216,905 = $600,733).

Economics

Savings associated with annual utility reductions is well and good, but how does this stack up against initial capital outlay and additional maintenance cost associated with the additional equipment? There are capital costs for the additional equipment and reductions for reduced sizing of other equipment. Refer to Figure 4 for capital costs associated with the modified plant design to incorporate the heat pump into the design.

Capital cost of the installation is an additional $925,000 relative to a plant without the heat pump. The heat pump will run at a minimum chilled water load of 546 tons (6,912 MJ) per Table D. Since this is the lowest load the heat pump will operate, this is the amount the main VFD chiller capacity can be reduced without impacting planned system redundancy; therefore, it is deducted from the main chiller cost.

As in the case of deducting the excess capacity from the main chiller sizing, the same can be done for the heating hot water generators. In our case, this applies to sizing of the steam boilers. The boilers can be reduced by the minimum heat pump hot water generation load when limited by capacity on the chilled water side. This corresponds to 12,432,000 Btu/hr (13,147 MJ/hr) load per Table G. Therefore, the boiler siz-

Bin Data (Raleigh, NC)			3 - 1,350 Ton VFD Chillers						
Hours	DB °F (°C)	WB °F (°C)	Load Tons (MJ)	Condenser Water Temp °F (°C)	KW/Ton	Electric (KW)	Mw-Hrs	Annual Cost $	Annual Ton-h (MJ)
119	90/99 (32/37)	76 (24)	3,254 (41,195)	83 (28)	0.732	2381.9	283.4	$21,259	387,226 (4.90X106)
924	80/89 (27/32)	72 (22)	2,734 (34,612)	79 (26)	0.650	1777.1	1,642.0	$123,153	2,018,016 (25.55X106)
1,994	70/79 (21/26)	68 (20)	2,212 (28,003)	75 (24)	0.540	1194.5	2,381.8	$178,634	2,217,328 (28.07X106)
1,809	60/69 (16/19)	59 (15)	1,690 (21,395)	66 (19)	0.515	870.4	1,574.5	$118,085	1,380,267 (17.47X106)
1,411	50/59 (10/15)	49 (9)	567 (7,178)	60 (16)	0.508	288.0	406.4	$30,481	582,743 (7.38X106)
1,246	40/-49 (4/9)	40 (4)	309 (3,912)	60 (16)	0.505	156.0	194.4	$14,582	385,014 (4.87X106)
904	30/39 (-1/4)	31 (-1)	157 (1,988)	60 (16)	0.517	81.2	73.4	$5,503	141,928 (1.80X106)
310	20/29 (-7/-2)	22 (-6)	45 (570)	60 (16)	0.529	23.8	7.4	$553	13,950 (176,607)
47	10/19 (-12/-7)	13 (-11)	0	60 (16)	0.529	0.0	0.0	$0	0
							6,563	**$492,251**	**7,126,472 (90.2X106)**

Table E. Main VFD chiller cost with heat pump.

Bin Data		Boiler Load/Plant Load Heating Hot Water		Annual	
Hours	DB °F (°C)	MBh (MJ)	Boiler* (Dth)	Dth	Cost
119	90/99 (32/37)	8,710 (9.189)	10.6	1264.0	$8,532
924	80/89 (27/32)	9,032 (9,529)	11.0	10177.5	$68,698
1,994	70/79 (21/26)	9,389 (9,905)	11.5	22831.3	$154,111
1,809	60/69 (16/19)	9,741 (10,278)	12.5	22533.8	$152,103
1,411	50/59 (10/15)	10,112 (10,668)	12.3	17400.0	$117,450
1,246	40/-49 (4/9)	10,685 (11,273)	13.0	16236.0	$109,593
904	30/39 (-1/4)	12,056 (12,719)	14.7	13293.2	$89,729
310	20/29	13,358 (14,093)	16.3	5050.0	$34,087
47	10-19	15,112 (15,943)	18.4	866.2	$5,847
MBh = 1,000 Btu/hr * Boiler and heat exchanger at 82% total efficiency				**109,652**	**$740,151**

Table F. Steam plant energy cost without heat pump.

ing can be reduced 12,432,000 Btu/hr (13,147 MJ/hr) without impacting plant capacity/redundancy. Note that care must be taken to ensure the boiler capacity can handle the load with the heat pump down for redundancy purposes.

An additional annual cost to consider is maintenance associated with the heat pump. Heat pumps are more complicated than a typical chiller with higher lift so maintenance needs to be considered. Based on information obtained on the current maintenance contract, the heat pump portion of the maintenance contract is $25,000. Annual cost savings is reduced to $600,733 – $25,000 = $575,733.

For the pharmaceutical manufacturing facility, the annual savings is $575,733 with a capital cost of $925,000 for the heat pump system. This provides a simple payback of less than 20 months. The majority of savings is associated with the more than 99% reduction in natural gas consumption. This also delivers a significant reduction in emissions.

Emissions Reductions

Another benefit of the heat pump is the associated reductions in emissions that inherently come with the reduction in energy consumption. From the electrical side, actual power consumption increases due to the additional power required by the heat pump to overcome the additional lift in generating the same amount of chilled water that is displaced by the lower lift main VFD chillers.

The difference in electrical energy consumption between the plant with the heat pump and the one without is 2,892 MWh referencing Tables C through E. Carbon dioxide emissions per kWh of electric generated is 1.334 lbm (0.605 kg) resulting in additional annual carbon dioxide production of 1,929 tons (1,754 metric tons).[3]

The reduction in natural gas consumption when using the heat pump verses a plant without is 109,025 Dth (115 X 106 MJ) referencing tables F and G. Carbon dioxide generated from natural gas is 120 lbm per Dth4. Based on the reduction in gas consumption, the carbon dioxide emission reduction is 6,541 tons (5,946 metric tons).

When combining the annual increase in carbon dioxide production from the additional electric consumption with the natural gas consumption reduction, the total carbon dioxide reduction is 4,612 tons (4,192 metric tons) per annum.

Bin Data		Total HTG Hot Water Load MBh (MJ)	HRC Heating MBh (MJ)	HHW Water Load		Annual	
Hours	DB °F (°C)			MBh (MJh)	Boiler* Dth	Dth	Cost
118	90/99 (32/37)	8,710 (9,189)	8,710 (9,189)	0	0	0	0
924	80/89 (27/32)	9,032 (9,529)	9,032 (9,529)	0	0	0	0
1,994	70/79 (21/26)	9,389 (9,905)	9,389 (9,905)	0	0	0	0
1,809	60/69 (16/19)	9,741 (10,276)	9,741 (10,276)	0	0	0	0
1,411	50/59 (10/15)	10,112 (10,668)	10,112 (10,668)	0	0	0	0
1,246	40/-49 (4/9)	10,685 (11,273)	10,685 (11,273)	0	0	0	0
904	30/39 (-1/4)	12,056 (12,719)	12,056 (12,719)	0	0	0	0
310	20/29	13,358 (14,092)	12,768 (13,470)	1,302 (1,374)	1.6	492.2	$3,322
47	10-19	15,112 (15,943)	12,417 (13,100)	2,344 (2,473)	2.9	134.4	$907
*Boiler plus HX at total 82% efficiency. MBh = 1,000 Btu/hr						**626.6**	**$4,230**

Table G. Steam plant energy cost with heat pump.

Special Design Issues

There are various design issues associated with the heat pump application that need to be given serious consideration that are not typical of plant design without a heat pump. Some of which are listed here:

1. Proper sizing of the heat pump looking at coincident chilled water and heating hot water load on an annual basis
2. Main chiller evaporator barrels need to be sized to accept the additional flow associated with a running heat pump and a lower delta-T across the main chiller(s).
3. Main chiller evaporator barrels are not so oversized as to adversely impact allowable minimum flow when installed in a primary variable pumping system.
4. Maintaining main heating plant in ready condition when in prolonged idle periods
5. Control valve/boiler sizing taking into consideration very low loading when heat pump is on relative to the entire design load with the heat pump off.
6. Time required starting the main chiller if the heat pump is carrying the entire chilled water load and the heat pump fails.
7. Consider summer demand charges and rate structure.
8. Proper control and sequence development
9. Provide means for start-up, testing and commissioning.

Proper sizing of the heat pump is critical to both operation and the economics. Not every central plant is a candidate for a heat pump installation. A coincident heating hot water and chilled water load is required. The heat pump pulls heat from the returning chilled water system and delivers it to the heating hot water side of the plant. Both demands are required simultaneously to make the installation of a heat pump applicable. Some means of determining both the heating hot water and chilled water load for a typical load cycle, which more often than not is on a yearly basis to capture all the seasonal HVAC loads. Once the loads are determined, they need to be overlaid to start the process of sizing the heat pump. Each application must be developed based on the required economic payback, utility cost structure, heat pump efficiency and performance constraints, and heating and chilled water demand overlay.

Not properly sizing the main condenser chiller barrels for the expected full flow rate when the heat pump is in operation can be an expensive error. When the heat pump is in operation, the main chillers see less than design delta-T through the barrel due to the lower return chilled water temperature being delivered from the running heat pump. If the main chillers are not sized for this additional flow, the plant capacity will be limited to the flow that can pass though the main chillers and the sequence of operations and associated controls will become more complicated to overcome this issue.

However, care must be taken as to not oversize the barrel so much that the flow through a VFD driven chiller cannot be reduced at low loads. If this is missed, savings from VFD pumping will be adversely impacted.

The installation of a heat pump can cause long periods when the main heating plant has no load. This is especially true for installations where HVAC demands require high levels of dehumidification or there are sizable process loads that are continuous. Consideration needs to be given to the type of heating plant and how to maintain it in a "ready" state to pick up load when the heat pump capacity cannot handle the load. In addition, heat pump failure needs to be considered as to how quickly the main heating plant can convert from standby to active temperature control in a short period of time. For the Novartis project, the steam valves were always charged and the heating hot water was always passing through the steam to heating hot water heat exchanger to keep it in ready standby.

Capital Cost Variance with 800 Ton Heat Pump

Item	Cost/variance
800 Ton (10,128 MJ) Heat Pump	$660,000
Heating/Hot Water Pumps for Heat Pump	$76,000
Associated Piping for Heat Pump	$194000
Electrical Power/Control	$70,000
Engineering	$75,000
Start-Up/Commissioning	$75,000
500 ton (6,330 MJ) main chillers size reduction	-$150,000
12,400,000 Btuh reduction in heating plant	-$75,000
Total Capital Cost Increase	**$925,000**

Figure 4. Capital cost variance with 800 ton heat pump.

The main heating plant may need to run at very low loads, due to the load carrying capacity of the heat pump. The main plant also needs to be sized for the full system load, should the heat pump be out of service. Consideration needs to be given as to how the system capacity control will adequately provide for both large and small heating hot water loading. For the Novartis project, the steam control valves of several sizes were provided in parallel feeding the steam to hot water heat exchanger to allow for wide ranges in load control without excessive hunting or control valve wear.

Chilled water temperatures can fall out of acceptable range if the heat pump is carrying the entire chilled water load and the heat pump fails. The heat pump carrying the entire plant load translates into the main chillers being off line. Can the process or HVAC accept this loss in chilled water flow while one of the main chillers is converting from standby to active operation? Time is required to go through the start sequence for one of the main chillers. This same problem also exists if the plant is running with just one chiller online without the heat pump. Another important consideration is that heat pump reliability is not as good as that of a chiller and needs consideration. Novartis decided that they could not accept this loss of chilled water. To resolve this issue, the sequence was written such that the heat pump will automatically adjust load when needed to ensure a main VFD chiller stays on line. If the load drops to a level where both the main chiller and heat pump cannot stay on line, due to minimum load constraints, the heat pump shuts down. Load analysis indicates that this should not occur, but it was programmed in since the load profiles were modeled and not from actual load data.

For simplicity, a blended annual electrical rate was listed in this article to show potential savings and economics of a heat pump installation. Using a blended rate is acceptable for the analysis, but variation in electric utility rates should be reviewed. As an example, demand charges can be substantial in summer. The additional power consumption associated with the heat pump system minus the reduced electrical load on the main chillers, condenser water pumps and tower fans need to be reviewed against actual "point in time" electric and natural gas costs to ensure that it makes sense to run the heat pump when electric rates are high. For the Novartis project, there was not a time the electrical rates where high enough to justify shutting down the heat pump.

Serious consideration needs to be given as to how the heat pump system will be controlled. The interaction of the heat pump needs to be considered for all loads, including all failure scenarios.

Start-up and testing of the heat pump can be challenging if not planned in advance. There needs to be enough simultaneous Heating Hot Water (HHW) and chilled water load to run the system. This can be a difficult hurdle in a plant start-up situation. The heat pump can be installed with cross connecting piping from/to the HHW and chilled water side of the unit to allow for false loading. Flow elements and temperature sensing devices are also needed to determine actual unit loading and for calculating unit efficiency verses manufacturers published data.

Conclusion

A heat pump can be a very effective means of lowering natural gas consumption. The analysis of both heating hot water and coincident chilled water load is essential to justifying the economics and properly sizing the heat pump. The installation of a heat pump requires acceptance of lower than industry standard heating hot water temperatures to allow cost effective installation. Resistance, by both designers and operators, to lower heating hot water temperatures based on increased energy consumption, due to greater airside and water side pressure drops around the HVAC heating coils is unfounded. If a heat pump is properly sized, selected, and a well thought out sequence is developed, the annual savings can be significant. The economics of first cost verses annual savings can be very attractive along with the reduced emissions as compared to a central plant installed without a heat pump.

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A Systematic and Scientific Approach for Implementation and Validation of Single-Use Equipment

by Jean-Loup Descamps, Jean-Baptiste Milandri, and Peggy Sander

This article presents the risk-based and value-based approaches developed during the single-use implementation with a focus on validation aspects.

Introduction

As part of a large-scale investment project to increase capacity, a new production area within the existing human plasma fractionation facility was planned at the French Laboratory for Fractionation and Biotechnology (LFB).This multi-product API facility would accommodate both existing and new products, and is built-up inside an existing building.

The success criteria laid down by LFB's management to the design team were:

- to increase batch size and throughput by 100%
- to upgrade the existing process design to keep LFB at the top of the technological innovation – re-engineering would be permitted as long as new clinical trials are not required as a consequence of process change
- to incorporate new products in addition to the existing ones
- to work with constraints within limited available space in an existing building
- to improve/maintain cost of goods manufactured

Introduction of single-use equipments along with use of concentrated buffers and in-line dilution were the key enabling technologies implemented in order to meet these goals.

This article describes the risk-based and value-based approaches developed during the single-use implementation with a focus on the validation aspects.

This being the first implementation of single-use equipments at a wide scale within the organization; a systematic and science-based approach was adopted at LFB. A broad multi-disciplinary team was set up to fully support the initiative.

Initial front-end studies based solely on using equipment and vessels in stainless steel did not prove economically viable nor meet the space constraints. To resolve these issues, implementation of single-use technologies where feasible were evaluated. The technical aspects of single-use implementation and the quality aspects of it were assessed concurrently by one integrated team. The steps that paved the way from the idea to the actual implementation of single use are described in Figure 1.

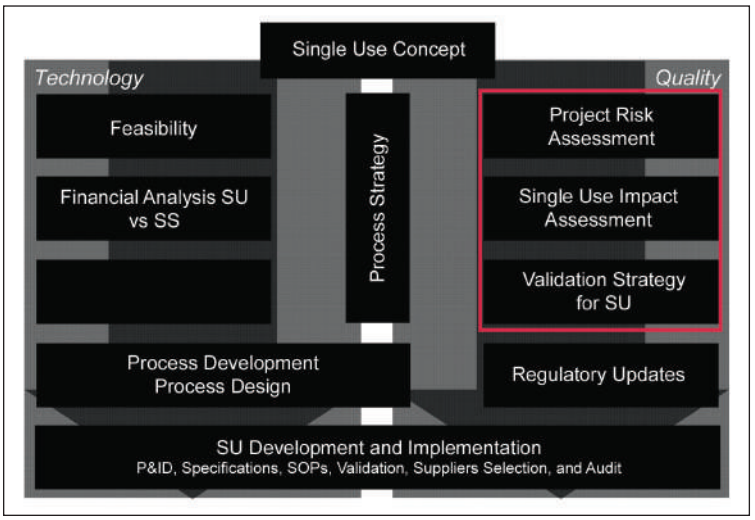

Figure 1. Single use implementation approach – the process steps.

For every milestone, a green light had to be received from both the technology

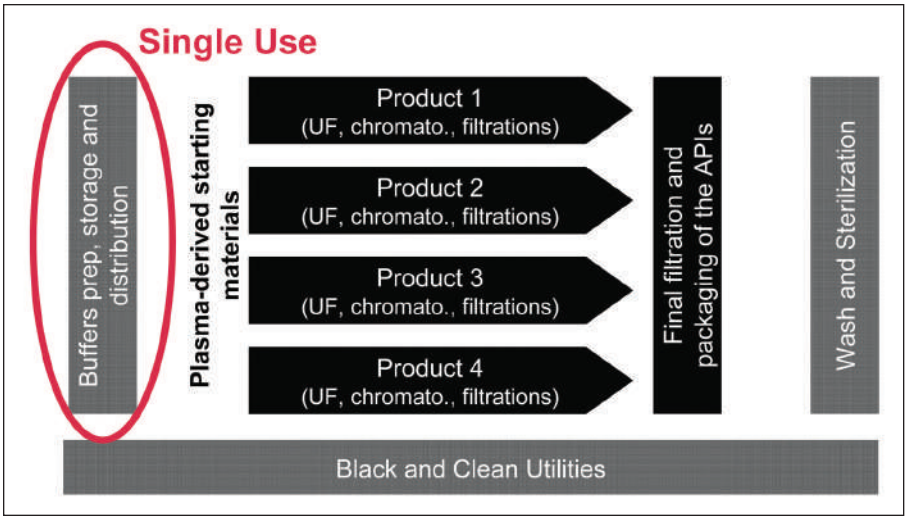

Figure 2. Extent of implementation of single use equipments – a systemic approach.

and the quality units of the assessment group. The technical aspects started with a systematic evaluation of replacing the equipment used at each process step by its single-use counterpart.

As presented in Figure 2, single-use equipment selection based on technical fit and the quality assurance assessment resulted in a rather limited switchover possible from stainless steel to single-use. Indeed, "only" the storage and the distribution of the buffers used in the various processes run in the new facility could be switched over to single use bags from stainless steel tanks and pipes. However, the change to single-use bags for these purposes did not completely meet the set targets as required. The huge number of bags required generated a dramatic increase in operational costs; therefore, space requirements offset potential benefits.

Combining single-use bags for storage with systematic use of concentrated buffers and in-line dilution at the point-of-use significantly improved the business case and was instrumental in meeting the technical project goals.

With the technological choices now made, validated, and further evaluated by project risk assessments focusing on quality aspects, the next step was to develop a validation strategy for single–use implementation.

As with the technical selection, a systematic, science- and risk-based approach was adopted. Figure 3 describes the different steps of the approach leading to establishing the single-use validation strategy.

The goal was to define the appropriate level of testing to be performed based on risks toward the patient, results from validation studies from single-use bag suppliers and extensive know-how historically gained by LFB about its products and processes.

On completion of project risk assessments, the focus shifted to single use impact assessments in order to evaluate and mitigate the risk of implementing single-use systems and concentrated buffers in manufacturing processes for the products already on the market.

This assessment led to identifying three risk mitigations:

- defining and performing stability studies
- evaluating the extractables and leachables data already available from the single-use bags suppliers
- calculating the risk for the product in containing high concentrations of leachables

Single-Use Impact Assessment

Single-use technology implementation brings about important changes in the process handling and also impacts different aspects of the product chain such as Purchasing, Quality Control, Operational Quality Assurance and Validation, Production, Process, and Regulatory Affairs - *Figure 4*. Impact analysis on these different functions was performed in order to identify criticality, associated risks, and actions to be taken in order to mitigate them. Process evaluation was assessed as the most important part of the "scope." For this reason and in order to secure and identify all potential risks, a global evaluation of single-use technology was performed focusing on the impact on the final product.

The goal of this assessment was to evaluate and mitigate the risk of implementing single-use systems and concentrated buffers in the manufacturing processes.

The Failure Mode and Effects Analysis (FMEA) method was applied across different departments (Suppliers Quality Assurance, Production Quality

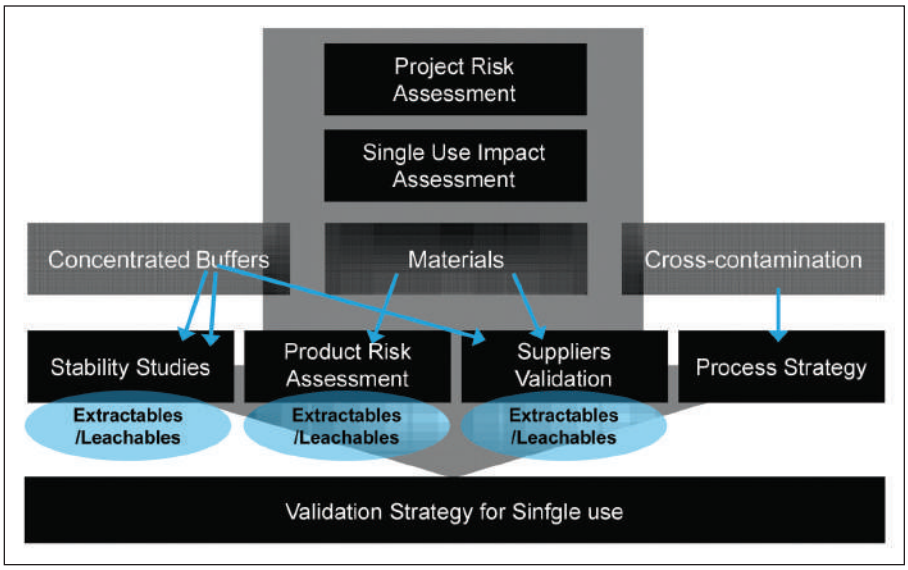

Figure 3. Global single use validation strategy – evaluation steps.

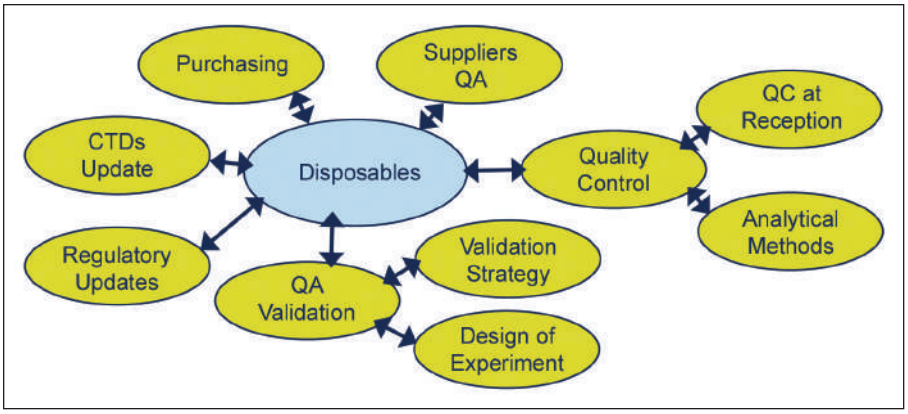

Figure 4. Single-use implementation – global evaluation and functional interactions.

Assurance, Product Validation, Production, Process) in several steps:

- Identification and evaluation of risks directly or indirectly linked to the implementation of single-use for each step of the bag's lifecycle (material receipt, production, quality control, disposal) and of the manufacturing process (from the buffer preparation in tanks to the in-line dilution equipment going through storage, transport, and connection to equipment outlet with multiple-tapping).
- Assessment of each risk were evaluated on:
  - Severity: assessing risks from "no impact" to quality, security or product efficiency and ultimately the risk to patient.
  - Detection: assessing risks from "absence of detection" to possibility/existence of automated detection of process non-conformity.
  - Occurrence: assessing risks from "no occurrence" to registration of the default process risk at each use.

This single-use impact assessment has shown that the main risks were:

- Product contamination by leachables due to:
  - Switchover from stainless steel to single-use – potentially inducing different quantities or new leachables in the final product.
  - Use of concentrated buffers in single-use bags potentially generating leachables or changing product behaviour as a result of addition of a process step (buffer storage) and of modifying buffer formulation to a more aggressive composition (10X concentration).
- Cross-contamination due to multi-use (bags used multiple times in process rooms and held at storage area in between uses) and the possibility of contamination of bags at each use.

An action plan has further been applied to address these main risks in order to mitigate them:

- stability studies
- suppliers agreement/validation
- product risk assessment
- preference for single-tapping scenario instead of multiple-tapping

Stepwise evaluations allowed the team to conclude that all risks have been reduced to an acceptable level.

Stability Studies

Some buffer solutions parameters are critical to the processing conditions required during purification steps, and deviations can result in lower yields and adversely impact product quality. Parameters such as pH, conductivity, and temperature can have a huge influence on the protein binding characteristics. Physicochemical parameters can vary during processing steps.

To ensure that changes introduced did not affect product quality, stability studies were performed on the buffer solutions used across the entire process (including process buffers for regeneration/cleaning/sanitization buffers).

The objective of this study also was to determine the variations of the parameters of the buffer solutions during storage and stability over maximum required storage time.

The scope of the study extended to 19 buffer formulations identified within the project scope. Instead of simply studying all the solutions, a science-based approach was adopted to reduce the number of tests to be performed.

Principal Component Analysis (PCA) method was used to define families of buffer solutions and their model solutions. The stability of the model solutions was tested and the tests results extended to the whole family members. This statistical study took the following into account for each formulation: the composition of the buffers in amino acid, salts, acid, base, and Tris (Trometamol). The components are defined as variables.

This statistical procedure performed a principal components analysis. The purpose of the analysis was to obtain a small number of linear combinations of the five variables which account for most of the variability in the data. In this case – as shown in Table A, three components were extracted since three components had eigenvalues greater than or equal to 1.0. Together they accounted for 71.8 % of the variability in the original data and thus provided a

Component Number	Eigenvalue	Percent of Variance	Cumulative Percentage
1	1,51674	30,335	30,335
2	1,22487	24,497	54,832
3	1,08779	21,756	76,588
4	0,630658	12,613	89,201
5	0,539941	10,799	100,000

Table A. Statistical procedure showing variance of each component.

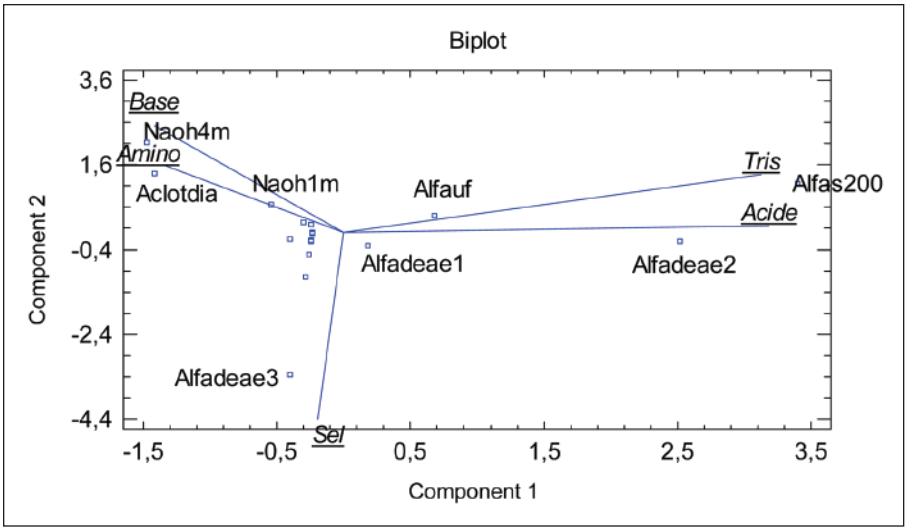

Figure 5. Biplot graph showing contribution of component on the buffer formulation position (software: *Statgraphics Centurion XV*).

representative statistical model of the formulation variability. The multiple linear regression determines each solution position and defines homogeneous family groups.

A biplot graph of two of the three components enabled identification of seven homogeneous families of solutions - *Figure 5*:

- amino acids family (e.g., solutions with glycine component)
- salts family (e.g., solutions with sodium acetate component)
- salts and acids family (e.g., solutions with sodium acetate and acetic acid components)
- acid family (e.g., solutions with sodium acetate and acetic acid components)
- base family (e.g., solutions with sodium hydroxyde component)
- tris family (e.g., solutions with trometamol component)
- neutral family (e.g., solutions with sodium phosphate component)

This biplot shows selected principal components 1 and 2 (X and Y axis). There is a point on the plot for each row in the tabular data file (solutions: Alfadeae2, Naoh1m…). Lines are also drawn for each of the variables (compositions: acids, salts…), representing their location in the space of the components. A weight close to 0 indicates little contribution of the variable to that component.

The statistical study could not define the model solution for each family. This choice had to be done according to industrial considerations as:

- frequency of usage
- relative concentration of components
- criticality of the process step where the solution is used

This approach proved very efficient as the number of studies required for improving the process understanding were reduced from 19 to 7. Any non-conformity in the tests of the model solution would have resulted in repeating the stability studies on all the solutions of the family.

On completion of the stability studies with the critical physico-chemical parameters and microbial contamination of the model solutions defined – the variability of the parameters were analyzed over extended storage times and under storage conditions representative of real production storage. The studies were performed at a smaller scale, which could be considered as a worst case due to higher critical container-content interaction (higher contact surface to volume ratio).

The first results provided a positive conclusion as no non-conformities were identified on the model solutions. This gave the project team the impetus and the confidence in moving to the next steps of the project.

Supplier Validation Evaluation

In order to mitigate the risk of introducing new product containers (single-use bags instead of stainless steel tanks), the suppliers of these bags were validated according to the following method:

- compilation of validation data from each potential supplier
- analysis of tests performed by vendors and comparison to suppliers already validated
- analysis of standard extractables/leachables studies done by suppliers against actual buffers used in the manufacturing processes
- determination of missing data (gap analysis)

Each supplier had made available full validation guides[1-8] for the chosen bags, including test procedures, results, and standards used for product-contact container and where available extractables/leachables studies with tested solutions. All suppliers of single-use components perform tests required as standard, such as:

- biological compatibility and compendial compliance (USP, EP)
- glass transition temperature
- permeability

The above are in compliance with USP 88, class VI; USP 87 et USP 85, meaning that procedures are similar. It is not always possible to get quantitative results, as sometimes results were expressed as conforms/does not conform or as complying to a range value. However, this evaluation showed that all results presented by suppliers were in compliance with the acceptance criteria. Some differences could be seen, but they were not considered significant.

All the single-use suppliers also have data on extractables studies with some typical solutions. Differences between data sets provided by suppliers had to be taken into consideration as conditions and procedures are not equivalent. Size

of the containers, storage temperatures, and duration of storage varied, but all suppliers simulated tests in extreme processing conditions.

Due to variations in testing methods, a systematic one-to-one comparison of the suppliers was not possible. Comparisons based on the buffers used in the manufacturing processes were preferred, which meant that some of their typical solutions were identical or close to manufacturing process buffers (e.g., same formulation but higher concentration).

According to the validation strategy, if the supplier has already done some extractables/leachables studies with solutions fitting with the model solution characteristics, the tests did not have to be repeated during the validation.

In addition, some specific tests could further be used as selection criteria between the suppliers as some of them did not perform all tests. This was used in combination with other specific properties and advantages of the different film composition of the bags:

- puncture resistance
- tensile strength resistance
- transportability
- limpidity of the film
- pH stability
- adsorption
- connection tests

In order to finalize the evaluation, an overview of the missing data needed for the supplier certification was made: identification of infra-red spectrum, film composition detail, certification of the absence of animal-derived compounds, gamma-irradiation validation. This specific evaluation was part of the supplier assessment and was performed in parallel with a more standard approach for supplier selection and accreditation (audit, technical and price evaluation regarding user requirements, assurance of supply, etc.)

This global approach proved to be a very strong and rational basis to select two suppliers who would provide all single-use bags required in the facility.

Product Risk Assessment

The goal of this assessment was to explore the toxicological impact of potential leachables in the final product. The first step was to evaluate the leachables quantities reported by the suppliers in their validation guide. Based on the data made available, the project team evaluated the risk as low. Reported values of leachables were in the ranges of ppm or ppb, and thus the expected level at process conditions was likely to be even lower.

Nevertheless, to consolidate the approach, it was decided to establish quantitatively the theoretical amounts of leachables that could be expected in the final product. These calculations evaluated by the toxicology experts concluded that the amounts of leachables found represented "no risk" for the patient. This is why, considering this global strategy, it was decided not to redo tests already done by vendors and instead, use their bibliography.

The scope of the study included bags, connectors, filters, manifolds, and tubing elements. Input data were issued from studies done by one of the possible supplier. Input data selected on the test list described by the supplier are described in Table A with the rationale detailing why they were chosen. The whole list of test and typical solutions tested can be found in the vendors validation guide with a precised description of test conditions and Quality Control Method used to detect leachables.

The quantification of the leachables were executed according to two scenarios:

- Worst case scenario: purification processing steps do not decrease the initial amount of leachables.
- Real case: purification process steps contribute to the elimination of the leachables (process steps allowing elimination of leachables have been defined with their elimination rate).

Assumptions on input data:

- Filters, manifold, connectors, and tubing were already being used in the former process without impact on the product, and hence not considered as contributors and excluded from this quantification.
- Bags which are considered as the highest contributors are evaluated for two categories of usage: regeneration/sanitization process steps and purification process steps. Regeneration/sanitization steps were not considered as being able to generate leachables in the product as their objective is to desorb non-target proteins and other biological contaminants from the equipment without any product contact time.

As described in Table B, the quantification of leachables in the final product was made considering the following data and parameters:

- identification of process steps using single-use bags, represented in the column "Process steps"
- determination of number and type of single-use bags used for each step, shown in the column "Single-use systems"
- determination of bag volume considering standard bag size from vendors and introduction of this data in the column "bag size"
- determination of bag filling volume regarding process need in the column

Input Data	Rationale
Identified amount of leachables brought by 500 mL bags (ethyl acetate, silyl siloxane, acetone, butanal, ethanol)	500 mL bags as the worst case
Data after 30 days storage at 25°C ±2°C	Similar storage conditions as routine storage conditions
Data on bags filled with: - WFI - HCl (pH 2) and NaOH (pH 11)	 Representative of salt solutions Representative of regeneration solutions

Table B. Synthesis of input data for product risk assessment.

"bag filling volume" (buffer volume required by the process including a safety volume)
- use of extractables data made available by suppliers (extractable found in the representative solution from the vendor is precised in the 1st line with its corresponding minimum and maximum value measured by the vendor chosen for this study)[1-8]
- use of ratio of contact surface by filling volume of bags used during supplier validation

For each process step, extrapolation of leachable amounts were calculated for each bag considering proportionality between:

- contact surface of the buffer with the bag used during the vendor test conditions of the representative solution
- contact surface of the buffer planned to be used in the future process operating conditions

Then a summation of this amount was calculated until the final product step provided a final theoretical amount of leachables in the final product, for both a worst case and a more realistic case (represented in each 2nd line of the green part of Table C showing intermediate process step or product storage step). This final amount was reported to the product volume in order to obtain a final concentration of each leachable, as indicated in the last line of Table C.

As presented in Table C, the results obtained from this study have shown concentration of some leachables around 500 ppb in the theoretical worst case and of about 1,5 ppb in the real conditions. All the above data were evaluated by toxicology experts with respect to:

- theoretical amount of leachables in final product
- criticality of leachables for human safety
- product dose
- dosage
- administration route

The initial conclusion from the preliminary studies was that the calculated amounts are within the detection limits of the analytical methods and toxicology experts conclude that these amounts are not critical for the product safety.

Conclusion

The systematic and scientific approach developed in the project gave the project team strong background knowledge to assess risks and consequently minimize additional testing for validation.

				EXTRACTABLE QUANTIFICATION (ppb - min / max) WFI					
Process steps	Single-use systems	Bags size (L)	Bags filling volumen (L) / Product volume (L)	Ethyl acetate		Silyl siloxane		Ethanol	
				Min. Qty	Max. Qty	Min. Qty	Max. Qty	Min. Qty	Max. Qty
				10	50	10	50	10	50
Buffer preparation	Manifold	NA		NA - No extractable contribution higher than actual situation					
	0,22 µm filter			NA - No extractable contribution higher than actual situation					
Chromatography	Single-use bag - slurry preparation	20	18	3,06	15,32	3,06	15,32	3,06	15,32
EXTRACTABLE CONCENTRATION ON THIS PROCESS STEP (µg/L)			**1400**	**0,0**	**0,2**	**0,0**	**0,2**	**0,0**	**0,2**
EXTRACTABLE QUANTITY ON THIS PROCESS STEP (µg)				**55,2**	**275,8**	**55,2**	**275,8**	**55,2**	**275,8**
Chromatography	0,45 µm filter			NA - No extractable contribution higher than actual situation					
	0,22 µm filter			NA - No extractable contribution higher than actual situation					
	Single-use bag - Equilibration	100	104,9	0,21	1,05	0,21	1,05	0,21	1,05
	Single-use bag - NaCl 2,22 M	500	427	0,14	0,69	0,14	0,69	0,14	0,69
	Single-use bag - Pre-elution	50	41	0,41	2,06	0,41	2,06	0,41	2,06
	Single-use bag - NaCl 2,22 M	-	-	See quantities in single-use bag for NaCl 2,22M used in the pre					
	Single-use bag - Elution	50	34	0,50	2,49	0,50	2,49	0,50	2,49
	Single-use bag - NaCl 2,22 M	-	-	See quantities in single-use bag for NaCl 2,22M used in the pre					
	In-line dilution equipment	NA		NA - No extractable contribution higher than actual situation					
	0,45 µm filter			NA - No extractable contribution higher than actual situation					
EXTRACTABLE CONCENTRATION ON THIS PROCESS STEP (µg/L)			**260**	**1,4**	**7,2**	**1,4**	**7,2**	**1,4**	**7,2**
EXTRACTABLE QUANTITY ON THIS PROCESS STEP (µg)				**375,9**	**1879,5**	**375,9**	**1879,5**	**375,9**	**1879,5**
Ultrafiltration	In-line dilution equipment	-	-	NA - No extractable contribution higher than actual situation					
	Single-use bag - Diafiltration	20	16	1,06	5,28	1,06	5,28	1,06	5,28
	In-line dilution equipment for regenera	-	-	NA - No extractable contribution higher than actual situation					
EXTRACTABLE CONCENTRATION ON THIS PROCESS STEP (µg/L)			**12**	**4,6**	**23,0**	**4,6**	**23,0**	**4,6**	**23,0**
EXTRACTABLE QUANTITY ON THIS PROCESS STEP (µg)				**55,2**	**275,8**	**55,2**	**275,8**	**55,2**	**275,8**
Filtration	0,45 µm filter			NA - No extractable contribution higher than actual situation					
	Depth filter	50	40	0,42	2,11	0,42	2,11	0,42	2,11
EXTRACTABLE CONCENTRATION ON THIS PROCESS STEP (µg/L)			**15**	**3,7**	**18,4**	**3,7**	**18,4**	**3,7**	**18,4**
EXTRACTABLE QUANTITY ON THIS PROCESS STEP (µg)				**55,2**	**275,8**	**55,2**	**275,8**	**55,2**	**275,8**
Filtration and filling	0,22 µm filter		NA						
	Repartition manifold		NA						
	Product content		NA	NA - No extractable contribution higher than actual situation					
INTERMEDIATE PRODUCT VOLUME (L)			**15**						
TOTAL : EXTRACTABLE QUANTITIES PROVIDED BY ALL THE PROCESS STEPS IN THE									
Quantity without regeneration steps in the intermediate product (µg)				541,4	2706,8	541,4	2706,8	541,4	2706,8
Concentration without regeneration steps in the intermediate product (µg/L - ppb)				**36,1**	**180,5**	**36,1**	**180,5**	**36,1**	**180,5**
FINAL PRODUCT VOLUME (L)			**5**						
TOTAL : EXTRACTABLE QUANTITIES PROVIDED BY ALL THE PROCESS STEPS IN THE									
Concentration without regeneration steps in the final product (µg/L - ppb)				**108,3**	**541,4**	**108,3**	**541,4**	**108,3**	**541,4**

Table C. Theoretical forecasts of leachables concentrations in the final product – worst case (extract).

The initial results from stability studies are now available and are very encouraging, leading to the conclusion that the methodology chosen demonstrates that it's possible to create a very strong basis for the validation of the single use systems and Common Technical Document (CTD) dossiers updates, while keeping the extent of tests at a moderate level without compromising the safety of the products, and thereby of the end users.

The key is to allocate time and the right resources to the study and to never compromise the systematic and step-by-step execution of the study.

With the same systematic and science- and risk-based approach, LFB is now extending the implementation of single use systems to its new and current manufacturing processes. But as a company entering large scale single-use processing, there are several challenges along that road that need to be addressed:

- Regulatory requirements and barriers for implementing disposables are being raised higher.
- Finding the appropriate validation strategies.
- Managing approval and the change control of suppliers increases constraints and related costs.

Further developing the science- and risk-based approach presented in this article could contribute to overcoming these challenges.

Glossary

API Active Pharmaceutical Ingredient

EP European Pharmacopeia

FMEA Failure Mode and Effects Analysis

LFB Laboratoire français du Fractionnement et des Biotechnologies

SOP Standard Operating Procedure

SU Single-Use

SS Stainless Steel

USP United States Pharmacopeia

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Case Study: Using Surrogate Testing to Determine Selection and Performance of Contained Dust Collection Systems

by David Steil

This article presents how a pharmaceutical manufacturer, dust collection equipment supplier, and certified independent laboratory together employed surrogate testing to validate performance of a planned dust collection system that would serve a new manufacturing area.

Introduction

The proper selection and operation of contained dust collection equipment is critical to pharmaceutical plants for a host of reasons, from environmental requirements and employee health and safety to production cleanliness and efficiency. The use of surrogate testing is a valuable tool in ensuring that contained dust collectors are meeting the requirements for containment relating to the hazards associated with the materials being processed and any applicable good manufacturing practice.

What is surrogate testing and why is it necessary? Historically, no performance data existed on contained dust collection systems until they were already installed. Surrogate testing offers a way to provide meaningful performance information *prior* to installation, to help pharmaceutical entities determine if the equipment will meet required guidelines and standards for a specific project. Surrogate testing involves the use of a substitute or surrogate compound to simulate an Active Pharmaceutical Ingredient (API) for verifying the effectiveness of dust containment options for handling hazardous materials. Test conditions are designed to mimic workplace operations as closely as possible without incurring the expense or health concerns of handling the actual API. This case study describes how a pharmaceutical manufacturer, who shall be referred to as the "customer," dust collection equipment supplier, and a certified independent laboratory together employed surrogate testing to validate performance of a planned dust collection system that would serve a new manufacturing area.

The Role of Surrogate Testing

In selecting dust collection equipment for pharmaceutical applications, it is critical to understand the toxicological properties of the material to be captured, i.e., the potent, toxic or allergenic properties of the compound as it relates to personnel exposure. This determines the Occupational Exposure Limit (OEL), a value specific to each individual API. The OEL is defined as the amount of material determined to be the maximum air concentration, expressed as a Time Weighted Average (TWA), to which a healthy worker can be safely exposed for an 8-hour shift, 40-hour work week, without potentially suffering adverse health effects. This value is typically expressed in micrograms per cubic meter of air (µg/m^3).

In most cases, some level of isolation and containment is required, due to the fact that the pharmaceutical dust is hazardous and cannot be released into the surrounding environment. There are several benefits to conducting a surrogate test program, but the most noteworthy is *the ability to verify effectiveness of isolation and containment equipment*. Surrogate testing makes it possible to verify at different points in the evaluation and purchasing process whether the contained dust collection equipment is performing as needed for the project. This is accomplished by manipulating the test compound to simulate workplace operations and performing air and surface sampling during the operational manipulations.

Testing can be performed on equipment handling an API with unknown toxicological properties, as in this case study example, or for verification of existing systems. Surrogate

testing also can be performed during Factory Acceptance Testing (FAT), again as illustrated in this case study, and/or Site Acceptance Testing (SAT) after equipment has been purchased to ensure proper performance once installed. By validating equipment performance during the engineering phases of a project, pharmaceutical manufacturers stand to reduce costs while also reducing risk.

Equipment to Be Evaluated

The equipment selected for evaluation by the customer was a cartridge-type contained system designed for high efficiency collection of dry dusts. This equipment is suited to a variety of pharmaceutical dust collection applications including tablet presses, coating machines, fluid bed drying, spray drying, blending, granulation, central vacuum systems, and general room ventilation. The equipment to be tested contained four cartridge filters rated at 99.999 percent efficiency (MERV 16) on 0.5 micron particles and larger with the capability to handle risk-based category 3, 4, and 5 compounds with OELs less than 1.0 µg/m^3 for an 8-hour time weighted average.

Any point of potential exposure to hazardous dust must be enclosed and maintained so the dust collector was equipped with soft-walled, safe-change containment technology for both the filter cartridges inside the collector and the discharge system underneath. The filter cartridges utilized the Bag-In Bag-Out (BIBO) technology with two cartridges removed per bag. The discharge system utilized continuous liner technology to contain the dust that would be released from the cartridges to the angled hopper below during automatic pulse-cleaning.

The surrogate testing commissioned by the customer was a Factory Acceptance Test (FAT) to verify performance. It was conducted with the idea that if the equipment did not function as expected, it would be easier to address modifications at the factory rather than at the customer site. The supplier's stated claim was that the equipment would perform at or below the standard threshold limit of 1.0 µg/m^3 for a TWA.

There were three possible outcomes to the surrogate testing depending on the equipment's measured capability to meet this desired containment threshold:

1. If results met or exceeded expectations, the customer would accept the contained dust collection equipment as designed.
2. If results were close, but not quite within the required range, the supplier would make modifications to the equipment and then repeat the test to verify if those changes were successful.
3. In the unlikely event that the equipment fell short of performance goals even after modifications, the customer

Figure 1. Dust collection equipment used in the surrogate test.

Non-Free Flowing Lactose Test Dust Specification
Description: A spray-dried mixture of crystalline and amorphous lactose

Chemical Analysis	**Typical**	**Specification**
Acidity or alkalinity	0.1 mL	0.4 mL of 0.1 N NaOH (maximum)
Clarity and color @ 400 nm	0.01	0.04 (maximum)
Heavy metals, µg/g	Less than 5.0	5.0 (maximum)
Loss on drying, %	0.3	1.0 (maximum)
Protein and light-absorbing impurities at 210-220 nm at 270-300 nm	 0.05 0.01	 0.25 (maximum) 0.07 (maximum)
Residue on ignition, %	0.02	0.1 (maximum)
Specific rotation	+54.8° to +55.2°	+54.4° to +55.9°
Water, %	4.8 to 5.2	4.5 to 5.5
Microbiological Standards	**Typical**	**Specification**
Total aerobic microbial count	Less than 10 cfu/g	100 cfu/g (maximum)
Escherichia coli	Negative	Negative
Total combined molds and yeasts count	Less than 10 cfu/g	50 cfu/g (maximum)
Staphylococcus aureus	Negative	Negative
Pseudomonas aeruginosa	Negative	Negative
Salmonella species	Negative	Negative
Powder Fineness *(Cumulative)*	**Typical**	**Specification**
On USS #30 (600 micron)	0%	0% (maximum)
On USS #140 (106 micron)	30 - 60%	20% (minimum)
On USS #200 (75 micron)	55 - 75%	50% (minimum)
Physical Characteristics	**Typical**	**Specification**
Bulk Density	0.67 g/mL	0.60 g/mL (minimum)
Tapped Density	0.78 g/mL	0.70 g/mL (minimum)
% Lactose (d.b.)	99% (+)	
Appearance and flavor	White, crystalline powder, slightly sweet	

Table A. Surrogate test dust specification.

would perform a risk assessment to determine the need for supplemental Personal Protective Equipment (PPE) or for other, more costly containment technologies.

The dust collection equipment is shown - *Figure 1*.

Testing Protocol and Methodology

To perform the testing, the dust collection equipment supplier engaged an independent laboratory accredited by the American Industrial Hygiene Association (AIHA). Together the supplier and laboratory outlined a test protocol conforming to the *ISPE Good Practice Guide, "Assessing the Particulate Containment Performance of Pharmaceutical Equipment."* As described by ISPE, this guide provides a standard methodology for use in testing the containment efficiency of solids handling systems used in the pharmaceutical industry under closely defined conditions. It covers the main factors that affect the test results for specific contained solids handling systems, including material handled, room environment, air quality, ventilation, and operator technique.

The customer wanted to apply all best available methodology to the task; so in addition to ISPE Good Practice guidance, the equipment supplier and laboratory also incorporated AIHA Good Industrial Hygiene Practices in developing the test protocol. This was completed in order to supplement the ISPE testing methodology specifically for assessing dust collection systems. The AIHA provides education, training, and publications on how to recognize and evaluate chemical hazards in a wide variety of situations (www.aiha.org). Utilizing multiple resources allowed for a comprehensive testing methodology to be developed to ensure compliance with applicable industry standards.

The testing methodology incorporated the following elements:

Surrogate Compound Selection

The first task was to select a test compound that would simulate the customer's API without posing a hazard to the operators or the surrounding environment. Lactose is the most common surrogate used due to its ability to be micronized, its free flowing or non-free flowing particle size distributions, its inactivity, and its cleanability. The free flowing particle size can range from 45 to 250 µm and the non-free flowing averages around 50 µm. The detection limit sensitivity of lactose in air is 0.005 µg/m^3 for an 8-hour Time Weighted Average (TWA) and 0.17 µg/m^3 for a 15 minute Short Term Exposure Limit (STEL).

In this test, non-free flowing lactose milled to provide a 50µm average particle size was the surrogate of choice. Table A shows the specifications for the surrogate test dust. It should be noted that the surrogate specified was 100 percent lactose, undiluted with other materials. In real-world processes, the API is incorporated in a specified concentration and is mixed with other inactive substances and excipients. By the time it reaches the dust collector, usually at the end of the process, the API might account for just a very small percentage of the dust being captured. By using an undiluted test dust, the collector would thereby be challenged with a "worst case scenario." A total of 62.5 kilograms of lactose was used to conduct the testing.

Test Room

The dust collection equipment was located in a dedicated and decontaminated area of the equipment manufacturer's factory. The test area was isolated and sealed off and personnel access was tightly controlled and limited to test personnel to keep the area pristine and avoid contamination - *Figure 2*. Prior to the FAT, test personnel pressure-washed the test room, cleaned the floor with a power scrubber, and manually wiped the exteriors of the equipment and other surfaces.

The area was maintained at a relative humidity of 50% (± 10%), a temperature of 20°C (± 5°), and a positive room pressure of > 10 Pa relative to the adjacent space. An air change rate of three to five changes per hour was maintained. Air sampling devices were installed in opposite corners on the east and west sides of the room, and numerous other sampling points were designated for surface swab tests.

Air and Surface Sampling Plan

The sampling plan called for a total of more than 47 air, surface wipe, and personal samples to be taken to evaluate dust collector performance as follows:

- *Background general area air samples and surface swab samples* to be collected prior to the liner change, continuous liner discharge, and filter change operations. The "before" testing was scheduled after cleaning of the area and about one hour prior to the test to make sure the background environment was clean and would not compromise results.
- *One single-event breathing zone sample* to be collected for each of two test operators during the liner change operation, during each of the three continuous liner discharge tasks, and during each of the four filter change tasks of the operational test.
- *One multi-event breathing zone air sample* to be collected for each of the two operators during the liner change operation, the three continuous liner discharge cycles, and the

Figure 2. Mezzanine adjacent to test room, sealed off with poly sheeting with dust collector platform visible at the right.

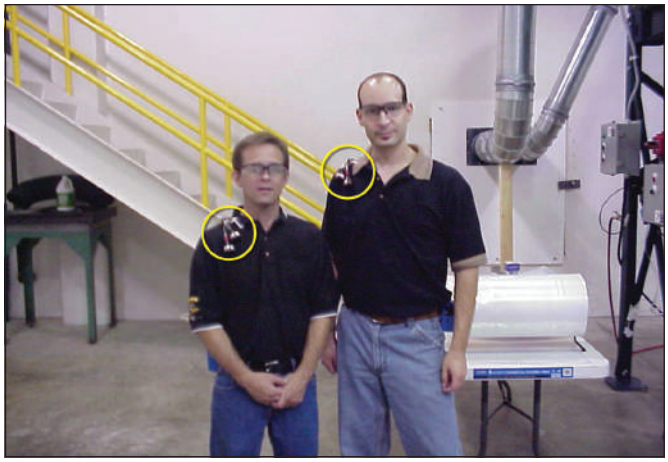

Figure 3. Operators each wearing single and multi-event air sampling pumps and filters (indicated by yellow circles) before the liner change operation.

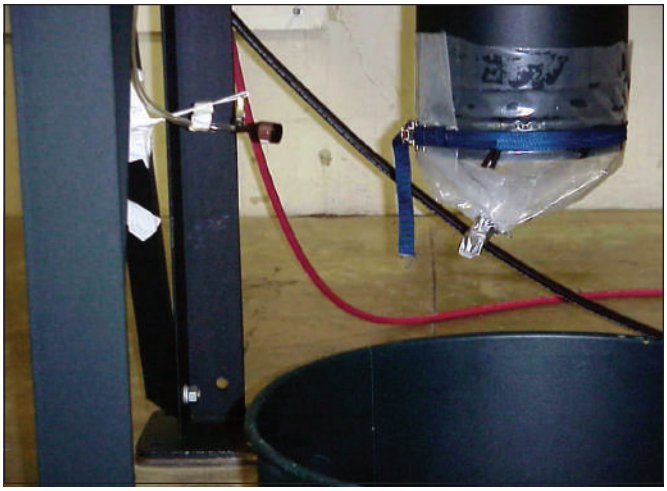

Figure 4. General area event sample collected 8" from bottom of discharge chute and collection bag during liner change operation.

four filter change tasks of the operational test. Figure 3 shows the operators each wearing single and multi-event air sampling pumps and filters.

- *Four general area event air samples* to be collected near the discharge chute of the dust collector during the liner change operation and each of the three continuous liner discharge cycles of the operational test - *Figure 4*.
- *General area event samples* to be collected near the top in Figure 5 and bottom of the bagging flange during the four filter change tasks of the operational test.
- *Two general area background air samples* to be collected during the liner change operation, three continuous liner discharge cycles, and the four filter change tasks of the operational test.
- *Surface swab samples* to be collected from the discharge chute after each of the liner change operations in Figure 6 from each of the three continuous liner discharge cycles, and from the top and bottom of the bagging flange after filter change tasks No. 2 and No. 4 only.

Test Sequence

The actual test conditions mimicked workplace operations as closely as possible to ensure meaningful results. Working from a charging area adjacent to the test room, an employee charged the lactose surrogate dust to the collection system on a pre-determined schedule. Two charge and discharge cycles using 12.5 kg of lactose per cycle occurred during the first simulated work-shift test day, and one additional charge of 12.5 kg also occurred on this day. This third charge of lactose was left in the dust collector until the following test day.

Test operators conducted an additional liner change operation on the following day to discharge the third charge of 12.5 kg of lactose left in the system the previous day. They performed two additional charges of 12.5 kg of lactose to the system to conduct liner discharges No. 2 and No. 3. The recirculating air conditioning system in the test room was turned off for the entire time so that it would not skew results.

Background Air and Swab Samples

These samples were collected after the cleaning of the test location. They were collected in specific areas both in the testing room and on the equipment. The purpose was to determine the validity of the air and swab samples collected during the surrogate test. If the background sample results showed a

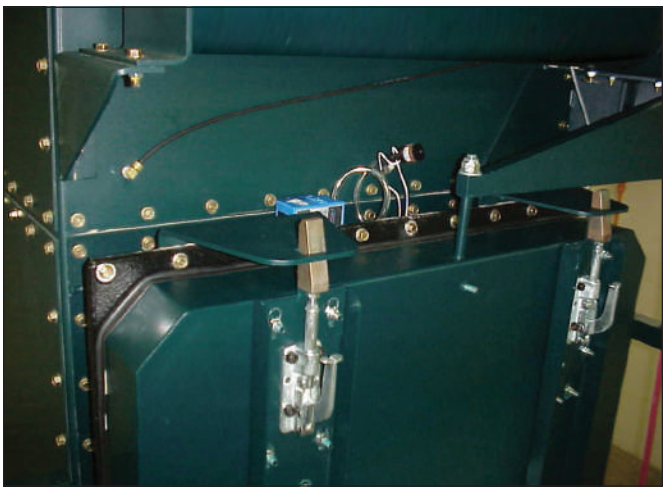

Figure 5. Location of general area air sample above top of bagging flange before filter change No. 1.

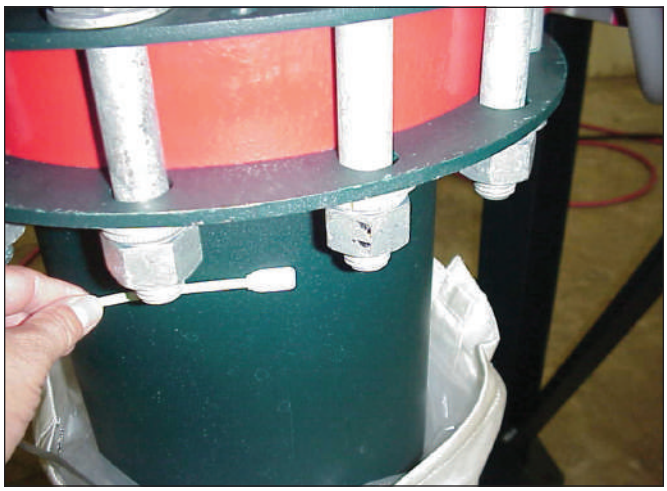

Figure 6. Location of swab sample collected from discharge chute after completion of continuous liner discharge No. 3.

high level of contamination, the results of the surrogate test would be skewed and inaccurate.

Personal Air Sampling

Air samples were collected on ultra high efficiency glass fiber filters enclosed in 25-millimeter (mm) cassettes using air pumps designed to draw a measured volume of air at a steady flow rate through the cassettes. Pumps were calibrated on-site before and after each sample period. The two test operators wore sampling pumps and filters attached in the breathing zone, which is defined as a hemisphere forward of the shoulders with a radius of approximately six to nine inches. Each operator wore two sampling pumps and filters – a "single event" unit to monitor specific short-term events of 15 to 20 minutes' duration; and a "multi event" unit to monitor total exposure for the duration of the test, covering a time period equivalent to a standard employee work shift. Since a real-world employee may perform many different tasks over the course of a shift, it is important to do short-term sampling as well as overall sampling to monitor possible spikes in exposure levels, pinpoint problem areas if any, and receive a more accurate picture of dust collector performance.

The testing equipment thereby simulated the respiratory rate of a human being; and the material collected on the filter media over time provided a snapshot into potential operator exposure to the surrogate under real-world conditions. Operator exposure is considered a concentration of an airborne contaminant to which an employee would be exposed without benefit of personal protective equipment, such as a respirator.

General Area Testing

Sampling pumps with air filters in cassettes as described above also were used for non-operator monitoring. As detailed previously (see Air and Surface Sampling Plan), general area event air samples were collected at specified equipment locations during the discharge cycles and filter changes to monitor surrogate emission levels associated with those tasks. In addition, two air sampling pumps with filters were located in opposite corners of the test room. These pumps ran throughout the entire testing event for general area background evaluation in the test room. The purpose of this additional sampling was to identify and measure whether any test dust was escaping into the ambient air or migrating to other areas of the test room. Again, the goal was to paint as complete a picture as possible by using multiple data points to monitor system performance.

Swab Sampling

Swab sampling or surface monitoring provided a supplemental measurement technique. Surface monitoring is typically used to assess the amounts of surrogate contamination on a surface. It is regarded as a subjective test and is not a standardized technique for establishing health risks; however, it is an important measure in establishing the containment performance of the equipment. This type of testing is typically used to verify the presence of the surrogate in locations where it should be absent.

Samples were taken over a 25 cm^2 (5 cm × 5 cm) area in several locations (see Air and Surface Sampling Plan) using laboratory swabs. These included the background general area samples taken prior to testing as noted above, and samples collected at specified equipment locations after the discharge cycles, and after the second and fourth filter change tasks.

Field Blank Samples

As a quality control procedure, a blank air sampling filter and surface swab also were provided to the laboratory for analysis. These "field blanks" – unused and unidentified samples submitted at the same time as the actual samples – helped to provide a quality control check to verify accuracy of the lab work.

Operator Tasks

As noted, the cartridge dust collector was equipped with two safe-change containment systems: the Bag-In Bag-Out (BIBO) system designed to prevent dust contamination during filter change-out, and the Continuous Liner Discharge (CLD) system to contain the dust during discharge cycles. The surrogate testing encompassed operator activities relating to both systems, as follows:

BIBO Filter Cartridge Change

The two operators performed this task, manipulating a total of 16 cartridges during the test period: eight cartridges saturated with lactose and eight new cartridges replaced into the system. To perform filter change-out, the operators opened the hinged access door and worked through the bags to accomplish safe change-out while avoiding direct exposure to the contaminated filters, removing the used cartridges and then installing the new ones - *Figure 7*. Each change-out operation

Figure 7. Operators performing BIBO filter cartridge change.

Figure 8. Continuous liner discharge operation.

took approximately 40 minutes to perform, and the operation was completed four times to simulate shift equivalence (206 minutes total).

Continuous Liner Discharge

During operation in the test period, the dust collector's cleaning system periodically sent pulses of air to the filter cartridges in the opposite direction of normal air flow (reverse air pulse) to blow material off the filter media. This pulse-cleaning action caused dust to accumulate in the angled hopper at the base of the collector. To release this material from the collector, the operators performed the continuous liner discharge operation to collect the material in a safe manner for disposal - *Figure 8*. They performed three discharge operations in which they released the material using a dual-butterfly valve system, and then crimped and cut the liner and extended new liner to receive the material (15 minutes). The operators next performed the liner replacement procedure. This includes creating the bottom of the new liner bag, bagging over the stub of the old liner, and securing the new liner (15 minutes). Three discharge cycles and a liner change were performed to simulate shift equivalence (126 minutes).

Results

In the sampling performed prior to the operational test, a background surface lactose concentration of 0.39 micrograms per 25 cm^2 was detected on the test room floor. The results for the remaining three background surface swab samples were below the 0.025 µg limit of quantification. The results of the two background general area air samples collected before commencement of the operational test also were below the limit of quantification, resulting in reported airborne concentrations of less than 0.018 micrograms per cubic meter (µg/m^3) for a sampling period of 110 minutes.

Of the 47 samples taken during the operational test, all were below the established OEL of 1.0 µg/m^3, and many of these were significantly below the established threshold. Focusing on the personal air sampling results, which are significant in that they simulate real-world operator exposure, the following measurements can be noted:

BIBO Filter Change-Out:

- Multi-event sampling from the breathing zone of Operator 1 yielded an airborne lactose concentration of 0.38 µg/m^3 (206 min).
- The multi-event sampling from the breathing zone of Operator 2 showed a concentration of 0.19 µg/m^3 (206 min).
- Single-event samples from the breathing zone of Operator 1 ranged from 0.14 µg/m^3 to 0.64 µg/m^3 (36 to 47 min).
- Single-event samples from the breathing zone of Operator 2 ranged from < 0.048 µg/m^3 to 0.40 µg/m^3 (36 to 47 min).

CLD Operations:

- Multi-event sampling from the breathing zone of Operator 1 showed an airborne concentration of 0.077 µg/m^3 (126 min).
- Multi-event sampling from the breathing zone of Operator 2 showed a concentration of 0.045 µg/m^3 (126 min).
- Single-event samples from the breathing zone of Operator 1 ranged from <0.083 µg/m^3 to < 0.25 µg/m^3 (8 to 24 min).
- Single-event samples from the breathing zone of Operator 2 ranged from nearly identical, ranging from < 0.084 µg/m^3 to < 0.25µg/m^3 (8 to 24 min).

Results: Background Samples and Filter Cartridge Changes
Background Samples • General area air: < 0.018 $\mu g/m^3$ (110 min), < 0.018 $\mu g/m^3$ (111 min) • Surface swabs: 0.39 $\mu g/25\ cm^2$, < 0.025 $\mu g/25\ cm^2$, < 0.025 $\mu g/25\ cm^2$, < 0.025 $\mu g/25\ cm^2$
Filter Cartridge Change (air) • Operator 1 multi-event: 0.38 $\mu g/m^3$ (206 min) • Operator 2 multi-event: 0.19 $\mu g/m^3$ (206 min) • Operator 1 single-event: 0.14 $\mu g/m^3$ (47 min), 0.46 $\mu g/m^3$ (42 min), 0.64 $\mu g/m^3$ (38 min), 0.60 $\mu g/m^3$ (36 min) • Operator 2 single-event: 0.12 $\mu g/m^3$ (47 min), < 0.048 $\mu g/m^3$ (42 min), 0.40 $\mu g/m^3$ (38 min), < 0.056 $\mu g/m^3$ (36 min)
Filter Cartridge Change (air) • General area event, top bagging flange: 0.12 $\mu g/m^3$ (92 min), 0.24 $\mu g/m^3$ (77 min) • General area event, bottom bagging flange: 0.22 $\mu g/m^3$ (92 min), 0.67 $\mu g/m^3$ (77 min) • General area background: 0.17 $\mu g/m^3$ (210 min), 0.19 $\mu g/m^3$ (210 min)
Filter Cartridge Change (surface) • Bagging flange, top left: < 0.025, 0.65 $\mu g/25\ cm^2$ • Bagging flange, top right: 0.67 $\mu g/25\ cm^2$ • Bagging flange, bottom left: < 0.025, 0.26 $\mu g/25\ cm^2$

Table B. Measurements obtained from background sampling and filter cartridge changes.

Results: Continuous Liner Discharge (CLD) operations

CLD Operations (air)
- Operator 1 multi-event: 0.077 $\mu g/m^3$ (126 min)
- Operator 2 multi-event: 0.045 $\mu g/m^3$ (126 min)
- Operator 1 single-event: < 0.13 $\mu g/m^3$ (15 min), < 0.083 $\mu g/m^3$ (24 min), < 0.25 $\mu g/m^3$ (8 min), < 0.13 $\mu g/m^3$ (15 min)
- Operator 2 single-event: < 0.13 $\mu g/m^3$ (15 min), < 0.084 $\mu g/m^3$ (24 min), < 0.25 $\mu g/m^3$ (8 min), < 0.13 $\mu g/m^3$ (15 min)
- General area event, 8" from bottom of discharge chute: < 0.13 $\mu g/m^3$ (15 min), < 0.083 $\mu g/m^3$ (24 min), < 0.25 $\mu g/m^3$ (8 min), <0.13 $\mu g/m^3$ (15 min)
- General area background: < 0.016 $\mu g/m^3$ (129 min), 0.044 $\mu g/m^3$ (129 min)

CLD Operations (surface)
- Discharge chute, above liner, liner change: < 0.025 $\mu g/25\ cm^2$
- Discharge chute, above liner, discharge #1: < 0.025 $\mu g/25\ cm^2$
- Discharge chute, above liner, discharge #2: < 0.025 $\mu g/25\ cm^2$
- Discharge chute, above liner, discharge #3: < 0.025 $\mu g/25\ cm^2$

Table C. Measurements from the continuous liner discharge (CLD) operations.

Table B summarizes the measurements obtained from in the background sampling and filter cartridges changes. Table C summarizes the measurements from the CLD operations.

The customer accepted the FAT surrogate testing results as evidence that the contained dust collection system as designed could be expected to provide the required level of emission control performance under real-world operating conditions to meet the applicable OELs.

Conclusion

Surrogate testing of contained dust collection equipment, performed under controlled parameters with an appropriate surrogate that mimics the particle characteristics and flowability of the API, provides a safe and effective method to help predict the potential real-world ability of the system to contain the process in compliance with emission requirements. The application of a rigorous testing protocol that meets or preferably exceeds both ISPE and AIHA guidance, as applied in this case study example, is recommended for optimum results.

It is important to note that surrogate testing should not be regarded as an all-inclusive determinant of contained dust collector performance. The collection equipment also must be determined to be functionally acceptable in its ease of service and operation, energy usage, reliability, return on investment and total cost of ownership to be reviewed and agreed upon by the customer and the equipment manufacturer. Viewed in this context, a well-designed surrogate test program is an important tool in the overall evaluation, verification, and purchasing process relating to the pharmaceutical industry.

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The article presents points to consider to successfully outsource maintenance activities in a pharmaceutical company.

Standardizing Equipment Maintenance Outsourcing

by Martin van den Hout

Introduction

The quality of maintenance work has a direct influence on the quality and performance of machinery. Outsourcing maintenance can have many benefits. In many companies, the pile of maintenance contracts has grown over the years without a well thought out strategy behind outsourcing. Managing the whole process of outsourcing can prove to be a time consuming activity. To be able to cost effectively manage all outsourced work in compliance with regulations, companies need to develop a complete outsourcing policy and efficient processes.

The outsourcing policy should answer a number of questions about the way a company is outsourcing maintenance. The first question is about the goals and conditions of outsourcing. Is it the intention to lower costs, to increase quality, to make costs more predictable, or some other reason?

The second question is if outsourcing maintenance will deliver these benefits. Maybe it is better to do the maintenance with your own technicians. Maybe your engineers can set up the maintenance plans and outsource the actual maintenance or the other way around.

If outsourcing proves to be a good choice, the third question is which type of outsourcing is most suitable for the organization. Many people think outsourcing can only be done in one way. But there are many different ways, ranging from hiring a few mechanics on an hourly base to fully outsourcing the whole organization, including all management and maintenance engineering. Table A shows an overview of the different basic types of outsourcing. Which type is best strongly depends on the type of organization, the design of the equipment to be maintained, and the goals and conditions.

The next questions are less strategic and more practical. How can we select a suitable service company? What should be the terms and conditions of the contract? How should we organize all the communication, document control, access to buildings and workshops, quality control, etc. The last, but certainly important question is how outsourcing maintenance will impact your own organization and morale of your staff.

This article will present two examples of organizations that wanted to improve the current way they were outsourcing maintenance.

The first organization is a producer of pharmaceutical products for animal health. It has improved its control over all its maintenance contracts in

Table A. Different types of outsourcing.

1. Hourly Rates – the contractor just supplies "hands." Invoices are based on the actual hours worked. The responsibility for the quality of the work and financial risks lie with the client.
2. Unit Rates – fixed prices for a unit of work, such as a square meter of paint work, or the overhaul of one valve.
3. Contract Work – based on a clear scope a price is fixed.
4. Service Contract – usually a combination of a number of preventative service visits per year and a fee for a stand by service in case of breakdowns.
5. Service Contract including repairs
6. Performance Contract – the contractor guarantees a certain reliability for the installation and gets a bonus or a fine if the installation performs better or worse.
7. Main Contract – is often defined as a performance contract. The difference is that one contractor is responsible for all the maintenance in a facility.
8. Demand-Supply Model – one party organizes and coordinates all maintenance activities for a production facility. This party does not perform the maintenance itself. It just takes care of management.
9. Independent Maintenance Department – In some cases a company sets up a service company itself. Usually, it will cooperate with a larger contractor. The maintenance staff of the client is transferred to the new company.

order to comply with internal and external regulations. The pharmaceutical company now has an efficient and secure system to make sure all its contractors perform the correct maintenance the right way and on time.

The company, located in Western Europe, develops and produces high standard animal health products. The company operates several production facilities. The maintenance on these facilities is partly done by outside companies.

To show the influence of organizational culture, type of equipment, and other factors, the approach of this company will be compared to a university that owns and maintains 400 buildings. It wanted to outsource more of its maintenance activities on Heating, Ventilation, and Air Conditioning (HVAC) equipment. The equipment is located in several types of buildings, ranging from modern office buildings to a medieval castle and from auditorium-style to high tech laboratory. Both cases are real examples which took place in the last year.

Maintenance of any production machine can always have a direct impact on production costs and quality. Therefore, the pharmaceutical company manages all maintenance of its facilities with the highest care.

Managing and securing quality of outsourced work is complex. Apart from the outside contractors, many departments within the company are involved in the outsourcing of maintenance.

The Technical Procurement Department is of course involved, but so are the local maintenance departments in the plants. Further, the company has a Central Maintenance Group where a Contract Manager is keeping track of all the contracts. Last but not least, the Operations Department and Safety Department are important stakeholders. All these departments have to work together when it comes to managing the contracts.

The company wanted to improve its management of outsourced maintenance. It wanted to get better control over the maintenance contracts for its production machinery and production related equipment. It also wanted to improve the efficiency of all processes relating to outsourced maintenance. In industry, a lot of time is spent on managing the contracts of outsourced maintenance. It takes a lot of time checking all the work order sheets, checking invoices, and keeping all technical data up to date. The company wanted to make the process of outsourcing more clear and make it easier to follow up.

All together the company had about 140 contracts on all types of maintenance on a wide variety of equipment. Managing all the contracts and securing the quality of the work performed cost the company a lot of time and money. Therefore, the company took a close look at all the processes and systems related to the outsourcing of maintenance.

When the company started out with this project, the basic thought among some of the people in the project team was that there should be a standard contract for all third parties that came to the plants to perform maintenance or services.

On the other hand, the company was not sure if it would be possible to use one standard contract for all maintenance work. A consultant was called upon for help.

Which Maintenance Activities Can Be Outsourced?

The first step was to set up a policy describing which types of maintenance work could best be outsourced and which types could best be done by the company's own personnel.

One of the main elements in this policy is what the goals of the company are for maintenance and reliability of its equipment. These goals, together with a number of conditions, determine which approach of maintenance is best suited.

The goals that the company defined are:

- The company's own technicians should focus on their core activities.
- The maintenance costs should be optimized and well controlled.
- All legal demands must be met.
- The quality of the work and service should be measured.
- Reduce the amount of administrative work.
- Independence from third parties
- Transparency
- Standardization
- Continuous improvement
- Reduction of downtime of machines and equipment

The question if outsourcing of maintenance for a particular piece of equipment is wise at all depends on a number of criteria - *Table B*. These criteria may be different for the different pieces of equipment in a facility. This means it may be wise to outsource some of the maintenance, but do some other types inside the company.

The first criterion is to consider whether the piece of equipment or the type of work is of *strategic* interest to the company. A reason to call a piece of equipment strategic may be, for instance, that knowledge of this machine is essential to stay ahead of the competition.

A production company can only survive if it can make its own products better and cheaper than the competition. This requires technical knowledge. This knowledge is not only recorded in the engineering drawings of the machinery. It is more important to have detailed knowledge and experience on process settings, fluctuations, adjustments, failure modes, and breakdowns, especially the knowledge gathered in day to day operations and maintenance.

This means that equipment requiring technology that is specific for one product is strategic and maintenance should be done by the company's own employees. If the equipment is more common, for example, an industrial cooler, it usually is not strategic and maintenance can be outsourced.

A second criterion is if the equipment requires *specialized expertise*. In the case of the industrial cooler, for example, certified maintenance personnel may be required. If a company has only a few coolers, it may not be economic to train its own staff to do the maintenance on them. This company decided to outsource all maintenance activities that required specialized expertise. Only in the case where this would lead to a situation where they came to depend on one single service company, would they train their own technicians to do the work.

Criterion	If	Then Preferably
1	Know how of a piece of equipment or process is strategic to a company.	Do the maintenance yourself and gather the knowledge.
2	Specialized knowledge or skills are needed to do the maintenance that are not economically feasible to get in company.	Outsource the maintenance.
3	Specialized knowledge or skills are needed to do the maintenance that are not available outside your company.	Do the maintenance yourself.
4	Your maintenance technicians have a very stable workload all year.	Do the maintenance yourself.
5	Your maintenance workload has peaks and slow periods.	Outsource the peaks.
6	Your Maintenance Department is not able to perform the work in a competitive way.	Outsource the maintenance tasks.
7	The equipment is critical. Equipment failure has severe consequences.	Set up a very good system proactively to monitor the work performed. Do not rely on KPIs and performance contracts.
8	You do not have sufficient data on equipment configuration and behavior.	Start with a simple way of outsourcing.

Table B. When and how to outsource maintenance tasks.

A third criterion is if the company has a *stable work load* throughout the year. If this is not so, it may be prudent just to have a staff for the slow periods and hire people to assist in the busy periods.

A fourth and sometimes very important criterion is if the company is able to perform the maintenance work just as economically as outside companies. Can it do the work competitively? This led to a lot of discussion. If a piece of equipment is not strategic, the work is not extremely specialized, and there are no peaks in the workload, a company could decide to outsource, but it does not have to. So, if the work is not done in a competitive way in house, does this not mean they should get their own workflow better organized? The company decided to keep the existing contracts for this category as they were. The Maintenance Department of the company was already working efficiently and could do most jobs competively, so the category is very small.

However, the university decided that its own Maintenance Department was not competitive and would not be able to do the routine maintenance on HVAC-equipment in a competitive way. This means a lot more of the routine maintenance was outsourced. This, as we will discuss later, has a much larger impact on the university's own organization, because a lot of work is transferred to outside companies. Because of this mix of criteria, a mix of several types of contracts can arise.

If You Decide to Outsource, What Type of Contract Should You Choose?

If a company decides to outsource the maintenance on a piece of equipment, the next question is what type of outsourcing contract is most suitable. This depends on a number of things.

One important aspect is *how critical is the equipment*. Equipment is critical if failure has severe consequences, for example, for safety, and quality of financial consequences. If failure of the equipment is unacceptable, it is not possible to fully turn over the responsibility for the maintenance schedules to a contractor.

If critical equipment fails, it is too late for corrective action. Accidents may have happened or a large amount of money may be lost. This means that a company outsourcing the maintenance must be in control beforehand. It must know that the contractor is doing the right maintenance. So, the contractor can be the one setting up the maintenance schedules, but the company has to check them before the contract period starts and make sure that they cover all the risks.

Moreover, the company not only has to make sure the company is doing the right preventative maintenance actions, but it also has to make sure the contractor is doing them the correct way. So, it is not only what the contractor does, it is how it does it. A way to guarantee this is by using the right criteria in selecting a contractor and by doing audits on the contractor's organization and way of working on a regular basis.

If equipment is not critical, it is possible to define and use Key Performance Indicators (KPIs) to measure the performance of the contractor. If he performs below standard, corrective action can be taken. If, for instance, a company outsources the paintwork of its window frames, it can complain afterward if it is not satisfied about the quality of the work. Painting window panes is not critical. The contractor is the one responsible for determining which maintenance tasks and frequencies are suitable.

A second criterion that determines which type of outsourcing is suitable for a company is *the way the company is organized* and wants to stay organized.

Fully outsourcing all activities, for example, may have a huge social impact on the existing maintenance organization. The company did not so much want to change the amount of outsourcing as improve the efficiency of the existing contracts. Therefore, social consequences were no issue at the company.

Another organizational aspect is the amount of information a company has on its equipment and failure modes. A contractor cannot take over the responsibility for the reliability of a piece of equipment if the configuration and history of the equipment are not clear. In other words, if a company does not have good records of past breakdowns, a contractor can not predict future behavior and take responsibility for it.

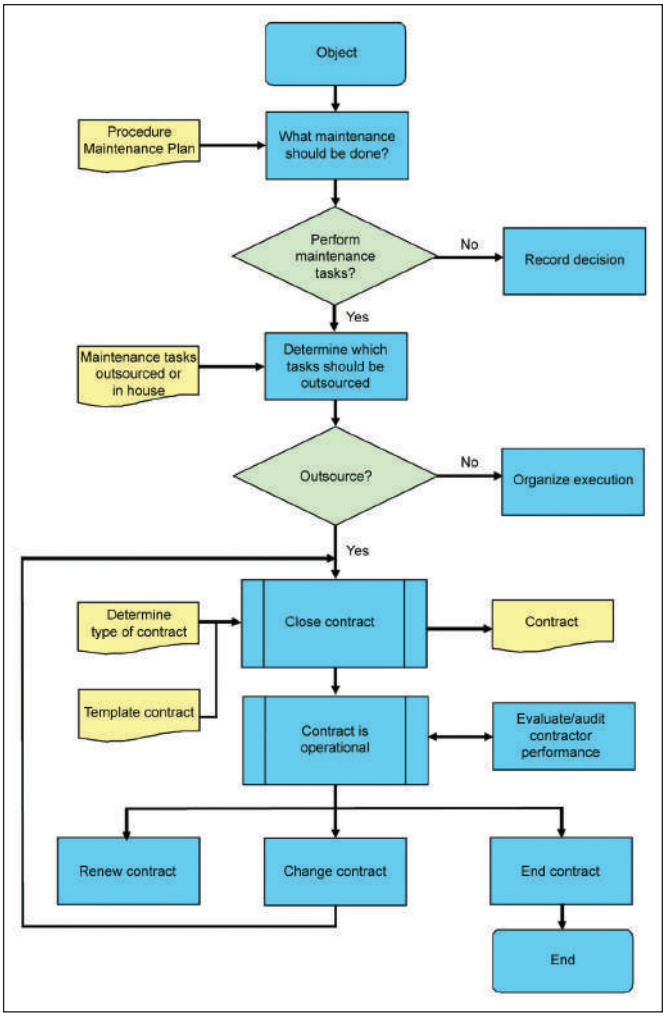

Figure 1. Charting the process steps makes responsibilities more clear.

Another important aspect of the policy is how the roles and responsibilities change in the own organization. This is an aspect that is often forgotten within companies during the outsourcing of maintenance.

Setting Up the Contracts

Once the policy was written, the pharmaceutical company and university both decided which types of maintenance contracts were suitable for outsourcing its maintenance and how they should be managed.

The pharmaceutical company decided to keep working with many different service companies in service contracts, sometimes including repairs - *Table A*. The reason for this was that a lot of the equipment was very specialized. If a main contractor had been chosen, he would have needed to subcontract all the actual work to the specialized service companies anyway.

The university decided on a completely different strategy. It decided to outsource all of its maintenance to one main contractor. Most of the equipment was not critical and not specialized so the main contractor would be able to perform most of the work with its own personnel. Outsourcing all the work to one single company made all the administrative tasks much simpler and would give benefits of scale, such as having technicians on location full time. It also would give an opportunity to a contractor to bring new ideas, methods, and process improvements. Contractors were actively motivated to do so. The readiness of the contractor to do so was one of the criteria the university used to select a contractor. The bidding companies were asked to write a plan on how they would approach this subject.

To be able to handle 140 contracts more efficiently and more securely, the pharmaceutical company studied the whole lifecycle of a maintenance contract carefully. Figure 1 shows a simplified version of this process.

This process runs from the first initiative to outsource some maintenance or to install a new piece of equipment via the signing of the contract, through start up phase and operational phase to ending the contract.

Looking closely at what needed to be done in each phase of the life of a contract, it became clear that during each phase another department should have the main responsibility for this phase. This way, the process and responsibilities became very clear to everyone.

Before this, there was a lot of uncertainty. For example, the contract manager also was dealing with some of the commercial aspects of the contracts. Now only the Procurement Department is handling those.

This clarity proved to be a critical factor in simplifying the whole process and securing the quality of the work.

For the managing of the contract, the company decided to use the philosophy of the Deming circle with its *plan, do, check,* and *act* steps - *Figure 2*.

Sign the contract (plan, by the Procurement Department), operate the contract (do, by the Maintenance Department), evaluate the contract (check, by the Contract Manager), improve the contract (act, all).

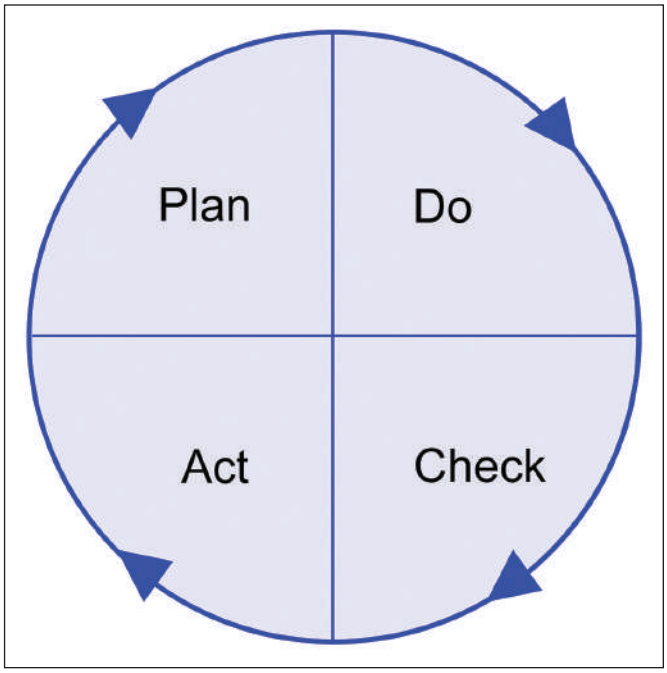

Figure 2. The Deming Circle.

To be able to manage these contracts more efficiently, the company wanted to set up a standard contract with standard clauses for every company that came to work at the company.

Before there were many different contracts. In practice, each outside service company brought his own standard terms and conditions and if they were found reasonable, the company accepted. This does not mean that the contracts were not studied carefully before, but it does mean there were many different contracts. Because of this, it became very difficult for everybody to keep track of all the agreements with all companies. In case of a breakdown, for example, it took the maintenance technicians of the company too much time to find the contract, read it, find the conditions of service, and telephone numbers of helpdesks before they could call a company for help.

The company felt this could be done much more efficiently. So together with the consultant, it set up standard contracts where every contractor worked under the same conditions. Also, the layout of all the contracts is the same so it's very easy to find what you are looking for in a contract.

The contracts not only describe the commercial and technical aspects of the agreements between the company and the contractors. The standard contracts proved to be an excellent opportunity to also make clear all the relevant safety and quality procedures. This can range from general safety rules to access rules for a certain department, specific safety instructions or specific training needed for a production facility. This way, by signing the contract, the contractor commits himself to following up on these procedures.

All relevant contacts and telephone numbers of both parties are included in the contracts; so in case of a problem, it is very clear who to call.

Another issue turned out to be the "small print" of the contract. Terms, such as travel expenses for service technicians, were very different from company to company. Most companies charged per kilometer driven, but some also charged the travel hours, over time, etc. These conditions were never very well known to anybody.

A very important chapter in each contract is an exact specification of what a contractor is supposed to do on a piece of equipment. Companies cannot get away with: "Well, we'll just do the annual check up. You know, the usual stuff."

Even though in many cases the equipment is very specialized and the supplier is the actual expert who is best suited to prescribe the maintenance needed, he must include it in detail in the contract. This makes it much easier for the maintenance staff to check if the work was actually done according to contract and to check the quality of the work. It also prevents mistakes. Now it is clear to everybody who has to do what.

Responsibilities, quality standards, safety standards, contact persons, access to the site, etc., are now all standard in the contracts.

At first, the company was afraid that the service companies would offer a lot of resistance in accepting the new contracts and conditions. For them, it would work the opposite way; they would have to let go of their standard contracts and accept that the company had its own templates.

Much to the surprise of everyone, most companies were very happy to come and discuss the new contracts. As one spokesman said, "this is an opportunity for us to really come to a good understanding with our customer of what the company really needs." They also really saw it as a benefit that all the terms and conditions were clear to, and fully embraced by, their customer. "If all companies would study their contracts so well, it would save us a lot of discussion afterward," a service manager of a company stated.

The main reason that contractors were willing to accept the new standard contract was that the templates were written in cooperation with some contractors. The goal was not to write a unilateral contract that would only take into account the interests of the company. The goal was to make clear mutual agreements and to have the maintenance done on time, the correct way.

The issue that led to most discussions with contractors was the extent of their responsibilities in case of damage. Like many companies, the company would like to hold the companies responsible without any financial limit. However, the contractors cannot accept this. Under most western laws, they are not responsible for consequential damages and further, their insurance will not cover it.

Once the standard contracts were written, a special software tool was built to manage all of the contracts. With this tool, all people concerned within the company could access the contracts swiftly at all times. This means that the breakdown technicians were not the only ones who could easily access the contracts to find out who is doing what maintenance and how to reach them. It also means that, for instance, the Contract Manager and Procurement Department have easy access to the contracts.

The university had to deal with other practical issues. They had only one contract, but outsourced much more work. The first issue was how outsourcing the maintenance tasks would impact the organizational structure, workload, and morale of its own maintenance personnel. The university did not want to cause social disturbance. It did not want to lay off people. It also had a backlog in the maintenance work. Therefore, it decided to keep the organizational structure about the same it was before. They outsourced only the maintenance on about 50% of their buildings, usually the larger, newer buildings. Their own workforce would keep working in the hundreds of (sometimes centuries old) smaller buildings in the inner city. In these buildings, it takes a lot of time simply learning to find your way around and there are many technical details not described in the drawings of the equipment. So, here their own workforce had an advantage. Some of its own employees were given other tasks in improvement projects, others were working on reducing the backlog. In a few years time, many of the technicians will retire. This will lead to a natural reduction of its own workforce, making it possible to outsource more buildings.

Another important issue was how to communicate all the details of maintenance, such as the technical details of break downs, hours spent on maintenance tasks, and the details of

ex-scope work. It was decided to set up a database, in which the contractor would directly report. He sends one monthly invoice instead of hundreds of small invoices and paper work orders.

In most cases, when outsourcing of maintenance fails, the company outsourcing the work agrees that they are just as much to blame for the failure as the contractor. Failure can come in many different forms. Two contractors had recently terminated their contract with the university, because they were loosing money on the contract. In other cases, outsourcing leads to a knowledge drain. A lot of the know how of equipment is not documented. It is in the heads of the people performing the maintenance. In some cases, this has led to long breakdowns, because the technicians were not familiar with the equipment. Other organizations complain about the amount of extra invoices for ex-scope work. They expect maybe five or 10% of extra costs on a performance contract and in practice it turns out to be 100% extra costs. One of the reasons for this is that many performance contracts only specify a percentage of uptime for the equipment. This means solving problems like small leakages, damaged insulation, cleaning the working area, etc., are not in the scope. Therefore, companies also should specify demands such as maintaining the general condition of the equipment and buildings or customer satisfaction.

Follow Up

On a regular basis, the pharmaceutical company evaluates all contracts. The company was already doing this, but life was made much easier. The consultant developed a simple tool in MS Excel to facilitate this evaluation. The tool contains a number of questions relevant to each type of contract. It consists of very concrete questions that will lead to a judgment of the contractor. Each question is multiple choice with five possible answers, ranging from one point to five points. The answers usually range from "never" to "always." Some examples of questions are: "Does the contractor actually perform the work?" "Is the quality of the work satisfactory?" or "Did the employees of the contractor leave a tidy workplace behind?" All together there are about 100 questions.

The numbers of the questions correspond with the relevant articles in the contracts. This was easy to achieve, because the contracts are standard now. The benefit is that if somebody wants to fill out the questionnaire, he or she can very easily look up in the original contract and see what was exactly agreed upon.

The evaluation is done yearly in principle by a team consisting of representatives of the Production Department operating the equipment, the Maintenance Department, Technical Procurement, and the Contract Manager. The Contract Manager is the person in charge of the whole process. They get an automatic notification if a contract is up for reviewing or evaluation. They can call together a team to do the evaluation.

The company has a few contractors that are on site almost continuously. These people are treated just like the company staff. This means that they get the same training and updates as the people who are actually on the company pay roll. This can concern safety procedures, but also Standard Operating Procedures concerning many other fields. All the others will be managed according to the new system.

The new system turns out to have a number of benefits. It is not fully implemented yet and not all the contracts are signed, but still a number of benefits are already becoming clear.

First of all, the new system saves a lot of time in looking for the exact content of the contracts. The quality of the work is also easier to manage. It is now very clear when a contract should be renewed, who is responsible, and what the contractor should do for its money. Also, the contracts are being evaluated, which improves quality.

The costs of contracts and invoices for out of scope work are dropping. One reason for this is that the scope is clearer to everybody. Another reason is that there is no small print anymore. Travel expenses, overtime, administrative costs, etc., are all very clear. In out of pocket expenses, the company expects a five to 10% reduction in costs.

Also, new agreements were made with the production departments on how to plan and communicate when an outside company is coming to work on the equipment. In the past, production employees sometimes complained that they did not know in enough detail who was coming and what they were doing on the equipment. Now the contractors bring a standard work order with them to the Production Department. In a standard layout, this clearly describes the content of the work. When the work is finished, it is always reported to a designated production employee.

The goal of the project was not to reduce the number of contracts. In many companies, it has shown that this may reduce management costs of the contracts significantly. Because the contracts and its contents are now much clearer, the company now has the possibility to combine some of the contracts into one single contract, which will reduce the costs further.

Lessons Learned

A company that wants to outsource maintenance also should have a clear policy first. This should describe why the company wants to outsource in the first place, what the goals of outsourcing are, and what types of outsourcing are appropriate.

Describing the whole process of outsourcing and managing the contracts in detail turned out to be very helpful in increasing efficiency and making responsibilities clear. Without this clear overview, it would never have been possible to set up a good system.

The company must have a good understanding of its equipment and the failures and settings of the equipment. Also, the company has sufficient knowledge of technology in general and of maintenance management. Without this knowledge, it will have to depend 100% on outside companies and those will not be able to discuss issues with the company on the right level.

Stay in control. A lot of companies sign contracts that are

set up by contractors, without knowing enough commercial or technical details of the contracts. Setting up your own contracts works, for both parties.

In the end, the owner of the equipment will always stay responsible. You cannot outsource that.

References

1. Deming, W. Edwards, *Out of the Crisis,* 9th print, MIT Center for Advance Engineering Study, Cambridge, MA, pg. 88.

About the Author

Martin van den Hout, CMRP, studied mechanical engineering at the University of Technology of Eindhoven, where he graduated in 1989. Since then he has been working in the field of maintenance and reliability. He started his career at a then brand new production plant of Fuji Photo and Film in the Netherlands. At Fuji, he learned a lot about the Japanese approach of maintenance and production according to the quality standards of the photographical industry. After working for Fuji for five years, he became Maintenance and Engineering Manager at one of the production facilities of BP Special Chemicals in the Netherlands. In the six years he worked at BP, the production was increased largely and maintenance costs, downtime, and other losses were reduced to a minimum. Since 2001 van den Hout has been a consultant in the field of asset management, maintenance and reliability, working for Egemin Automation as Senior Managing Consultant. He has worked in many companies in the pharmaceutical industry as well as in the food and chemical industries. He is a former member of the board of the Dutch Maintenance Society and has written several articles on the subjects of maintenance management and engineering. He can be contacted by email: martin.vandenhout@egemin.nl.

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ISPE Leaders Express Concern for Japan

Editor's Note: The following messages were published on the ISPE Web site immediately following the tragic events in Japan.

A Message from Andre Walker, ISPE Board Chair 2011

On behalf of the leadership of ISPE, I wish to extend our sincerest sympathy to all ISPE Members in Japan following the tragic earthquake and tsunami that is affecting so much of your country. Our thoughts are with all our Japanese colleagues in this sad and difficult time. We understand the scale of the loss, the immense task now in front of you, and the pain that must be in your hearts. Our prayers are for strength and courage in the people of Japan as you work together to overcome this tragedy. The ISPE family stands at your side.

• • •

A Message from Bob Best, President and CEO

I cannot find the words to properly describe how concerned we all are about all of ISPE's Members living and working in Japan. The events of the past week are horrific. We feel pain when we watch the news reports about the tsunami. We fervently hope that none of our Japan Affiliate Members have suffered loss of loved ones or friends.

I know how much work goes into the preparation of a major event, especially one so special as the Japan Affiliate's 10th Anniversary Annual Meeting. We are sure it was both difficult and disappointing to make the decision but it is definitely the correct one under the present circumstances. As always our colleagues in Japan have done their best but the recent events are beyond anyone's control.

The necessity of canceling the Japan Affiliate's 10th Anniversary Annual Meeting should not and does not lessen the Affiliate's great achievements over the past decade. From its start the Japan Affiliate has been a benchmark for other Affiliates. All of ISPE's Members in Japan can take great pride in what has been done and what the Affiliate will soon continue to do. I look forward to being there in person when you can properly celebrate in the months ahead.

Please let us know if there is any way we can assist you. You will remain in our prayers and in our hearts.

Message from Tatsuro Miyagawa, Chairman of the Japan Affiliate, and Toshio Omori, Chairperson, Organizing Committee, 10th Anniversary Annual Meeting

To all of the ISPE Related People,

On behalf of the Japan Affiliate, we would like to express our sincere appreciation for your sympathies as well as letters of encouragement. At the same time, we pray for those who suffered serious loss while traveling in Japan or working here on business trips.

As the days go by since March 11, we are being told of even greater numbers of lives lost as well as injured among the Japanese people, and physical damage to companies. Moreover, a nuclear power station, as one of our most important infrastructures, was seriously damaged by the tsunami and we are still facing great danger despite the massive efforts made by the related people.

Under this extraordinary situation, the Japan Affiliate has decided to call off the Annual Meeting April 12 to 16. We believe that it is our priority to concentrate our efforts on the duty to help reconstruct and restore as soon as possible the affected areas of Japan. We also recognize that this is part of our very important responsibility as members of pharmaceutical-related community.

We do indeed regret having to announce the cancelation of the Annual Meeting, for our speakers and all of the people who have been involved in the preparation for this special event, but most of all for those who had already registered to join this most special event in the Japan Affiliate yearly calendar.

Finally, we wish for you to understand that the Japan Affiliate deeply appreciate your understanding of our decision. In the meantime, we will be doing our best for the robust growth of Japan by this time next year in 2012.

We thank you again for your kind support and understanding during this extremely challenging time.

FDA on Final Process Validation Guidance: Focus on Concepts, Not Terminology

by Rochelle Runas, ISPE Technical Writer

"Focus on the concepts and not the terminology" was a recurring directive from the FDA in a presentation on the final *Guidance for Industry – Process Validation: General Principles and Practices* (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf) at the ISPE 2011 Tampa Conference.

ISPE 2011 Tampa Conference attendees in February were the first to hear direct from the FDA the agency's thinking behind the final guidance. The guidance, published 25 January 2011, replaces the 1987 guidance. Industry has been anticipating the final guidance since a draft of it was released in 2008 to mixed reviews and interpretations.

"Don't get hung up on terminology, get hung up on the concepts," said Grace McNally, Senior Policy Advisor, FDA CDER Office of Compliance, Division of Manufacturing and Product Quality. McNally presented "Process Validation: Lifecycle Approach" as part of the ISPE educational session, "Pharmaceutical Inspections and Compliance – Current FDA Enforcement Trends."

The term "critical" was not defined in the guidance, said McNally. To further explain FDA's stance on this, McNally read straight from the guidance:

> The terms *attribute(s)* (e.g., quality, product, component) and *parameters(s)* (e.g., process, operating, and equipment) are not categorized with respect to *criticality* in this guidance. With a lifecycle approach to process validation that employs risk based decision making throughout that lifecycle, the perception of criticality as a continuum rather than a binary state is more useful. All attributes and parameters should be evaluated in terms of their roles in the process and impact on the product or in-process material, and reevaluated as new information becomes available. The degree of control over those attributes or parameters should be commensurate with their risk to the process and process output. In other words, a higher degree of control is appropriate for attributes or parameters that pose a higher risk. The Agency recognizes that terminology usage can vary and expects that each manufacturer will communicate the meaning and intent of their terminology and categorization to the agency.

The final guidance also does not include the terms: Prospective Validation, Retrospective Validation, Concurrent Validation, IQ or OQ, Tech Transfer, Critical Quality Attribute, Critical Process Parameter, and Worst Case.

The final guidance aligns process validation activities with a product lifecycle concept and with existing FDA guidance, including the FDA/International Conference on Harmonisation (ICH) guidances for industry, *Q8(R2) Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System*. Although the guidance does not repeat the concepts and principles explained in those guidances, FDA encourages the use of modern pharmaceutical development concepts, quality risk management, and quality systems at all stages of the manufacturing process lifecycle.

The goals of the final guidance are: to further the goals of the cGMPs for the 21st Century Initiative, such as advancing science and technological innovation in pharmaceutical manufacturing; to put more emphasis on process design elements and maintaining process control during commercialization; communicate that process validation (PV) is an ongoing program and aligns process validation activities with product lifecycle; emphasize the role of objective measures and statistical tools and analyses in making science- and risk-based decision making; and emphasize knowledge, detection, and control of variability.

Training of field investigators on the final guidance is underway, McNally said.

McNally also addressed industry concerns regarding a perceived expectation that FDA is no longer doing three lot applications.

"What strikes me as strange is that the criteria is the number of batches," said McNally. "It's not about the number of batches, it's about what are you looking for in those batches and that is your performance criteria. The onus is on you to scientifically come up with what those criteria are and how to meet those criteria. And that's going to be based on your product and process understanding. There's nothing wrong with three batches if you find that is the number of batches relevant to your product and process understanding. The number of lots is not appropriate for the FDA to dictate because it's going to be different for each company and product. What we were trying to avoid was the situation of a company saying "there were three lots made because it was according to routine procedure, but there were no comparisons between lots or any real analysis of data."

McNally also reviewed basic cGMP requirements [211.100(a), 211.110(a), 211.110(b), 211.160(b), 211.165(c), 211.165(d), 211.180(e), 211.42, 211.63, 211.68, and 211.84] that form the basis for the process validation guide. "If you're not complying with these basic requisites, then you might as well forget about process validation." Key GMP concepts that have been in existence for some time and McNally recommended focusing on are: process control, performance, and process and control variability.

FDA on Final Process Validation Guidance...

Continued.

"Key GMP concepts that have been in existence for some time and McNally recommended focusing on are: process control, performance, and process and control variability."

"Design well, demonstrate it works, then monitor the process."

For purposes of the guidance, process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.

"The key focus of the guide is on variation, understanding, detecting, responding, and controlling it from input through output," McNally said.

Process validation involves a series of activities taking place over the lifecycle of the product and process. The guidance, focused toward the commercial process, describes the process validation activities in three stages:

- Stage 1 – Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.
- Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

The guidance describes activities typical in each stage, but in practice, some activities in different stages might overlap. McNally emphasized that although the guidance is focused on

Concludes on page 5.

New Risk-MaPP Resources: Blog and FAQs

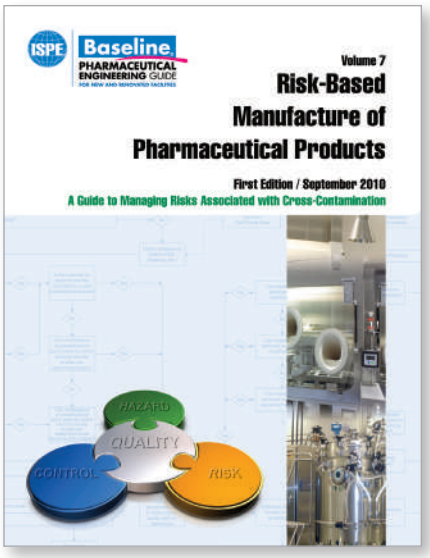
ISPE published the Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP) in September 2010. The Guide provides a scientific risk-based approach, based on ICH Q9 Quality Risk Management, to manage the risk of cross contamination in order to achieve and maintain an appropriate balance between product quality and operator safety. The Guide has generated much discussion. In response to industry needs, ISPE has set up a blog and developed an FAQ document dedicated to the issues related to the Risk-MaPP Baseline Guide.

Risk-MaPP Blog

This blog will allow industry to keep abreast of the latest regulatory thinking in regard to Risk-MaPP and managing the risk of cross-contamination as well as a forum to share experiences in implementing the principles in multi-product facilities and to seek advice and answers in the use of the Guide.

Risk-MaPP FAQs

ISPE has created an FAQ document dedicated to frequently asked questions on Risk-MaPP and its approach to managing the risk of cross contamination. The first version of this document highlights questions around limit setting which were raised during some of the launch sessions in the fall. This document will be updated as needed to include other frequent questions as they arise. This is a must have complement to your Risk-MaPP Guide.



To view these resources and others, including Risk-MaPP related conferences, webinars, Knowledge Briefs, white papers, articles, and training, visit the Risk-MaPP Resources section of the ISPE Web site: http://www.ispe.org/risk-mapp.

How Does One Become a Certified Pharmaceutical Industry Professional (CPIP) and Maintain the CPIP Credential?

by Robert Wagner

Editor's Note: This is another of several briefs to provide information about the Certified Pharmaceutical Industry Professional (CPIP) certification. Each article provides insights or useful information on CPIP certification.

The ISPE Professional Certification Commission (PCC), a governing body within the ISPE governance structure, has established an "applicant friendly" procedure to obtain the global CPIP credential. The commission has established a logical and sequential process to obtain professional certification. In a nutshell, the process begins with eligibility followed by examination.

The first step in the credentialing process is the fulfillment of the eligibility criteria. The eligibility criteria consist of three components: education, experience, and moral character.

The education requirement can be fulfilled with a Science/Technical/Engineering/Math (STEM) bachelor's or higher (or globally equivalent university degree) from an educational institution accredited by a generally-recognized accrediting body (e.g., ABET, SACS, UK Science and Engineering Research Council) plus five years of demonstrated pharmaceutical or pharmaceutical industry-related experience.

Alternatively, for individuals with a non-STEM degree, 10 or more years of demonstrated pharmaceutical or pharmaceutical industry-related experience would fulfill the eligibility criteria as well. In either case, attestation of the education degree is accomplished with the submission of an official degree awarded transcript with the application.

The demonstration of pharmaceutical or pharmaceutical industry- related experience is accomplished by providing documented evidence of Technical Knowledge, Leadership and Professionalism, Integration/Innovation/Change Advocacy, and Quality and Continuous Improvement Focus in the application. The experience documentation that is submitted with the application needs to be confirmed by a witness(es) with working knowledge of the described experience.

The education transcript, application with experience documented, attestation of moral character/abiding by the ISPE-PCC Code of Ethics and Standards of Professional Conduct and nominal processing fee are submitted to ISPE Headquarters. The submitted package of information is screened for completeness. Once the application is confirmed to be complete, the submitted experience is reviewed by the Eligibility Committee to assure that the work experience provided meets the standards of a high quality professional certification program.

After being determined eligible by the ISPE-PCC, the candidate may register for the CPIP examination. The examination covers the seven knowledge elements: Product Development, Facilities and Equipment, Information Systems, Supply Chain Management, Production Systems, Regulatory Compliance, and Quality Systems. The CPIP credential will be awarded upon successfully passing the examination.

The actual CPIP test is computer-based containing 150 multiple choice questions in British English language and is administered by Thomson Prometric through their Professional Testing Channel (PTC) global testing center network. The location of the PTC test centers can be found at www.prometric.com. Once the candidate has paid the test fee of US$300.00, the ISPE-PCC will send a conformation email containing the candidates test admissions number, test center candidate identification requirements, and instructions for contacting Thomson Prometric to schedule a date and time to take the test.

Once the Certification is confirmed, the credential is maintained via recertification to assure that the certified professional maintains industry knowledge and skills. CPIPs are required to attain no less than 15 professional development (hours) (e.g., video, e-learning, live seminars) during each renewal cycle every two years and agree to continue to adhere to CPIP's Professional Code of Conduct.

The entire process for this globally recognized professional credential can be found at www.ispe-pcc.org, as well as in the CPIP Eligibility Application and Recertification Handbooks.

FDA on Final Process Validation Guidance...

Continued from page 3.

"McNally advised that readers should consider the final process validation guidance and other guidance and use best scientific rationale to support process validation choices."

manufacturing and not product development, if approached rationally, validation must begin in the product development phase.

Regarding existing products and processes, implementation of the recommendations in the guidance for legacy products and processes would likely begin with activities described in Stage 3, McNally said.

In Stage 2, McNally said the agency did not see much of a need to clarify Facilities, Equipment, and Utilities as there is enough literature out there. (See ISPE Guidance Documents, including Baseline® as well as GAMP® Guidance, www.ispe.org/guidancedocuments.) The guidance does not specifically discuss the validation of automated process control systems (i.e., computer hardware and software interfaces), which are commonly integrated into modern drug manufacturing equipment. These topics are covered in detail in GAMP. (See the recently published GAMP Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems (Second Edition), www.ispe.org/guideancedocs/gamp-gxp-process-control-systems.)

The principles in the guide apply to all drug types, application drugs and monograph drugs. Recommendations can apply to all types of drug manufacturing and adjusted to the technical nature of the process, e.g., batch, continuous, and PAT.

In addition, the Process Validation Workgroup did not seek to sync up all aspects of the final guidance with all other agency guidance or other guidance from other regulators that speaks to process validation. The FDA also acknowledges that there are other earlier FDA guidances or from other regulators on this subject that does not exactly match with the lifecycle model. McNally advised that readers should consider the final process validation guidance and other guidance and use best scientific rationale to support process validation choices.

Regarding submissions, different centers or offices within CDER may have different policies regarding validation information to be submitted. "The application program may not specifically mention 'process control,' but you have to satisfy GMPs. You have to satisfy both."

Few audience members had questions during the Q&A portion of the session. When asked by an audience member whether the guidance applied to aseptic processing or sterilization, McNally suggested that the more prescriptive guide for a particular area should be followed. "This is not the only guidance out there on process validation," she said.

McNally asked the audience if they thought there were enough good guidances out there on product and process design. An audience member responded that it would be nice to see specific examples for Stage 1 to get an idea of where exactly to start.

In summary, McNally said you should ask yourself the following questions when considering process validation:

- Do I have confidence in my manufacturing process? Or, more specifically, what scientific evidence assures me that my process is capable of consistently delivering quality product?
- How do I demonstrate that my process works as intended?
- How do I know my process remains in control?

ISPE Announces Partnership with US Environmental Protection Agency's Energy Star Program

Sustainable Facilities Community of Practice to Spearhead Involvement

ISPE has announced that it has partnered with the US Environmental Protection Agency (EPA) on its successful Energy Star Program. Through participation in the program, ISPE aims to improve pharmaceutical industry exposure to the program and help ISPE Members identify green initiatives and drive cost savings for their companies globally.

"Sustainability and environmental stewardship have long been a part of the ISPE culture and goals," said Bob Best, ISPE President and CEO. "And helping our Members to deliver cost effective GMP solutions has always been an integral part of ISPE's mission. Therefore, the Energy Star Program is a perfect fit for us. By helping to disseminate the ideas behind the program, we hope that our Members around the globe will be more successful in improving energy efficiency throughout the industry."

The Energy Star Challenge for Industry calls upon businesses to create a five-year plan to reduce energy intensity by 10% or more. Companies that publically join the Challenge and meet the goal are recognized by the US EPA for their efforts, and gain the right to capitalize on one of the most recognizable names in energy efficiency by communicating publically that they have completed the Energy Star Challenge.

The driving force within ISPE for Energy Star information and participation will be the Sustainable Facilities Community of Practice (COP). Interested parties may join the Sustainable Facilities COP to gain information, engage in conversation, share best practices, and report progress on the Challenge. More information on the Sustainable Facilities COP can be found at www.ispe.org/sustainablefacilities. More information on the Energy Star Challenge can be found at http://www.energystar.gov/index.cfm?c=challenge.bus_challenge.

ISPE Announces Enhanced Communities of Practice Web Sites

ISPE Communities of Practice (COPs – www.ispe.org/cops) enable like-minded professionals to connect through an interactive on-line community offering global networking opportunities and access to a community-specific body of knowledge. Now, ISPE is converting its COP online communities to enhanced COP Web sites. To start the conversion, the four COPs specified below changed to the new format of the Web site, effective 18 February 2011. All other COPs will continue to use the existing online community format and will be converted to new COP Web sites during the next few months.

The development of the new COP Web sites is taking place in phases beginning with:

- Biotechnology COP (www.ispe.org/biotechcop)
- Commissioning and Qualification COP (www.ispe.org/cqcop)
- Investigational Products COP (www.ispe.org/ipcop)
- GAMP® COP (www.ispe.org/gampcop)

One of the many benefits of the new COP Web sites is the ability for COP members to easily access information about the COP and its activities by simply visiting the COP home page. To access community discussions, simply click on the "Community Discussions" tab on the left side of the COP Web site. As is currently the process, you must be a COP member and log in to the discussions to begin participating. Note that anyone can read discussions but only ISPE Members can post and respond to questions.

ISPE welcomes your feedback and any questions you may have about the new COP Web sites. Please email us at businessinitiatives@ispe.org with comments, suggestions, or questions.

Bryan Wright Named New ISPE European Regulatory Affairs Advisor

Long Time MHRA Official to Offer Insight, Guidance

Bryan Wright joined ISPE as European Regulatory Affairs Advisor, effective 1 April 2011. In his new capacity, Wright will act as liaison between ISPE and European regulatory authorities to help expand relationships between regulatory bodies and ISPE, shape ISPE educational offerings, and keep ISPE Members informed of relevant regulatory developments originating from European regulatory authorities.

"We are extremely fortunate to add Bryan Wright to ISPE's strong regulatory team," said Bob Best, ISPE President and CEO. "Bryan's 22 years of regulatory experience will be invaluable to ISPE as we continue our mission to help our Members facilitate global GMP solutions that will bring the pharmaceutical industry into the future."

Wright comes to ISPE after taking early retirement from the MHRA. He joined the MHRA as an Inspector in 1989 and for the last five years has been Group Manager for the GMP and GDP Inspectorate. As a senior manager within the MHRA, Wright had oversight of the significant growth in Inspectors in that Agency in recent years in response to regulatory demand.

Wright has previous experience in community and hospital pharmacy and holds a degree in pharmacy and a Masters in pharmaceutical sciences. Over the course of his 22 years with the MHRA, Wright has managed most areas of the Inspectorate at various times, and his regulatory career encompasses GMP, GDP, GCP, GPvP, and the GLP monitoring authority.

About his early retirement from MHRA and subsequent role with ISPE, Wright said: "I am looking forward to new challenges, including utilizing the skills and knowledge I have gained from my years in the regulatory field in my new role with ISPE."

Wright assumes the duties of the European Regulatory Affairs Advisor position from John Berridge, who will now turn his full attention to his role as Project Manager for the Society's PQLI® Initiative, as well as other strategic projects for ISPE. Wright joins Bob Tribe, Asia-Pacific Regulatory Affairs Advisor, on ISPE's Regulatory Affairs team. PE

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International

European Medicines Agency and Swissmedic Extend Confidentiality Arrangement[1]

The European Medicines Agency and Swissmedic have extended their confidentiality arrangement for a year. The arrangement allows the two agencies to continue to exchange confidential information relating to the medicines used in the context of the 2009 (H1N1) influenza pandemic.

WHO Addresses Improving Access to Generic Medicines[2]

Dr. Margaret Chan delivered opening remarks at a joint WHO/WIPO/WTO technical symposium on access to medicines, patent information, and freedom to operate. Her speech can be found at http://www.who.int/dg/speeches/2011/medicines_access_20110218/en/index.html.

New Cooperation Agreement between PIC/S and EMA[3]

On 28 December 2010, PIC/S and the European Medicines Agency (EMA) signed a new cooperation agreement by which they have agreed to strengthen their cooperation in the field of Good Manufacturing and Distribution Practice (GMDP) in areas of common interest with a view to the sharing of resources and avoidance of duplication of activities.

The cooperation will focus on the training of inspectors in the field of GMDP as well as include mutual participation to each other's meetings, exchange of information, and cooperation in the auditing of GMP inspectorates.

European Medicines Agency and U.S. Food and Drug Administration (FDA) Announce Pilot Program for Parallel Assessment of Quality by Design Applications[4]

The European Medicines Agency and the U.S. Food and Drug Administration are launching a three-year pilot program that will allow parallel evaluation of relevant quality data components, known as Quality by Design (QbD), of selected applications that are submitted to both agencies at the same time. The pilot was scheduled to begin on 1 April 2011.

QbD in pharmaceuticals involves an enhanced systematic and science-based approach to development and manufacturing to better ensure product quality. Several guidelines and question-and-answer documents have been developed by the International Conference on Harmonization (ICH) in order to facilitate the implementation of QbD. Taking into account the global perspective of pharmaceutical manufacturing, and to facilitate the harmonized implementation of the ICH concepts, the EMA and FDA agreed that experts from both agencies should exchange their views using real applications.

Under this program, both agencies will assess the parts of the applications relevant to QbD, such as development, design space, and real-time release testing. The evaluation will be performed separately by each agency with regular communication and consultation throughout the review with the aim of having a common list of questions to the applicants and a harmonized evaluation of their responses.

Asia/Pacific Rim

Australia

Australia's TGA Releases Publication on Counterfeit Medicines[5]

The Therapeutic Goods Administration released a publication defining counterfeit medicines and devices, risks associated with counterfeit products, what products are counterfeited, the role of the TGA, and how to report suspected products. The publication can be found at http://www.tga.gov.au/consumers/advice-medicines-counterfeit.htm.

Submissions to Australia's Call for Input: Review to Improve Transparency of the Therapeutic Goods Administration (TGA)[6]

The purpose of this paper is to provide stakeholders with early information on the opportunity to contribute to the transparency Review of the TGA. On 16 November 2010, the Parliamentary Secretary for Health and Ageing, the Hon. Catherine King MP, announced a comprehensive review of the way the TGA communicates its regulatory processes and decisions. This is consistent with the resolve of the Gillard Government to ensure that the Australian public is better informed about the benefits and risks of therapeutic goods, including all medicines and devices, and to address community concerns that have been raised about the lack of information made available by the TGA.

China

China's SFDA Publishes Good Manufacturing Practice for Pharmaceutical Products (2010 Revised Edition)[7]

The Good Manufacturing Practice for Pharmaceutical Products (2010 revised edition) (hereinafter referred to as the new version of GMP) was recently issued and came into effect as of 1 March 2011 after five years of amendments and two rounds of public consultation.

Since its first promulgation in 1988, China's Good Manufacturing Practice for Pharmaceutical Products (GMP) has experienced two revised editions respectively in 1992 and 1998. The new version of GMP consists of 14 chapters and 313 articles with high increase of length compared with the 1998 revised edition. Borrowing advanced international experiences and in light of the actual conditions of China, under the principle of attaching equal importance to the "software and hardware," the new version of GMP follows the concepts of quality risk management and whole process control of drug manufacturing, attaches more importance to the scientific nature, instruction function, and maneuverability so as to be consistent with the WHO GMP.

WHO: Chinese National Regulatory Authority Meets International Standards[8]

A WHO-led team concluded at the end of a comprehensive review by experts from six countries, that the national regulatory authority of China, the State Food and Drug Administration (SFDA), and affiliated institutions meet WHO indicators for a functional vaccine regulatory system.

New Zealand

New Zealand Launches New Medicines Monitoring Scheme[9]

This is a new medicines monitoring scheme, the aim of which is to highlight *potential* safety issues identified from reports of *suspected* adverse medicine reactions sent to the Centre for Adverse Reactions Monitoring (CARM), stimulate further reports, and increase the information on these potential safety signals.

Europe

European Union

New version of EudraGMP Allows Access to Information from All Member States[10]

The European Medicines Agency has launched a new version of its EudraGMP database giving the general public access to information on manufacturing inspections performed by regulatory authorities from all European Economic Area (EEA) countries.

EudraGMP, which was first launched in May 2007, contains information on all manufacturers of human and veterinary medicines located in the EEA, and other manufacturers outside the EEA that have been inspected by European regulatory authorities. It includes details of the manufacturers' manufacturing and importation authorizations and Good Manufacturing Practice (GMP) certificates.

The latest version of the database allows public access to the authorization and GMP certificates coming from all countries in the EEA, including all European Union (EU) Member States plus Iceland, Liechtenstein, and Norway. Previously, limited information coming from only some European countries was available to the public.

European Medicines Agency Sets Out Work Priorities for 2011[11]

The European Medicines Agency will focus on preparing for the implementation of the new pharmacovigilance legislation during 2011, while continuing to carry out its core business efficiently and effectively, according to the work program 2011.

The work program states that the pharmacovigilance legislation, which comes into force in 2012, will have a major impact on the Agency's work, and that the Agency will be affected by the ongoing debate within European institutions on the upcoming falsified medicines legislation.

The document also explains that the Agency expects to see a further increase in the number of procedures it handles this year, but will remain focused on carrying out its core business of monitoring the benefits and risks of medicines. This work will continue amid the changes that the new legislative requirements will bring over the course of the year.

European Medicines Agency Announces Start of Process Improvement of Core Business Procedures[12]

The European Medicines Agency has launched a project to improve processes of its core business, as announced in its "Road Map to 2015" in January 2011. The project responds to one of the road map's objectives, namely to ensure a continuous high-quality delivery of the Agency's core business in an increasingly complex regulatory and scientific environment, while making optimal use of available resources.

Finland

Finnish Medicines Agency Announces Revised Regulation on Clinical Trials on Veterinary Medicinal Products[13]

The Clinical Trials on Veterinary Medicines regulation has been revised. The Finnish Medicines Agency (Fimea) regulation 3/2010 entered into force on 1 January 2011, replacing the previous National Agency of Medicine regulation 3/2005.

The regulation applies to all clinical trials on veterinary medicinal products performed on the approved target-species. Fimea is authorized under Section 88a of the Medicines Act to issue the regulation. During the revision process, the regulation content has been adjusted to ensure compliance with the wider legislative environment.

The scope of the new regulation will be brought under further scrutiny over the course of the coming year, as the new European Directive on the protection of animals used for scientific purposes is transposed into Finnish law. During this process, the advance notification requirement for clinical trials on animals specifically bred for use in procedures also will be revisited.

Hungary

Hungarian National Institute of Pharmacy Publishes Validation Criteria for New Applications[14]

Validation criteria for new applications can be found at http://www.ogyi.hu/page.php?item=755.

Ireland

Irish Medicines Board Publishes Strategic Plan 2011 – 2015[15]

This strategic plan sets out the Irish Medicines Board's strategic goals for the five year period from 2011 to 2015. The goals were identified following a review of the environmental conditions and relevant developments expected during the time period identified.

The plan presents a clear roadmap to stakeholders and staff showing how the strategic goals will be achieved. It was approved by the Board of the Irish Medicines Board in November 2010 following a public consultation process.

Irish Medicines Board Publishes 2009 Annual Report[16]

The Irish Medicines Board (IMB) published its annual report for 2009 which details key activities and performance highlights from the year. While maintaining its core focus of protecting public and animal health through the regulation of medicines, medical devices, and healthcare products, the IMB recorded significant increases across all its departments' outputs.

Malta

Maltese Medicines Authority Launches Starekeholder Survey[17]

The Medicines Authority proactively soliciting feedback so as to: assess its performance as perceived by different stakeholders; measure satisfaction with services; increase awareness of needs and expectations to add-value to public health and the pharmaceutical operations; and act on relevant opportunities for improvement in line with

the objectives, priorities, and resources of the Medicines Authority. You are invited to participate in our stakeholder's survey by clicking on the following URL: http://www.medicinesauthority.gov.mt/stakeholdersurvey.htm.

Netherlands

Dutch Medicines Evaluations Board Releases Statistics about its Performance[18]

In 2010, the Medicines Evaluation Board (MEB) heavily invested in putting the authorization process in order. The MEB handled and concluded more than 21,000 cases. In 2010, the activities were strongly linked to processes on a European level and the MEB invested in more transparent communication.

United Kingdom

Britain's MHRA and Others Publish Best Practice for Ensuring the Efficient Supply and Distribution of Medicines to Patients[19]

This guidance has been developed and is supported by eleven organizations, including the MHRA, following detailed consideration of the current problems with the supply chain, especially those caused by increased exports of medicines from the UK. It sets out best practice for ensuring the efficient supply and distribution to medicines to patients.

Britain's MHRA Publishes Annual Report on the Regulation of Medicines Advertising[20]

The MHRA published a fifth annual report, "Delivering High Standards in Medicines Advertising Regulation," covering the period from September 2009 to December 2010. It provides details of the activities of the Advertising Standards Unit, including vetting of advertising and complaints investigated and the development of guidance with self-regulatory bodies to promote high standards.

North/South America

Canada

Health Canada Publishes Quality System Framework 2011[21]

Quality System Framework (QSF) outlines a quality system approach for compliance and enforcement activities shared by Health Products and Food Branch (HPFB) and Regions and Programs Branch (RAPB) of Health Canada. This quality system, under the mandate of the Health Products and Food Branch Inspectorate (HPFBI), was developed and implemented to ensure strong functional linkages, fairness, consistency, and a high standard for quality in all Inspectorate program activities.

Health Canada Finalizes Good Manufacturing Practices (GMP) Guidelines 2009 Edition, Version 2 (GUI-0001)[22]

Version 2 of the present edition of this document includes recent regulatory amendments to Part C, Division 2 (GMP) of the Food and Drug Regulations, clarification of existing requirements, and the new interpretations pertaining to crimping requirements (C.02.029 Sterile Products, Interpretation 80.11).

USA

US FDA Announces Medical Device Innovation Initiative[23]

The Innovation Initiative supports the development of innovative products by addressing some of the barriers that can impede a product's timely progress to market. The Medical Device Innovation Initiative proposes actions CDRH could take to help accelerate and reduce the cost of development and regulatory evaluation of innovative medical devices safely and based on sound science. These actions include: facilitating the development and regulatory evaluation of innovative medical devices; strengthening the U.S. research infrastructure and promote high-quality regulatory science; and preparing for and responding to transformative innovative technologies and scientific breakthroughs.

US FDA Publishes MAPP on Applying ICH Q8, Q9, and Q10 Principles to CMC Review[24]

This MAPP outlines and clarifies how the Chemistry, Manufacturing, and Controls (CMC) reviewers in the Office of Pharmaceutical Science (OPS) should apply the recommendations in the ICH Q8(R2), Q9, and Q10 guidances to industry.

US FDA and Georgetown University Medical Center Announce Partnership[25]

The U.S. Food and Drug Administration and Georgetown University Medical Center (GUMC) announced a new partnership to stimulate innovation in regulatory science, ethics, education, and training. The partnership enhances the capabilities of both institutions to meet their common goal of improving public health.

Terms of the partnership are spelled out in a Memorandum of Understanding that supports a range of new activities including: joint research and public health activities in areas such as novel technologies, public health preparedness, ethics, and bioinformatics; joint mentorship of doctoral and post-doctoral students in collaborative research relevant to FDA's mission; scientific staff exchanges and professional development opportunities, including selected FDA staff serving as adjunct faculty in teaching and clinical activities at GUMC and selected GUMC staff participating in research and other activities with FDA; and shared access to and development of important training and continuing education activities.

US Supreme Court won't review drug patent deal[26]

The Supreme Court let stand a ruling that drug companies can pay rivals to delay production of generic drugs without violating federal antitrust laws.

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Practical Application of Quality Risk Management to the Filling Process of Betamethasone Injections

This article presents risk analysis performed on the Betamethasone Injections filling process and the conclusions obtained from the analysis.

by Rodolfo Díaz, Germán Fernández Otero, and Cristian Muzzio

Introduction

In the last years, the pharmaceutical industry has begun to incorporate the new paradigm promoted by the US FDA through the risk management/Quality by Design (QbD) approach:[1-3] "Quality cannot be tested into products; it should be built-in or should be by design." To ensure that quality is built into pharmaceutical products, the most up-to-date technologies and concepts of risk management should be incorporated into the manufacturing process. As part of this new approach, work was performed to evaluate the filling process of Betamethasone Injection in order to reduce its associated risks, where *risk* is understood as "the combination of the probability of occurrence of harm and the severity of that harm."[2] In addition, is the aim of the present work to illustrate the application of different Risk Management tools and the permeability of the local pharmaceutical industry to these ideas.

Betamethasone (BTM) is a powerful glucocorticoid used in the treatment of diverse allergic and inflammatory pathologies. It is available in different pharmaceutical forms like tablets, drops, ointments, creams, and injections. In this last case, soluble or insoluble derivatives of BTM or the combination of both can be used according to the desired therapeutic effect. Soluble derivatives of BTM (i.e., betamethasone sodium phosphate) are used when a fast effect is required whereas insoluble derivatives (betamethasone acetate or betamethasone dipropionate) are used when a depot effect is needed. Several works[4-6] have been devoted to this drug due to its properties and applications. BTM dipropioniate and acetate are practically insoluble in water, thus forming in this medium a white suspension that settles fast. The Stokes' law drives the speed of the settlement. This means that the viscosity of the medium, the density of both medium and particle and the particle size, have strong influence on the settlement rate. Due to formulation requirements, medium should be aqueous so density and viscosity could not be significantly changed. Particle density is a fixed attribute of the drug. Particle size is defined considering therapeutic requirements: particle should not be too fine since this could reduce the extent of the depot effect and should not be too coarse since irritation in the application area may occur. Normally, an average Particle Size Distribution (PSD) between 5 to 10 microns is suitable.

During the filling process of BTM suspension into vials, the suspension is contained in an agitated tank. Due to the fast sedimentation of the water-insoluble BTM, an inappropriate medium agitation leads to an inhomogeneous distribution of BTM in the vials that can adversely affect the quality of the final product. While a too low agitation speed would result in an accumulation of BTM in the bottom of the tank because of sedimentation, a too high agitation speed would produce an increment in the concentration of BTM near the walls of the tank. Furthermore, if the tank stirrer stops for a short period of time, the concentration of BTM in a few vials might reach unacceptable values, and these values could not be detected in a classic quality control because of the statistical nature of the sampling process.

Due to the aforementioned difficulties related to the filling process of BTM and the high risk of producing a poor quality product, a risk-based analysis was performed to improve the understanding of the filling process and reduce its associated risks. As a consequence of the risk

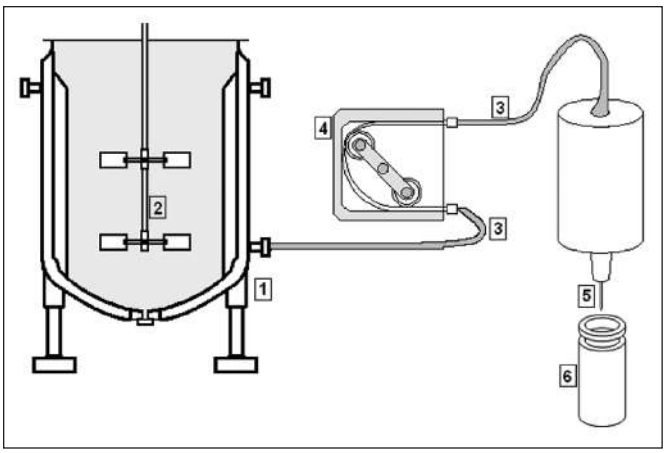


Figure 1. Schematic illustration of system setup: 1. tank 2. tank stirrer 3. silicone tube 4. peristaltic pump 5. filler nozzle 6. vial.

analysis application, a new device for in-line monitoring of the process was developed. The description and features of this device would exceed the scope of the present study so they will be described in a future work.

Betamethasone Filling Process

The filling system mainly comprises a tank, a peristaltic pump, a filler nozzle, a silicone tube, and a tank stirrer - *Figure 1*. A recirculation circuit is also present, but not shown in Figure 1. At present, the stirrer speed is manually controlled by an operator. After the suspension has been homogenized in the tank, it is impelled through the silicone tube toward the filler nozzle, where a pre-calibrated volume of suspension will fill the vials. The vials are filled every time they are under the filler nozzle. The release of suspension from the valve is automatically controlled by a mechanical switch. It is clear that speed of agitation and height of the suspension in the tank are critical factors that could adversely affect the final quality of the product. Since the process is not fully monitored and automated, several sources of risk arises (human failure or lack of training are among the sources to consider). The risks include the modification of product attributes (like uniformity of dose) up to unacceptable values. A large part of these modifications might not be detected in the final quality control of the product performed in the laboratory, due to the statistical nature of the assays and the short-term variability that can take place in the process conditions (e.g., short variations in the stirrer electrical power supply), which could affect few vials in the batch. Therefore, an analysis of the filling process through the Failure Mode, Effects, and Criticality Anaylsis (FMECA) tool was carried out to increase the understanding of the process and reduce its variability and possible risks.

What is FMECA?

Failure Mode, Effects And Criticality Analysis (FMECA[7,8]),

Unit Operation: Filling		
Critical Quality Attributes	**Description**	**Commentaries with respect to the influence during the filling process**
Aspect	NA	This parameter is visually evaluated in the primary container. It does not allow to distinguish slight modifications in the insoluble API concentration.
Identity	NA	This parameter is not modified by changes in the insoluble API concentration.
Filling Volume	A	This parameter is modified by inappropriate dosification or air addition in the suspension.
Potency (due to difference in the insoluble API titre)	A	This parameter is modified by sedimentation of the insoluble API.
Potency (due to stability)	NA	Stability studies demonstrated stability at normal atmosphere and light. Therefore, Nitrogen inertization or light protection is not required.
Impurity (incorporated during the process)	AEC	Available cleaning validation, routine verifications. Process which does not generate stress on the product.
Content Uniformity	A	This parameter is modified by sedimentation of the insoluble API.
Osmolarity	NA	This parameter is not modified by changes in the insoluble API concentration.
Density	NA	This parameter is not affected by slight changes in the insoluble API concentration.
pH	NA	This parameter is not affected by slight changes in the insoluble API concentration.
Related Substances (due to stability)	NA	Stability studies demonstrated stability at normal atmosphere and light. Therefore, Nitrogen inertization or light protection is not required.
Sterility/Microbiology	AEC	The aseptic filling process is performed in a class 100 classified area, qualified and with a routine of ambient, personnel, and surfaces monitoring. Validation of aseptic process and qualification of sterilized equipment is available.
Pyrogens	AEC	The aseptic filling process is performed in a class 100 classified area, qualified and with a routine of ambient, personnel and surfaces monitoring. Validation of aseptic process and qualification of sterilized equipment is available.
References	NA	Attribute not affected by the filling process, based on process comprehension and previous knowledge.
	AEC	Attribute affected by the filling process. Effects reduced by means of an existing control strategy.
	A	Attribute affected by the filling process. High potential risk.

Table A. Critical Quality Attributes and the influence on the filling process.

		Criterion	Examples and Related Notes
Severity			
Low	L	Therapeutic action or product safety is not affected.	Appearance differences (slight difference in color)
Medium	M	Product quality defects that do not compromise product safety. Efficacy might be affected.	Appearance is affected. Product does not meet organoleptic specifications.
High	H	Defects that compromise product safety and therapeutic action. Serious and permanent secondary effects on patient's health may be related. Product recall is mandatory. Container integrity is compromised.	Product contaminated. Stability affected. Dose higher or lower than required.
Probability			
Low	L	Less than once every twenty batches	N/A
Medium	M	Once or twice every twenty batches	N/A
High	H	3 or more times every twenty batches	N/A
Detectability			
Low	L	Defect needs a specific laboratory assay to be detected.	There is no associated alarm, there is no continuous monitoring. The deviation might not be detected by Quality Control.
Medium	M	Defect does not need a specific laboratory assay to be detected, but cannot be detected by visual inspection on the product.	There is an alarm indirectly associated to the deviation. The deviation can be observed in a record. There is an indicator that can be seen by an operator. The deviation might be recognized in the process documentation.
High	H	Defect can be detected by visual inspection on the product.	There is an alarm directly associated to the deviation. There is continuous monitoring.

Table B. Definitions of severity, detectability, and probability of occurrence levels.

an extension of FMEA, is a methodology developed to detect and analyze potential failure sources for products or process, which includes the identification of the potential failure mode and its causes, the evaluation of the associated risks (criticality or severity), and the definition of mitigation strategies. Originally designed in the late '40s for military purposes,[7] this technique has been widely spread among different industries including aeronautics and space, military, and commercial. Although FMECA is one of the most used reliability analysis methodology in the initial stages of the process or product development, it also can be employed to introduce modifications in preexisting processes or products and to analyze the future potential impact of such modifications. FMECA comprises a series of steps that can be summarized as follows:

- Define the system boundaries and the critical aspects to consider.
- Conform a multidisciplinary group.
- Collect data and information related to the critical aspects to consider (e.g., charts, manuals, reports, functional descriptions).
- Define the criteria associated with the different levels related to rate, detectability and severity of failure.
- Generate a FMECA worksheet, which includes the following columns: failure mode (hazards), failure causes, failure consequences, failure detectability, failure severity, failure rate, and mitigation strategies.
- Complete the FMECA worksheet by making use of analyst process comprehension and previous knowledge.
- Consider applying the FMECA again to analyze risks added from the application of mitigation strategies.

The development of these steps is depicted in the following section.

Process Analysis and Risk Control

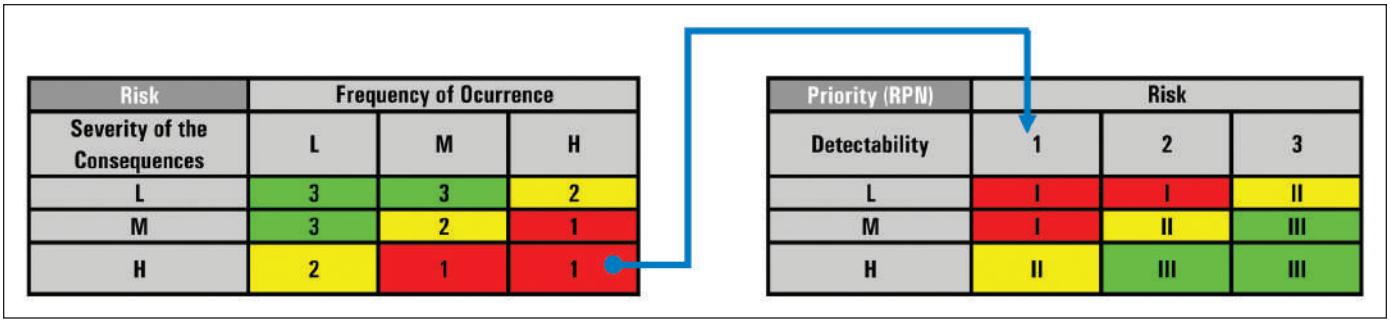
The analysis of the BTM filling process was performed by a multidisciplinary team comprised of qualified personnel from different sectors of Química Montpellier S.A. (i.e., Galenical Development, Analytical Development, Quality Assurance, Maintenance, and Technical Direction), along with R&D personnel from Hitec S.R.L. The diversity of approaches proved very valuable, as can be seen from the conclusions extracted. The risk-based analysis of the BTM filling process considered the following:

- Objective: risk reduction of the BTM filling process.
- Scope: filling process including tank stirrer, filler nozzle, and in-line monitoring equipments.
- Risks: limited to the quality risks related with the patients' health.
- Data Collection: manufacturing records, volume control records (registered during the filling process), equipment qualification reports, equipment manuals, calibration reports of pump and tank stirrer, reports on product composition, analysis methods, stability studies, deviations, complaints.

The risk assessment of the filling process was divided in to "Risk Identification," "Risk Analysis," and "Risk Evaluation."

Risk Identification

Focused on the identification of hazards, and its possible causes and consequences,the risk identification step did not



Risk	Frequency of Ocurrence		
Severity of the Consequences	L	M	H
L	3	3	2
M	3	2	1
H	2	1	1

Priority (RPN)	Risk		
Detectability	1	2	3
L	I	I	II
M	I	II	III
H	II	III	III

Table C. Definitions of risk and RPN levels.

consider probability of occurrence nor severity. Table A shows the Critical Quality Attributes (CQAs) of the product and the grade in which each CQA is affected by the process. A short commentary that relates the attribute and process conditions is also included. As a conclusion, three CQAs were identified as potentially affected during the filling process, i.e., the CQA that should be analyzed according to the scope of the present work: filling volume, potency (due to difference in the insoluble API titre), and content uniformity. In the present risk assessment, both content uniformity and potency are considered, owing to the greater difficulty in reducing their Risk Priority Number (RPN). Conversely, RPN related to filling volume can be readily reduced by improving detectability in a non-invasive way. Hence, filling volume is not further considered in this study.

Risk Analysis

In the present work, risk analysis was considered as defined in ICH Q9,[2] i.e., "the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative

N°	Identification of Hazards and Scenarios		Causes of the Hazard	Consequences of the Hazards	Harm (limited to patients)	Freq	Sev	Risk	Det	RPN
1	During the filling process, the tank stirrer speed is very low, or the stirrer is even stopped. The operator does not detect the failure.	A	Stirrer stops due to failure in the electrical supply.	The product settles in the tank. As a consequence, the concentration uniformity of the insoluble API is modified.	Lack of therapeutic effectiveness or overdose (depending on the filling step).	M	H	1	H	II
		B	Stirrer stops or its speed decreases due to failure in stirrer.			L	H	2	L	I
		C	Low stirrer speed due to value incorrectly set, because of human failure or lack of training.			L	H	2	L	I
2	During the filling process, the tank stirrer speed is very high. The operator does not detect the failure.	A	stirrer speed increases due to failure in stirrer.	The foreseen dose is modified due to addition of air in the suspension and adsorption of solids by surface tension to the air bubbles (it leads to solid separation). In addition, concentration of floccules near the side walls of the tank may increase due to centrifugal force.	Lack of therapeutic effectiveness or overdose.	L	H	2	L	I
		B	High stirrer speed due to value incorrectly set, because of human failure or lack of training.			L	H	2	L	I
3	During the filling process, the speed of recirculation is very low, or the recirculation is even stopped. The operator does not detect the failure.	A	The peristaltic pump stops due to failure in the electrical supply.	The product settles in the tube. As a consequence, the concentration uniformity of the insoluble API is modified.	Lack of therapeutic effectiveness or overdose.	M	H	1	H	II
		B	The peristaltic pump stops or its speed decreases due to failure in the peristaltic pump.			L	H	2	L	I
		C	Low recirculation speed due to value incorrectly set, because of human failure or lack of training.			L	H	2	L	I
		D	The recirculation tube is obstructed			L	H	2	L	I
4	During the filling process, the speed of recirculation is very high. The operator does not detect the failure.	A	High recirculation speed due to failure in the frequency inverter.	The foreseen dose is modified due to addition of air in the suspension and adsorption of solids by surface tension to the air bubbles (it leads to solid separation).	Lack of therapeutic effectiveness or overdose.	L	H	2	L	I
		B	High recirculation speed due to value incorrectly set, because of human failure or lack of training.			L	H	2	L	I
5	During the filling process, the stirrer speed is not appropriate to the height of the suspension in the tank. The operator does not detect the failure.	A	Level indicator or filled units was not verified due to human failure or lack of training.	The foreseen dose is modified because of addition of air in the suspension due to the fact that the stirrer speed is higher than the one indicated in the manufacturing records.	Lack of therapeutic effectiveness or overdose.	L	H	2	M	II
6	After a stop of 5 minutes, the operator does not discard units in a number equivalent to a volume of 100mL.	A	The instructions depicted in the product manufacturing records are not followed due to human failure or lack of training.	The product settles in the "tank-filler machine" circuit. As a consequence, the concentration uniformity of the insoluble API is modified.	Lack of therapeutic effectiveness or overdose.	L	H	2	L	I

Table D. RPN associated to different hazards, before applying mitigation strategies.

process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk." The criteria for high, medium, and low levels related to severity, detectability, and probability of occurrence have been defined and listed in Table B. These estimations are utilized in risk evaluation in order to decide the appropriate mitigation strategy and the residual risk acceptance. It is worth noting that assessment of severity is limited to potential harm to patient's health, according to the constraints imposed in the definitions. In Table C, RPN is defined and listed.

Risk Evaluation

Risk evaluation is the last step in risk assessment. Different causes can lead to undesirable CQA values. This work only considered the CQA potentially affected by deviations in the filling process (CQA qualified with "A" in Table A). These causes, their consequences on product quality, and the potential risks on patient's health are summarized in Table D. As can be readily seen, most of the items reach unacceptable RPN values according to the levels and criteria defined in the preceding section. Thus, a mitigation strategy was necessary to reduce the risk to an acceptable level. The cost-effectiveness of different mitigation were considered, always prioritizing the patient's safety.

Risk Reduction

Different mitigation strategies have been proposed to reduce the RPN, mainly focused on the detectability improvement. For example, the following strategies can be enumerated: addition of a low and high speed alarm, directly associated to the stirrer axis; addition of a low and high recirculation pump speed alarm, directly associated to the speed into the recirculating tubes (flow meter); installation of a tank level

N°	Identification of Hazards and Scenarios		Causes of the Hazard	Mitigation Strategy	Freq	Sev	Risk	Det	RPN
1	During the filling process, the tank stirrer speed is very low, or the stirrer is even stopped. The operator does not detect the failure.	A	Stirrer stops due to failure in the electrical supply.	Detectability may be increased by installing an in-line device in order to measure the suspension concentration. The device should be installed as close to the filler nozzle as possible, and it should include an alarm system to indicate deviation from the parameters.	M	H	1	H	II
		B	Stirrer stops or its speed decreases due to failure in stirrer.		L	H	2	H	III
		C	Low stirrer speed due to value incorrectly set, because of human failure or lack of training.		L	H	2	H	III
2	During the filling process, the tank stirrer speed is very high. The operator does not detect the failure.	A	stirrer speed increases due to failure in stirrer.		L	H	2	H	III
		B	High stirrer speed due to value incorrectly set, because of human failure or lack of training.		L	H	2	H	III
3	During the filling process, the speed of recirculation is very low, or the recirculation is even stopped. The operator does not detect the failure.	A	The peristaltic pump stops due to failure in the electrical supply.		M	H	1	H	II
		B	The peristaltic pump stops or its speed decreases due to failure in the peristaltic pump.		L	H	2	H	III
		C	Low recirculation speed due to value incorrectly set, because of human failure or lack of training.		L	H	2	H	III
		D	The recirculation tube is obstructed		L	H	2	H	III
4	During the filling process, the speed of recirculation is very high. The operator does not detect the failure.	A	High recirculation speed due to failure in the frequency inverter.		L	H	2	H	III
		B	High recirculation speed due to value incorrectly set, because of human failure or lack of training.		L	H	2	H	III
5	During the filling process, the stirrer speed is not appropriate to the height of the suspension in the tank. The operator does not detect the failure.	A	Level indicator or filled units was not verified due to human failure or lack of training.		L	H	2	H	III
6	After a stop of 5 minutes, the operator does not discard units in a number equivalent to a volume of 100mL.	A	The instructions depicted in the product manufacturing records are not followed due to human failure or lack of training.	Detectability may be increased by installing a timer with alarm for operation interruption, and a system for automatic discard, which allows to eliminate the units related to the process restart.	L	H	2	H	III

Table E. RPN associated to different hazards, after applying mitigation strategies.

alarm. However, further analysis leads to a better solution for hazards number 1 to 5 in Table D: the development of an in-line device that could continuously monitor the suspension concentration close to the filler nozzle. Unlike the previous mentioned strategies, this type of equipment would measure the suspension concentration directly and continuously, ensuring the product potency and uniformity. In addition, the equipment would not only provide a continuous real time quality assurance, but also be a tool to improve the process knowledge by performing in-line measurements, which could be correlated with variations in process conditions. However, the required equipment had to be developed in compliance with process requirements: it should be non-invasive, sterilizable, and perform fast measurements.

After two months of development, the prototype device and its insertion housing were finished and the in-line measurements obtained were compared to a reference off-line method, which demonstrated the good agreement between both methods. The measurement systems comprises a Trb 8300 turbidity transmitter along with an InPro 8100 single optical fiber turbidity sensor (Measuring range: 10 to 4000 FTU – 0 to 250 g/l), and a housing specially designed and developed for this project. Further details of the new in-line method, including the results from a comparison with the reference method, will be published soon.

As a consequence of the potential implementation of the new device, detectability of most of the items in Table D were improved, leading to the decrease in RPN as listed in Table E. Since the strategies implemented are non-invasive and do not include changes in the process, it was concluded that they do not introduce new risks into the system under study, nor increase existing risks. As a result, no further risk evaluation is required.

Conclusion

The use of ICH Q9 and a formal risk management tool (FMECA) applied to the BTM filling process yields the risk reduction of the BTM filling process by focusing on the critical points and establishing the more appropriate mitigation strategies. Among the mitigation strategies considered, the in-line continuous monitoring would substantially reduce the probability of releasing out-of-specification units in comparison to conventional quality control assays, which are usually limited by its statistical and destructive nature. It is reasonable to estimate that it will not take a long time until the BTM filling process can be controlled and optimized by making use of in-line technologies, thus reducing significantly both the risks and the costs of production (as a consequence of decreasing the scrap and reprocessed units). However, the introduction of new and evolved technologies in existing pharmaceutical processes will require the previous application of a risk management tool along with the accumulated knowledge of experts from different sectors of the company in order to enhance the process efficiency and avoid the undesirable appearance of unexpected risks. In this regard, the present study is expected to serve as base of future works in the field of risk analysis and technology application within the Process Analytical Technology (PAT[9]) framework.

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