Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2010, Vol. 30 No. 1
www.ISPE.org

Case Study: Project Execution Strategy for MAB Building 95, Overall Winner, 2009 Facility of the Year Awards

by Rochelle Runas, ISPE Technical Writer

This case study focuses on the plan, design, and construction of the unique concept and layout of Roche's biotech facility, MAB Building 95, Overall Winner of the 2009 Facility of the Year Awards.

Introduction

Nestled tightly in the middle of a busy residential area in Basel, Switzerland is Roche's MAB Building 95. Distinguished by its state-of-the-art architecture, the facility was conceived for the commercial production of therapeutic Monoclonal Anti Bodies. The successful plan, design, and construction of the building's unique concept and layout, in a challenging location, garnered the 2009 Facility of the Year Award for Overall Winner.

Now in its fifth year, the Facility of the Year Awards (FOYA) program, co-sponsored by ISPE, INTERPHEX, and Pharmaceutical Processing magazine, 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. Roche's MAB Building 95 was selected as Overall Winner among four other FOYA Category Winners. This year's FOYA winners were chosen from submissions for innovative facilities built in Belgium, France, India, Italy, Ireland, England, Germany, Japan, the Netherlands, Spain, Switzerland, and the United States.

This article is a case study on the MAB Building 95 project, which was delivered in 35 months, six weeks ahead of schedule, and nine percent under budget.

Project Business Driver

The $370 million MAB Building 95 project, which took place 2004 to 2007, was delivered as an ultra fast track project to provide additional production capacity for bevacizumab (API of Avastin®), a successful new cancer medication. The primary project business driver was to make the product available to patients as quickly as possible.

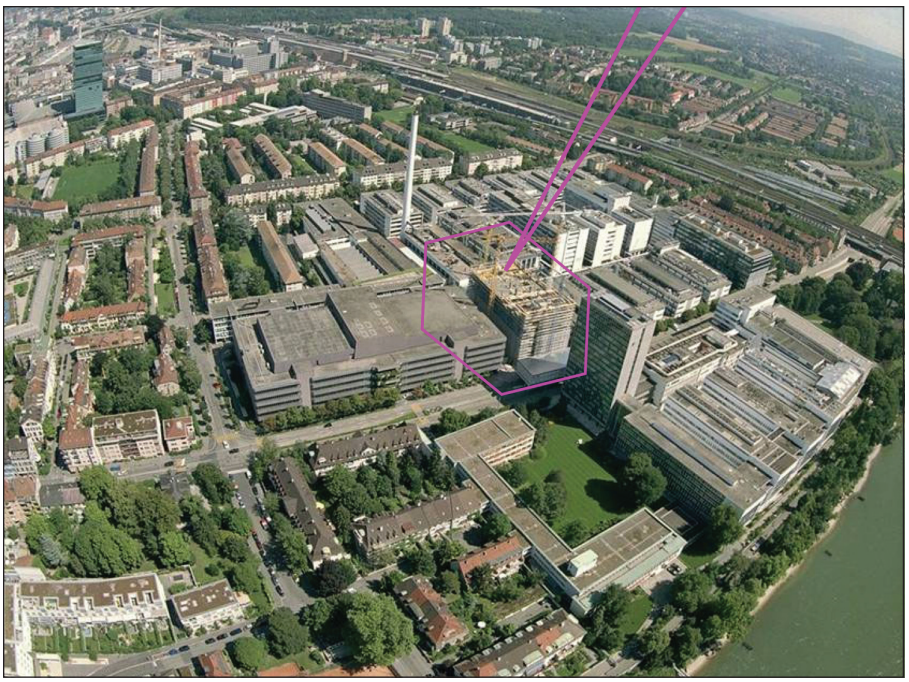
"These new medicines bring the patient large advantages," said Erich Hochuli, Head of Roche Biotech Production Basel. "They work more purposefully and have fewer side effects."

Roche's MAB Building 95 by night.

In addition, the Roche Basel site is being transformed from its traditional chemicals and pharmaceuticals production background to a center of excellence for biologics and pharmaceuticals. Roche representatives say MAB Building 95, the first large production biotech facility in Basel, is the nucleus for this future.

The MAB Building 95 project was running in parallel to Roche's Biologics IV center project in Penzberg, Germany. "We were facing a lot of challenges in the

"The confines of the MAB Building 95 project site, where a chemical production plant once stood, restricted the size of the construction plot to 60 by 30 meters with no available lay-down areas."



Aerial view of MAB Building 95 under construction.

MAB project, but one was very specific: running two investments of this size and complexity in parallel," said Horst Hohler, Head of Roche Pharma Global Engineering. "There are many reasons why MAB was so successful. Most important, however, has been the excellent cooperation and communication within the integrated highly motivated project team." Closely coordinated, both projects seemed to have benefited from the shared experience. The Biologics IV center won the 2008 Facility of the Year Award for the Project Execution category.

Project Overview

Roche's Basel site, continuously occupied by Roche since 1896, lies close to the heart of the historic city, bounded by the River Rhine on the west and urban housing on the other three sides. A major commercial route to the German border runs through the site.

The confines of the MAB Building 95 project site, where a chemical production plant once stood, restricted the size of the construction plot to 60 by 30 meters with no available lay-down areas. Despite the many challenges posed by this small and unique footprint, the project produced a multiproduct facility, 40 meters tall with eight floors aboveground and two floors underground, allowing for the simultaneous production of two different products. It comprises 6 x 12.5 m^3 fermentation capacity plus two downstream processing lines for purification, and associated utilities, laboratories, and offices.

MAB Building 95 has a 100% glass façade on all four sides. For such a challenging architectural task, the project team turned to Herzog & deMeuron, Roche's long term architectural partner and world-renowned for their work on the Beijing National Stadium (a.k.a. Bird's Nest) for the 2008 Olympic Games, the Allianz Arena in Germany, and the Tate Modern in London, among others.

Process Overview

Because the priority business driver was to make innovative new Monoclonal Anti Bodies available to growing patient groups as quickly as possible, when setting project goals, teams focused their attention on the robustness of the process and minimizing supply risk rather than process innovation. Therefore, the production process to manufacture MABS is well established with the process arrangement based on proven, reliable, and successful technology.

The MAB installation achieves multiple line arrangements by the utilization of solid piping spool pieces and transfer panels. The configuration can be changed quickly with minimal effort and minimal operations disturbance. By using fixed piping instead of valves, the

Benchmarking Survey Data – The Building

Height between Floors Production	5.0 m
Building Footprint (Aboveground Floors)	60 x 30 m
Building Footprint (Belowground Floors)	60 x 37 m
Building Height from Ground Level	40.0 m
Usable Area Production	ca 5,600 m^2
Usable Area Laboratory / Office	ca 1,400 m^2
Total Building Area	19,500 m^2
Total Volume	100,000 m^3
Glass Façade	8,400 m^2
Connected Load – Electricity	ca 3.7 MW
Connected Load – Cooling Energy	ca 11 MW
Connected Load – Steam	ca 16.500 kg/h
Handled Air (Installed Volume)	ca 550.000 m^3/h
Number of Air Handling Units	23

risk of accidental cross-contamination is eliminated. Thus, the facility is truly multiproduct, enabling parallel production of two different products with campaign volume and duration configurable in wide ranges.

Process lines, operated via recipes, are highly automated and fully controlled by a Distributed Control System (DCS). The Manufacturing Execution System (MES), which is linked to the Roche Enterprise Resource Planning System (SAP), was phased in as the processes reached stability.

Building Concept and Layout

The production process dictated equipment arrangement and layout, which the architecture had to balance against the overall aesthetics of the building and the restricted site footprint. With its vertical process arrangement, MAB Building 95 is often described as a high-rise production.

Benchmarking Survey Data – The Process

Main Equipment/Number of Apparatus	305
Number of All Equipment	963
Number of Process Units	200
PFDs	125
P&IDs	318
Rs	10,070
Isometric Drawings	8,100
Number of Pipe Runs	6,750
Piping Process	ca. 43,000 m
I/O (Number of)	ca. 15,000
Number of Instruments (Sensors and Valves)	ca. 12,000
Computer Human Interfaces (CHI)	110
Length Building Electrical Wiring	ca. 75,000 m
Length Automation Electrical Wiring	ca. 440,000 m

Utilizing a top down process flow resulted in the tank farm with all media and buffer tanks located on the second top floor. This makes MAB Building 95 the only production building with liquid storage 35 m above ground. This unique layout, providing liquid flow under gravity (with support from pressurized nitrogen when necessary), works well and saved many pumps – beneficial for the facility's sustainability, investment costs, and maintenance effort and costs, said representatives from Roche.

The West side of the building is occupied by the fermentation process with designated laboratories and process service rooms located in the northwest. The East side of the building is occupied by the purification process with designated laboratories and process service rooms located in the northeast.

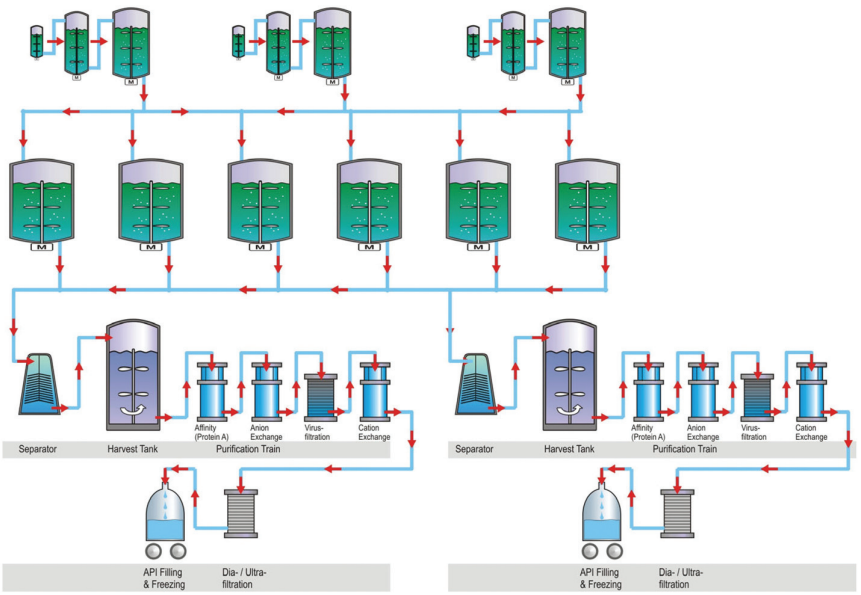
The layout of the building is symmetric for all aboveground production floors. The central supply shaft services all floors with utilities, HVAC, electrical wiring, and process piping. The two belowground floors accommodate API storage cold rooms, utility units, CIP units, HVAC, as well as changing rooms, MCC rooms, and central computer server rooms. The top floor (eighth) accommodates solely HVAC. All production rooms are class C/D cleanrooms following cGMP zone classifications.

Process Arrangement

Fermentation:
- Cell Banking
- Inoculum Trains
- Fermenters, 14 m³ each (cap. 12.5 m³)
- Two Disc Separators
- Two Harvest Tanks

Purification:
- Two Independent Purification Lines, each with:
  - Three Chromatographic Columns
  - Ultrafiltration
  - Cryo Vessels

Utilities:
- Purified Water, WFI, Clean Steam
- CIP, SIP (Closed Loop, Fully Automated)
- HVAC, Autoclaves
- Utilities supply is located in the basement and top floor and supplied through a central utility shaft.

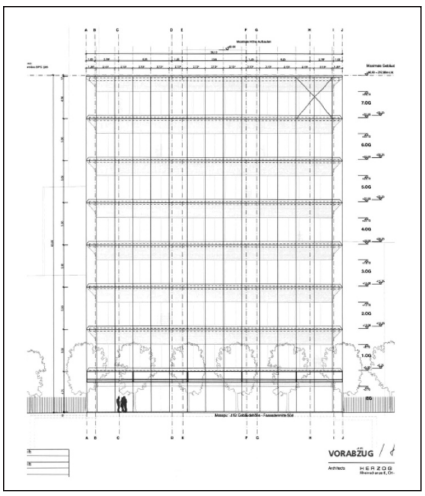


Design Process in 3D CAD

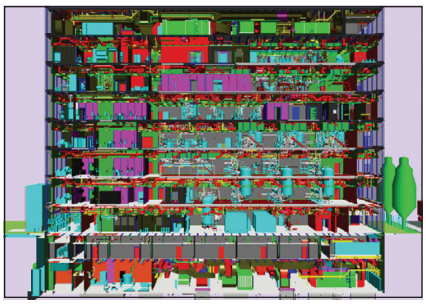
Everything that was to be built for MAB Building 95 was first modeled in an all inclusive 3D CAD model. The starting point – the architectural drawings, were transferred from 2D CAD systems into the 3D CAD model. With that, the building dimensions were defined. This meant that any change in building dimensions triggered an even greater number of changes in other disciplines,

"We established the sacred line, Change is evil,"

- Daniel Riekert, MAB Building 95 Project Manager



Architectural drawing.



West side (fermentation) in 3D CAD.

increasing the model size. "We established the sacred line, Change is evil," said MAB Building 95 Project Manager Daniel Riekert.

In the next design phase, equipment was modeled and equipment layout was optimized. The 3D model provided an efficient tool to not only make quick changes in the layout, but also to obtain immediate feedback on the consequences. The most critical area with the highest installation density was the central service shaft.

Once equipment arrangement was established, piping was planned. This was solely done using the electronic tools of the 3D CAD system. Isometrics planning involved paper only once: at the end for the plots to go to manufacturing and construction. All piping was modeled for process and utility systems, independent of size. State-of-the-art 3D CAD systems have multiple layers, each to accommodate a different design discipline. The project team used 25 layers. Because the model grew so complex and dense, only up to two layers could be shown at once for visualization.

Parallel to piping, HVAC ducting, sanitary routing, and electrical wiring routing were modeled.

Finally, the interior walls and hanging ceilings were included, a unique challenge for the project team as every wall or ceiling penetration had to be equipped with a GMP qualified sealing.

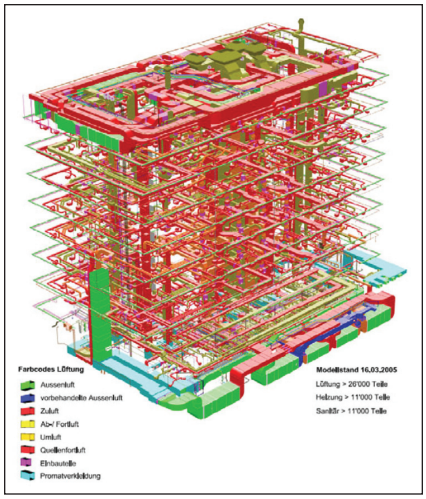
"The power and efficiency of the 3D CAD model ultimately becomes apparent as one imagines to overlay all the discipline layers," said Riekert. "It is the only tool that allows reliably arranging everything properly and identifying upfront clashes that become more costly to remediate the later they are identified."

Integrated Project Schedule

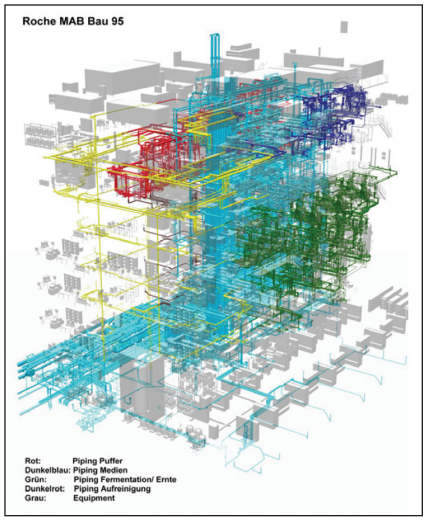
Since the facility had to be arranged vertically and all systems are fully integrated (piping as well as automation), the normal option of sequential completion proved to be too slow when modeled in the schedule. This forced the project team to develop the strategy and tactics necessary to complete the whole facility as a single entity, i.e., work on everything in parallel.

High emphasis was placed on meticulous planning and scheduling of tasks. Each item in the facility 3D CAD model was linked to an activity in the project schedule. The construction logic was established, reassembling the 3D CAD model from excavation to 100% mechanical completion. This construction logic was transferred to the schedule to confirm the schedule scope. The resulting integrated schedule was used to set specific interrelated design, manufacturing, FAT, delivery, installation dates. Suppliers were fully integrated into team scheduling, synchronized timing, and delivery routes.

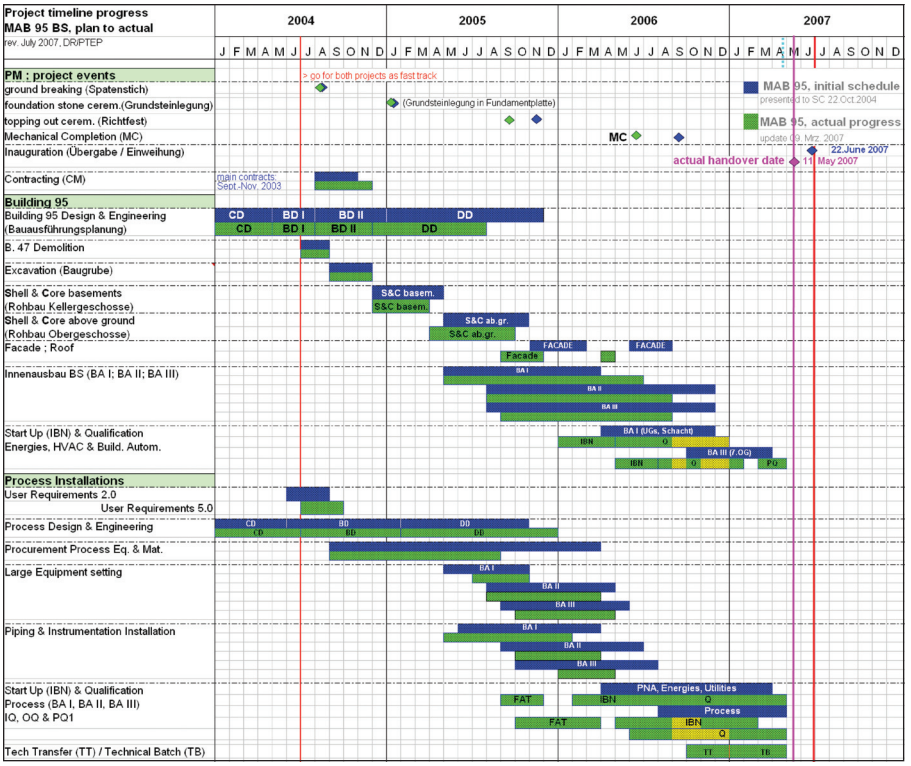
Progress was monitored in real time, down to the pipe spool level, and the schedule was updated daily. Great attention was focused on weekly progress reviews where the achieved physical progress for all disciplines was audited and corrective actions were agreed upon if any schedule slippage was identified. A primary focus for the project team was the synchronization of the interfaces between phases. This assured seamless workflow not only in the distinct project phases, but also through these interface periods. This removed productivity



HVAC layer in 3D CAD.



Equipment and piping layers in 3D CAD.



Project overview schedule.

reduction often seen during funding period activities when a project team is focused on securing funding for the next project phase.

The following are highlights of the many activities that ran in parallel and the multiple acceleration programs the project team employed:

- After the project start in July 2004, the building's basic design was accelerated to apply earlier for a construction permit, typically a lengthy process due to site location in a residential zone.
- Demolition of existing building started immediately with excavation work starting two months later.
- Procurement for the building shell trade contractor and the other major building trades started immediately to facilitate an early construction start.
- An extensive procurement program based on competitive bidding was coordinated with the Biologics IV project in Penzberg.
- Exhaustive acceleration program during detail design mainly for piping isometrics, HVAC ducting, and electrical wiring supported an early start of mechanical installations.
- A sophisticated building construction schedule secured six weeks for a basement floor and three weeks for a super structure floor.
- Infrastructure mechanical installation in the basement began, while the concrete for the aboveground floors had yet to be poured.
- Acceleration program for piping and HVAC installation.
- Since all mechanical systems were interconnected, commissioning, start-up, and qualification of utilities and process units were performed in sequence.
- The start-up team was staffed as much as possible with future production crews.
- Introduction of technical batches (non-qualified runs under production conditions) during start-up allowed for early detection of flaws and reduced time for remedial work.

Construction Outside of the Box

The confines of the site made it necessary to rethink construction set-up. Besides just in time materials delivery, all containers for construction staff were placed on top of steel structures, leaving the place underneath free for traffic. Even the sky space above major roads was occupied.

The project team organized and coordinated trades and workforce on the construction site (at peak time, more than 500 workers) to assure uninterrupted workflow and under the pressure of constant competition for space to work. Project sourcing for trades, labor and machinery was Europe-wide. At peak loading, 24 different languages were used on the site. "This put 'tool box' safety talks into a completely new area," said Project Manager Daniel Riekert. "Putting Safety first in team thinking

Construction staff occupied an office that was elevated above the main public roadway.

and enforcing this every day, rewarded the project with just 4 lost time accidents on 1 million workhours, no fatalities and therefore an exceptional safety track record, by factors better than typically seen. Fast track does not mean consessions to Safety, rather it can be done in a compatible manner."

The team established and managed a "just in time" delivery concept of equipment, materials, and pipe spools to the workforce. At peak times, one truck off-loaded every 20 minutes. To reduce congestion in and around the tight project site, cutting-edge communication technology was applied whenever possible in the day-to-day running of the project. Extensive use was made of video conferencing, documentation was exchanged via the Internet prior to joint reviews, site access was restricted to key personnel, and all project participants were encouraged to conduct as much communication as possible through electronic media. This allowed a large reduction in travel time and cost.

Commissioning/ Validation Strategy

Commissioning and start-up was performed by 18 start-up teams and seven support teams, which operated on a seven day/week-two shift model for the majority of the project.

Qualification was performed by seven start-up teams and seven support teams (production staff), which operated on a five day/week-one (extended) shift model for the majority of the project.

The whole facility is based on the modular design concept, which served as the basis for both process and automation design. Through this technique, a "high copy effect" was achieved when implementing the required functionality. This allowed the team to adopt a bracketing concept to the modular design.

The Technical Acceptance Tests (TATs) performed on every installed system were highly standardized and reproducible. This led to a considerable reduction in man-hours and to a significant efficiency increase.

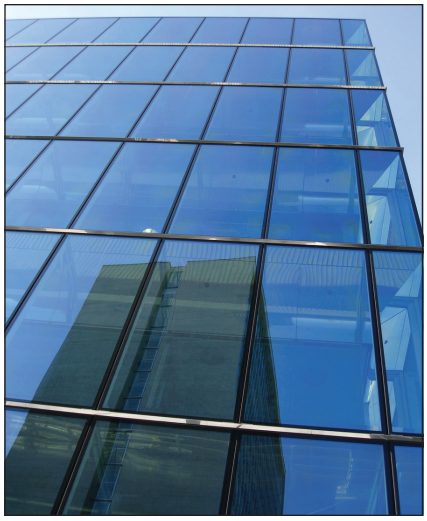
Further efficiency increases and a reduction of qualification timelines were achieved by using documentation from Technical Start-Up and Factory Acceptance Tests (FATs) for the qualification projects. These measures required close coordination of the start-up and qualification teams.

Project Management Approach

High ethical standards were set for project management and leadership. The primary areas of focus were on:

- teamwork and team motivation
- engagement and empowerment of team members
- building an environment of integrity and trust in the team
- working together with contractors and suppliers in a spirit of open team partnership

"No blame, fix the problem," was an overriding principle that led Roche's integrated project team. A Roche philosophy is to take ownership and actively manage project risks instead of delegating them. Support was provided by all parts of the Roche organization and their experts as critical issues surfaced or interfaces were to be managed. The project was able to call for additional support anytime and was given priority. Peer reviews for design and project management were carried out by colleagues from the worldwide Roche engineering network.



Roche's MAB Building 95.

Much effort was invested in project definition (e.g., user requirements) and project execution planning during project initiation, where organizational setup, roles, responsibilities, and execution strategies were defined to support achievement of project goals. Best practice engineering processes were applied in all disciplines.

Key Project Participants

Owner: Roche Biotech Basel
Engineering: Roche Pharma Global Engineering and Roche Basel Site Engineering
Designer/Architect: Herzog & deMeuron, Basel, Switzerland
Main/General Contractor: Linde-KCA, Dresden, Germany
Construction Manager: Bovis Lend Lease, Munich, Germany (Liquidated)

Engineering Subcontractors
Axima – Basel, Switzerland (HVAC, Sanitary in CD, BD)
IB Mayer – Ottobrunn, Germany (HVAC, Sanitary in DD)
ZPF – Basel, Switzerland (Statics)
Emmer – Basel, Switzerland (Façade Planning)
Kiwi – Dübendorf, Switzerland (Electro Planning)
IP Hage – Neckartenzlingen, Germany (Cleanroom Planning)
P. Burkart – Schindellegi, Switzerland (3D CAD Isometric Planning)
CTE – Liestal, Switzerland (Automation, DCS Planning)
Penta-Electric – Basel, Switzerland (Automation, DCS Planning)
Netzhammer – Basel, Switzerland (Automation, DCS Planning)
Etavis – Basel, Switzerland (Automation, DCS Planning)
onoff – Basel, Switzerland (Automation, MES Planning)
Penta-Electric – Basel, Switzerland (Automation, MES Planning)

Third Party (Qualification)
LSMW – Stuttgart, Germany
VTU – Graz, Austria

Current project control best practices are standard processes in Roche and are successfully applied in all Roche projects. Special efforts were made on controlling the scheduling of critical path items and on the enabling of early commissioning of 100% completed systems. Together with focused acceleration programs, these were the most important planning measures for schedule reduction.

Sophisticated resource planning including the application of different shift-models ensured staffing levels, avoidance of work overload, especially on the user side and automation, and enabled recruitment of the plant operatives to be complete early in the project.

Since the production group had to be established from scratch by recruiting knowledgeable operators, some of whom were new to biotechnology and without specific experience, intensive training programs were established. In cooperation with the Zürich College in Wädenswil, training was provided in theoretical background, and experience with large scale production was shared by colleagues from Roche Penzberg and Genentech.

Major Equipment Suppliers

Equipment Type	Manufacturer	Location
Fermentation	Bioengineering	Wald, Switzerland
Fermenter Vessels	Bioengineering	Wald, Switzerland
Separator	Alfa Laval	Tumba, Sweden
Purification	Millipore	Molsheim, France
CIP, SIP	GEA Dissel	Niedersachsen, Germany
PW-, Pure Steam-Generation	Pharmatec	Wiesbaden, Germany
Filter	Pall	Dreieich, Germany
Filter, Columns	Millipore	Molsheim, France
Filter Stations	Sartorius	Goettingen, Germany
Cryovessels	Stedim	Fribourg, Switzerland
Cryovessels	Zeta	Graz, Austria
Media Prep. Vessels	Mavag	Neunkirch, Switzerland
Buffer Storage Tanks	Glatt	Wiesbaden, Germany
Buffer Storage Tanks	Karasek	Gloggnitz-Stuppach, Austria
Water Tanks	Apaco	Grellingen, Switzerland
Autoclaves	Sauter	Basel, Switzerland
Wash Machines	Sauter	Basel, Switzerland
HTST System	Calorifer	Elgg, Switzerland
Membrane Valves	Gemü	Ingelfingen, Germany
Steam and Condensate	Ramseyer	Flamatt, Switzerland
MCC Cabinets	ABB Swiss	Baden-Dättwil, Switzerland
Trafos	ABB Secheron	Baden-Dättwil, Switzerland
Low Voltage Cabinets	Balzaretti & Frey	Udligenswil, Switzerland
HMI (Human Machine interfaces)	Gecma	Kerpen, Germany
Laboratory Furniture	Renggli	Rotkreuz, Switzerland

Major Trade Contractors

Trade	Contractor	Location
Master Builder	Batigroup	Basel, Switzerland
Facade	Ernst Schweizer	Hedingen, Switzerland
Facade Cleaning Lift	PK Küpfer	Glattbrugg, Switzerland
Piping	MCE	Salzburg, Austria
Insulation	Novisol	Basel, Switzerland
HVAC, Sanitary	Axima	Basel, Switzerland
Steel Structures	Schauenberg	Kirchzarten, Germany
Insulation	Novisol	Basel, Switzerland
Elektro	Selmoni	Basel, Switzerland
Elektro	Etavis	Zürich, Switzerland
Automation, Controls, BMS	Siemens Swiss	Zürich, Switzerland
Cleanroom Systems	Daldrop & Huber	Neckartailfingen, Germany
Doors	Dreier	Kleinlützel, Switzerland
Suspended Ceilings	Isolag	Zürich, Switzerland
Raised Floors	IFM	Buchdorf, Switzerland
Plasterer	Canonica	Basel, Switzerland
Roofing	Marx Flachdach	Muttenz, Switzerland
Fire Alarm System	Siemens Cerberus	Männedorf, Switzerland
Smoke Ventilation Systems	Mistral	Wien, Austria
Floors PVC	Regio	Allschwil, Switzerland
Floors Epoxy	Repoxit	Winterthur, Switzerland
Lifts	Schindler	Ebikon, Switzerland
Painter	Heinrich Schmid	Lörrach, Germany
Painter	Schweizer Söhne	Basel, Switzerland
Carpenter	Tschudin	Basel, Switzerland

Procurement Strategy

The project core team's behavior toward procurement was very cost-conscious. That guiding behavior, coupled with an economy of scale at market, resulted in substantial savings. What was planned was built with no significant changes during execution.

In the competitive bidding process, the Roche team resourced to bid 200 packages in a planned sequence. Packages were split among several suppliers to mitigate risk. Procurement was closely coordinated with Biologics IV, the sister project in Penzberg, Germany running parallel to MAB Building 95. Reimbursable cost contracts with prime contractors and incentives were beneficial.

For the project core team, procurement didn't end with the contract award. A high emphasis was placed on safeguarding timely delivery to the site.

Conclusion

Delivering an ultra fast track biotechnology facility is a huge challenge for a project manager by itself. To combine this challenge with the added dimension of a restricted site footprint, city center construction logistics, residential neighborhood, and a star architect with strong views on design and material selection called for innovative project management techniques. The project team at Roche Pharma Biotech Production Basel shined while delivering an ultra fast-track, completely unique, vertical MAB facility. Every aspect of this project had to be flawlessly executed to accommodate the many challenges of the site, location, and facility design.

"Delivering the project under budget and six weeks ahead of schedule seemed unimaginable when we started," said Riekert. "But the enthusiastic commitment of the project team to rise beyond limitations, delivered a world class project we are very proud of and will keep in best memories."

Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2010, Vol. 30 No. 1
www.ISPE.org

Case Study: Utilizing Electron Beam Surface Decontamination to Transfer Sterile Syringe Barrels into an Isolated Aseptic Syringe Filling Line

by Oliver Vogt

This case study presents a project within Hospira, Inc., utilizing an Electron Beam Surface Decontamination system integrated into an isolated aseptic syringe filling line to transfer pre-sterilized syringes into the filling line.

Introduction

The increase in popularity of pre-sterilized ready to fill syringes over the last two decades has spawned an ever increasing amount of equipment technology offered by equipment manufacturers to fill and process these types of syringes. High speed automation has reached filling and processing speeds exceeding 600 syringes per minute for pre-sterilized nested syringes (syringes held in a tub). Due to the primarily aseptic nature of the filling process, these syringe filling and stoppering machines are generally installed utilizing barrier isolation systems or Restricted Access Barrier Systems (RABS) technology. The high processing speeds coupled with aseptic processing requirements demand an effective, safe, and reliable means of transferring the pre-sterilized empty syringe barrels from a warehouse environment into an unpacking area, a tub staging area, and finally, into the aseptic processing area of the filler. This transfer needs to be performed without compromising the sterility of the empty syringes inside the tub or the integrity of the aseptic filling and processing environment during transfer of the tubs into the aseptic filling machine.

Aseptic Process Challenges

The main challenges for an aseptic pre-filled syringe line is the transfer of process commodities in the form of plunger stoppers and empty syringe barrels that have to be introduced into the aseptic area of the filling machine environment. As the outer packaging of any process commodity is exposed to warehouse environments, decontamination of the package exterior or the removal of the outer packaging would be the logical response to assure no contamination can be introduced into the aseptic filling and processing area ("the critical area") by the commodities. However, the removal of the outer and potentially contaminated packaging material has to be done outside of the critical area, which demands some degree of environmental protection and personnel control. The question now becomes, how well is the sterile tub protected from contamination during the exposure to a non-aseptic environment after the outer protective bag is removed and how can you assure that any contamination on the outer bag cannot transfer from the outer bag onto the tub during the opening and removal process. The next concern involves the interface of the tub transfer into the isolator, which can not compromise the integrity of the aseptic environment inside of the isolator.

The transfer of sterile commodities or process materials into aseptic processing zones has been accomplished using a variety of technology. In the case of pre-sterilized syringes, the primary concern is not the sterility of the syringe, but the assurance that the aseptic processing zone used for the filling and plunger insertion of the syringe is not compromised by the repeated introduction of pre-sterilized syringe tubs that have to be transferred from an environmental high risk area, such as a warehouse. The following represents a short technology list used for this application. It is not intended to serve as a scientific selection criteria for technology, but rather information of some of the common

issues around each approach. Implementation of any of the described technologies into pharmaceutical manufacturing processes requires the evaluation of detailed information, process understanding, and generation of meaningful data to guide the selection process, especially in the area of business considerations (total cost of ownership), line speed, and process robustness (risk).

Rapid Transfer Port (Alpha-Beta Port)

This solution involves the docking of a transfer container or bag that is fitted with a special docking port. The port matches a receiving port on the isolator wall and the two ports are designed so their exposed surfaces are completely covered by each other when properly docked. The contents and inside of the transfer container or ported bag have to be sterile at the time of docking and transfer, which can be accomplished in a separate off-line process, i.e., autoclaving or gamma-irradiation.

Pros:

- Simple implementation
- Low capital cost
- Ideal for transfer of small commodities, i.e., plunger stoppers or mechanical components for the filler (filling needles, fill pumps, etc.) – plunger stoppers are offered in this configuration

Cons:

- Commercial availability and cost of large ported bags
- Ergonomic problems of frequent docking and unloading tubs from the bag through the docking port at higher fill speeds
- Bag integrity for a large, bulky, and heavy bag exposed to frequent handling activities

Manual Alcohol (IPA) Spray and Wipe

The outer bag is wiped with alcohol wipes or sprayed with alcohol and wiped down manually, before the tub in the bag is introduced into a transfer chamber that is part of the isolator. The outer bag is then removed automatically or manually through gloves in the transfer chamber that connects with the isolator. The outer bags have to be collected in a waste bin. The sterile tubs, still closed at this point can now be introduced directly into the filler area, where they have to be opened manually through glove ports or automatically. Integrity of the isolator is assured through positive air pressure against the opening of the transfer/bag removal chamber

Pros:

- Simple implementation
- Low capital cost

Cons:

- Ergonomics of manual process for high speed applications
- Ongoing storage, distribution, and consumption of alcohol (flammable)
- Generation of alcohol vapor and associated risks
- Inability to kill spores and to validate a manual process

Vapor Hydrogen Peroxide (VHP) Surface Decontamination

A chamber, sized large enough to hold the number of tubs the filler consumes during a surface decontamination cycle, is loaded with tubs that are still covered with the outer bag. The chamber is closed and all tubs within are exposed to a VHP decontamination cycle. Once the cycle is complete, the bag exterior and the interior of the VHP chamber are now sanitized and the chamber can be opened to the filler isolator. Tubs have to be removed from the bags, loaded and opened, before filling can proceed.

Pros:

- Effectiveness of VHP cycle known and validation approach is well defined
- Batch process: opening of VHP chamber and isolator are separated and critical areas are protected

Cons:

- Batch process: size of chamber and cycle time are interrelated and have to match filling speed - this will limit maximum filling speed as VHP cycles are time consuming.
- Capital cost of chamber
- Ergonomics of loading/unloading the chamber, physical demand on operators
- Not an off-the-shelf solution offered by OEMs – integration challenge.

High-Intensity UV-Light Surface Sanitization

A chamber, sized large enough to hold the number of tubs the filler consumes during a surface decontamination cycle, is loaded with tubs, whose outer bag has already been removed in the staging area. The chamber is closed and all tubs within the chamber are exposed to UV-Light for predetermined cycle-time. Once the cycle is complete, the tub exterior and the interior of the UV chamber are sanitized and the chamber can be opened to the filler isolator. Tubs have to be removed from the chamber, loaded and opened, before filling can proceed. Applied light energy is typically expressed as areal power (microwatts/cm2) × exposure time.

Pros:

- Batch process: opening of UV chamber and isolator are separated and critical areas are protected.
- UV does not create a “residual” concern and does not penetrate past the surface – does not reach the syringes inside the tub.
- Fast cycle time
- No consumption of chemicals

Cons:

- UV-Light has good microbial kill power, but effectiveness is sensitive to shadowing, and UV-light is very limited

Tub Transfer Technologies	Capital Cost	Microbial Kill Energy	Cycle Time/ Throughput	Ease of Integration w/Isolator	Chemical Residuals	Ease of Validation	Global Regulatory Acceptability	Cost of Operation	Score
A-B ported bag	10	5	1	6	10	10	7	1	5.4
Alcohol Wipe	7	1	4	7	5	1	1	2	3.2
VHP-Chamber	2	8	3	4	4	5	3	3	4.1
UV-Chamber	4	6	6	7	10	6	5	10	6.6
E-Beam Tunnel	1	10	10	10	6	7	10	9	8.3
Weight10%	15%	20%	10%	5%	15%	10%	15%	100%	
10 = best solution, 1 = worst solution									

Table A. Decision analysis.

in its matter penetration ability, similar to visible light. There is no standard unit to express applied surface light intensity.

- Capital cost of chamber made with costly quartz components
- Ergonomics and of loading/unloading the chamber and precision of positioning multiple tubs within the chamber (no shadowing)
- Process costly to fully automate
- UV light source has relatively short life span and degrades over time.

Electron Beam (E-Beam) Radiation Surface Sanitization

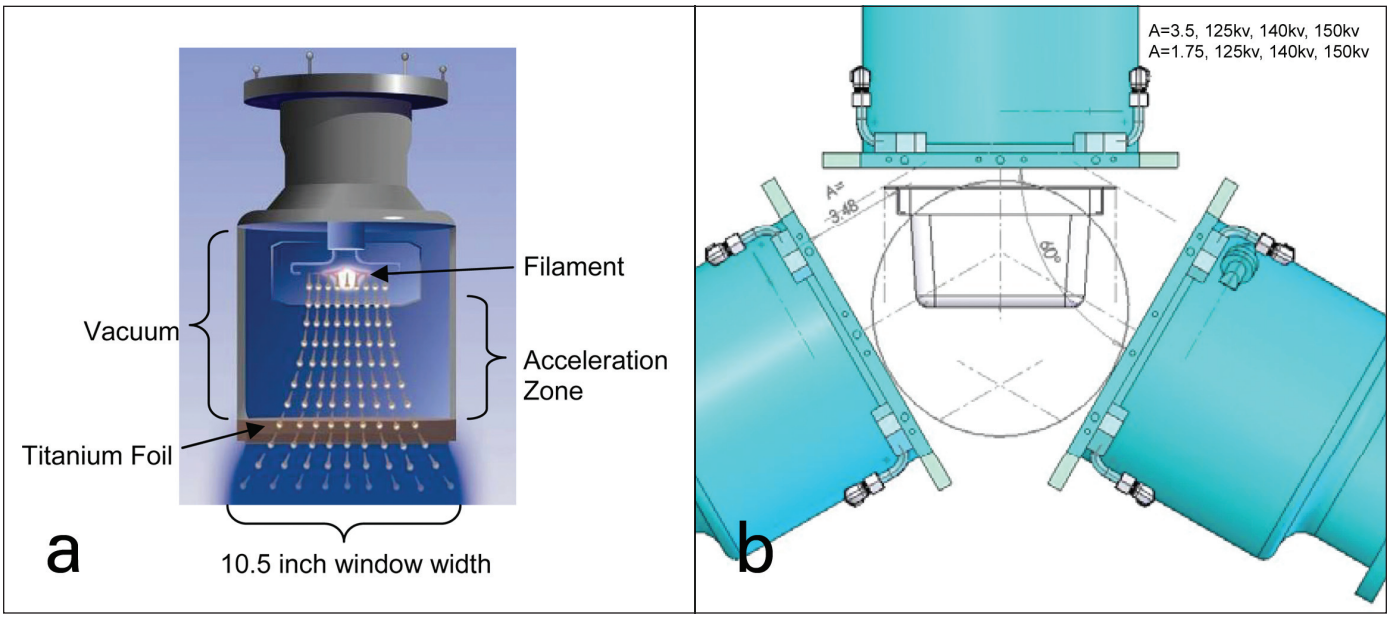
This latest addition to the arsenal of equipment offerings utilizes electron beam emitters that generate ionizing radiation. Three emitters are arranged in a way that the entire surface of a tub is sanitized during transport of the tub passing the emitters. The inside of the emitter chamber has to be sanitized through a separate process. The emitter chamber is usually designed as a separate isolator system so it can be closed and its inside can be decontaminated using VHP. The integrity of the filling machine isolator is achieved through air over pressure between the filler isolator and the e-beam "isolator." The kiloGray (kGy) is the SI unit for absorbed radiation dose. 1kGy = 1kJ/kg.

Pros:

- E-beam has highest microbial kill power due to matter penetration ability of ionizing radiation
- Power can be controlled through beam control parameters.
- Continuous high speed process that can be directly integrated with the isolator of the filling equipment and can be decontaminated using VHP.
- Validation and dose requirements well defined (ISO 11137)
- Commercially available technology
- No consumables

Cons:

- Large capital cost
- Complex technology
- E-beam generates Ozone (Oxygen Ionization)



Figures 1a and 1b. Electron beam emitter cross section and emitter arrangement in the tunnel (photo: Courtesy of Advanced Electron Beams, Wilmington, Maryland and Metal+Plastic, GmbH Radolfszell, Germany).

Hospira has selected an e-beam tub surface decontamination system for its highest speed syringe filling line in McPherson, Kansas. The primary reasons were the numerous advantages that an e-beam system offers for an in-line continuous process that must be integrated with a high speed isolated syringe filling line. Different applications, especially slower speed processes may lead to a different conclusion as the high initial procurement cost of an e-beam system are best absorbed by a high volume process. Another strong point of consideration in the selection of the technology is the global acceptability of this manufacturing line by contract filling customers. Broad acceptability by international regulatory bodies is critical and the utilization of e-beam technology is perceived to provide one of the highest standards of compliance.

E-Beam Technology Overview

E-Beam Emitter

Electron beams are a source of ionizing radiation, similar to Gamma radiation, and has been successfully used for sterilization for pharmaceutical and medical device applications for decades. The mechanism of microbial disinfection is well understood and the development, validation of this type of technology is covered by "ISO 11137 Sterilization of Healthcare Products by Radiation" documentation. Electron beams differ from Gamma in that they do not depend on the decay of a radioactive isotope (i.e., Cobalt 60) to generate the sterilizing energy. In an electron beam system, free electrons are accelerated with a voltage differential and directed toward a product. The voltage level applied directly impacts the energy of the electrons which in turn impacts the depth energy will penetrate into a substrate. For all ionizing radiation applications, the term dose refers to the amount of absorbed energy, typically measured in Kilogray (kGy).

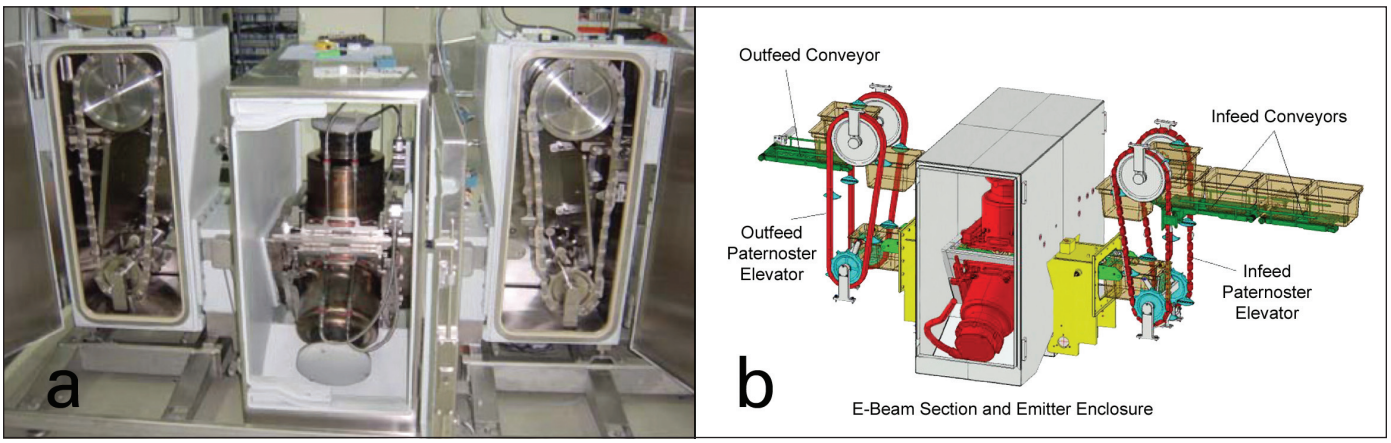
Due to the size of traditional electron beam systems, the use of the technology was historically limited to bulk sterilization at contract irradiation facilities. The development of smaller, low voltage electron beam technology has opened up new applications for in-line surface sterilization applications.

The equipment Hospira has chosen for this application utilizes three electron beam emitters. The emitters are integrated into a surface sanitization tunnel and tub transport system. The electron beam emitters deliver energy in the 80-150kV range.[1] At this voltage, beam energy does generally not penetrate more than 200 microns,[1] limiting the technology to surface decontamination applications. The high dose-rate of e-beam emitters allows for delivering a sufficient dose at transport conveyor speeds of up to six tubs per minute. Low voltage electron beam irradiation is particularly attractive in applications where only surface decontamination is required. By focusing energy at the surface, the bulk properties of the packaging and its contents are not affected.

E-Beam Process Control

As the direct output of dose by the emitters can not be measured continuously throughout the process, critical process parameters of each emitter and the tunnel have to be monitored by the equipment. If any of the critical parameters exceeds validated high or low limit values, alarms and equipment stops have to be triggered. The functionality of these alarms has to be thoroughly tested. The most critical aspect of dose for the tunnel is the conveyor speed, the most critical aspect of dose for the emitters are emitter operating voltage and amperage. The critical operating parameters have to be linked through validation studies to a resulting decontamination dose. Conveyor belt speed directly affects the received dose of the sanitized object. Dose uniformity across the emitter window can be tested with dose mapping studies. A sample of the uniformity of a 10 inch emitter is presented below. The 10 inch face width of the emitter is not limiting the maximum width that can adequately be decontaminated with this type of emitter. The electrons emitted create a cloud of radiation energy that widens with distance from the emitter and loses energy with increased distance from the emitter. Dose mapping studies are designed to verify adequate dose over the surface area of the object that requires radiation. The combined e-beam coverage from all three emitters, which fire at the same time, exceeds the size of the tub.

The failure of an emitter has to be considered a major maintenance event, and subsequent testing is needed to assure the replaced emitter(s) produce an adequate dose with the same operating parameter limits as the emitter that has failed. Replacement of an emitter usually requires the opening of the e-beam tunnel and can be accomplished within three to four hours. After replacement of an emitter, the tunnel



Figures 2a and 2b. E-beam tunnel view (shielding panels removed, transport labyrinth shown left and right, emitter arrangement shown in center).

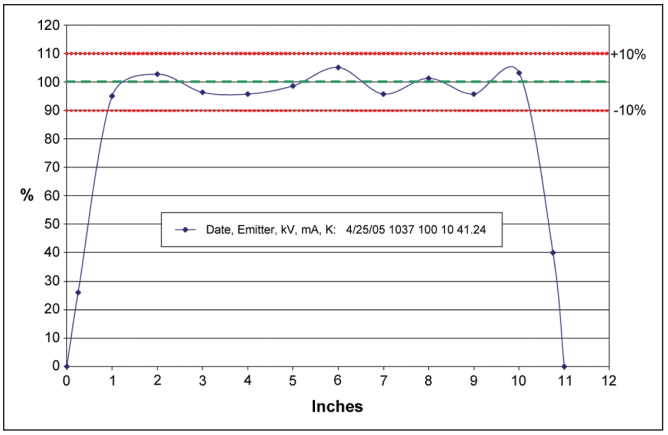


Figure 3. 10 inch uniformity.

will require a VHP cycle, and if the filler was not properly isolated from the tunnel during emitter replacement, the filler campaign also may be in jeopardy.

All critical process parameters monitored throughout the batch are available at the end of the run in the form of a batch history report that is generated by the systems controls. Alarms and other information are reported and documented.

E-Beam Safety

Radiation Safety

Electrons are charged elementary particles that quickly lose energy travelling through air or solid matter. Radiation in the form of electrons and scattered X-Rays, created by electrons hitting matter, is only present when the emitters are operating. The object or item that has been irradiated is not radioactive. Shielding in the form of lead and metal protects the environment around the tunnel and the absence of any radiation presence can easily be measured and monitored. The conveyor and transport system of the e-beam tunnel is designed using a labyrinth at the loading and exit area to eliminate a direct line of sight between an operator and the e-beam emitters. The requirements and compliance aspects of operating an e-beam radiation piece of equipment are well defined and generally no operator/personal radiation monitoring should be required for this low-energy application. The operation of a well shielded e-beam tunnel does normally not create an additional radiation exposure for operators. The annual occupational dose limits for uncontrolled public access should not be exceeded during operation of the e-beam system. The OSHA limits for ionizing radiation are:[4]

Annual Exposure Limit:	100 mrem (milli-rem) = 1 mSv (milli-Sievers)
Hourly Dose Rate:	2 mrem = 0.02 mSv (0.02 mSv = 20 µSv)

The equipment is designed with maximum safety precautions. Shielding is the primary measure, but safety interlocks on shielding and critical access doors, lighted "in use" indicators, emergency shut-down buttons, area radiation detectors (with local alarm capability), and continuously monitoring radiation level near in-feed, out-feed, and sides of the e-beam tunnel are additional means to provide maximum redundancy. Periodic leakage surveys with handheld survey instruments are conducted to assure nothing has changed over time that could potentially affect radiation safety of the equipment. Dosimeters placed around the area of the e-beam equipment are monitored with quarterly results and there is no need to monitor personnel as long as the area is maintained to unrestricted area levels as mentioned above.

Ozone Generation

E-beam emitters generate small amounts of ozone by ionizing oxygen in air. The e-beam tunnel removes air continuously from the emitter zone to assure no harmful concentrations of ozone are present at any time during the process. Ozone detectors monitor the area and exhaust duct concentration and trigger alarms if concentrations exceed 0.1ppm in the area or 1.0ppm in the exhaust ductwork. These limits, of course, are dependent on air flow rates through the e-beam and from the adjacent filler isolator. The materials of construction that are potentially exposed to minute amounts of ozone were selected to resist ozone attack. There is no concern regarding ozone attack on the tub as the tub material also is ozone resistant and exposure time and concentrations are very low (alarm limits are set for exceeding 1ppm).

A concern is raised if ozone is generated inside of the tub in case of e-beam penetration of the tub Tyvek cover and secondary sheet (liner). Dose penetration studies have shown that this is not a concern. Dose penetration was consistently measured below the top Tyvek cover (lid) of the tub, but was consistently below 1kGy under the second Tyvek sheet (liner). The correct functioning of the ozone extraction system is monitored by the equipment. The tub is also opened before filling and exposed to unidirectional airflow. If products are considered highly sensitive to chemical degradation, the concern should be extended to the incoming sterilized syringes. In general, the syringes are sterilized with ETO (ethylene oxide), which has the potential for chemical residuals as well.

E-Beam Validation

The effectiveness of ionizing radiation killing microorganisms is well established. Therefore, validation of radiation systems are easily executed using a Dosimetric Approach. The radiation dose an e-beam emitter produces on the surface of an object can be measured with radio-chromatic film. This film responds to radiation dose by proportionally changing its color. This color change can be measured and referenced against a verifiable standard with photo-optical methods, i.e., spectrophotometer or Scanned Image Analysis. Commercially available film[3] comes in bulk roll stock or pre-cut and held in measurement strips or coupons.[2] The roll stock can be cut to dimensions and applied to any solid surface. This is very helpful in dose mapping studies to verify the proper dose is distributed over the surface area of concern.

References for relation of dosimetric measure and decontamination effectiveness, and requirements for the validation and routine control of radiation sterilization have been published in ANSI/AAMI/ISO 11137,5 Sterilization of healthcare products:

- Part 1: 2006: requirements for development, validation, and routine control of a sterilization process for medical devices.
- Part 2: 2007: establishing the sterilization dose.
- Part 3: 2006: guidance on dosimetric aspects.

These international standards are written primarily for medical device sterilization, but the validation principles apply equally well for the sterilization of, for example, packaging for pharmaceutical products, and in fact, for this process, employing low energy electron beams. ISO 11137 serves as a guide for developing, validating, and operating the process, but certain aspects of the standard are not applicable (i.e., sterility testing, product release, dose audits, etc.) as they are specific to "sterilization."

Dose Determination

The amount of bioburden that the process has to safely deal with has to be determined through bioburden studies. However, as the tub is delivered sterile and is protected by the outer bag until opening, the question is to determine how much contamination will the tub see between outer bag removal and arrival under the e-beam? The bag opening, removal, tub handling, and tub loading process can be controlled though process design or automation. The worst case scenario should be defined and address the maximum handling manipulations, the maximum hold times without the outer bag in place, and the maximum environmental monitoring limits. For this application (decontamination), a minimum sterilization dose exceeding 25kGy (to achieve a 10 ^-6 SAL) is not required and a lower SAL (e.g., 10^3) can be utilized along with the projected worst case average bioburden levels to determine the minimum acceptable dose from the dose tables in ISO standard 11137 Part 2.[5]

Routine bioburden testing is not recommended for this application. In order to assure maximum process robustness over time, the tub bioburden should be monitored periodically to verify the bioburden does not exceed established limits determined during initial start-up and validation. Periodic monitoring also will detect unexpected changes in bioburden levels through seasonal affects, change in personnel, or changes to the facility.

Equally important is the determination of the low dose point on the tub surface area as all minimum dose requirements have to be met by the equipment settings at the low dose point.

Dose monitoring through dose measurement strips[2] also is completed prior to starting a new isolator campaign and in the case of an emitter replacement. In order to facilitate this type of dose monitoring, the use of strips is preferred over film,[3] as it does not require film cutting preparation. Rather than using a standard production tub, a custom designed tub that receives dose parallel to the e-beam emitter window at a fixed distance allows the use of strips and can be used as a standard reference tub to quickly evaluate emitter performance. Receiving emitter radiation energy perpendicular to the emitter provides data related directly to emitter dose uniformity compared to a standard production tub with a contour that varies in distance from the emitter. This also is useful when qualifying a new lot of dosimeters or during annual line requalification.

Penetration also is of concern for the Tyvek lid of the tub, as not all areas of the Tyvek lid are glued to the tub rim, especially in the corner area, where a small area of the Tyvek lid is not attached to allow for ease of lid removal. On the other hand, penetration of the Tyvek lid is not desirable as the glass barrels underneath can be damaged. Suppliers of syringe tubs place additional Tyvek sheets over the empty syringes to provide an e-beam energy absorption layer to protect the glass. This configuration has to be requested from the supplier.

The dosimeters need to be traceable to a standard and they need to be certified for use in a low energy application as low energy applications have not much penetration power. All measurements have to take into account a known level of uncertainty.

Potential E-Beam Issues

Emitter Life Expectancy

This is an ongoing debate and will be resolved in time as real data regarding emitter life expectancy becomes available from end-users. Emitters carry a sizeable replacement cost and

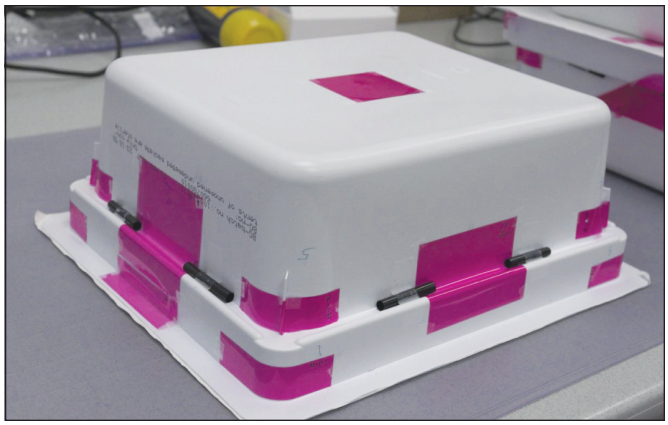


Figure 4. Low dose point determination using dose mapping with radio-chromatic film (tub is shown upside down to allow view of tub underside). Pink color of film indicates the tub was exposed to radiation.

Figure 5. Specially shaped reference tub with dose sensitive strips.[2]

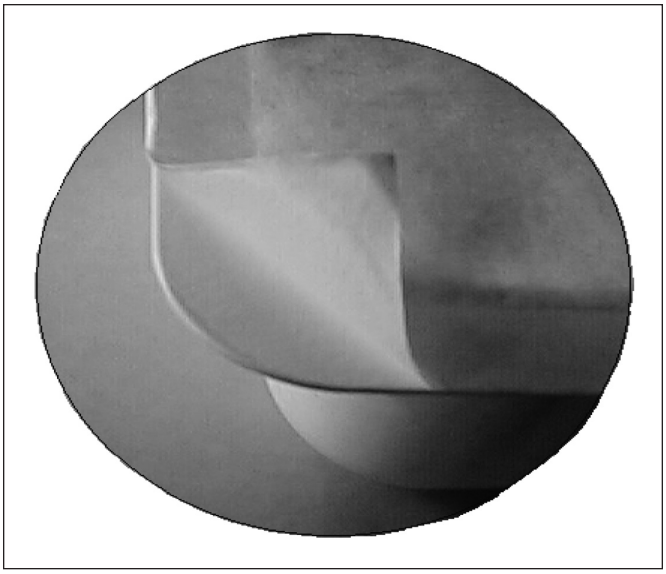


Figure 6. Not glued section of Tyvek lid in tub corner.

warranties regarding their life expectancy should be negotiated and defined with the equipment supplier.

Emitter Arc Flashing

Occasionally, and especially during the initial burn-in phase of an emitters life cycle, the e-beam emitter can shut down due to internal arc flashes. Arc flashes can occur in the high voltage system (power supplies, cables, connectors, emitters). However, e-beam controls monitor for this condition and protect the emitter from arc damage by shutting power off to the emitter instantly. Unfortunately, a loss of power to an emitter also means the loss of dose. As the emitters operate in a dose range that exceed the minimum operating requirements, the short duration of an emitter shutdown (i.e., 0.2s)[1] can be tolerated and will not generate and under-dosed tub. In the rare occasion of multiple arcs, the unit will stop. Upon re-start, the tub in question will be potentially overdosed and it is conveyed through filler without being opened or processed.

Process Interruptions

In case of a "hard stop" or equipment failure, which can occur at any time during the process, any tub that is within the radiation zone will be discarded and not enter the filling zone.

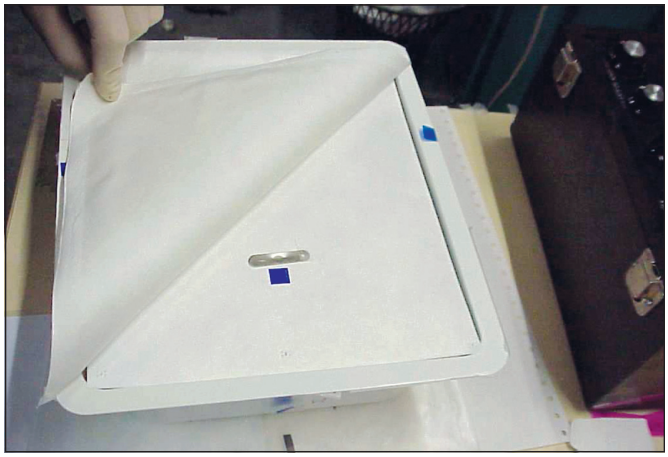


Figure 7. Additional Tyvek sheet under lid (liner).

Conclusions

Low energy e-beam surface decontamination systems are an effective means to facilitate the continuous transfer of presterilized syringe tubs into an aseptic filling area for high speed manufacturing lines. When e-beam emitters are installed in a tunnel system whose air pressure can be balanced against subsequent aseptic filling zones and whose interior can be

Figure 8. E-beam tunnel.

Figure 9. E-beam tunnel tub infeed.

Figure 10. Isolated syringe filling line. Output: 350 syringes per minute.

surface sanitized via VHP, they are ideal for the integration with barrier isolator systems.

The initial investment cost is high, but the total cost of ownership is expected to be low for high speed applications. They are very safe to operate and their validation is relatively "straight forward."

References

1. http://www.aeb.com/.
2. http://www.gexcorporation.com/.
3. http://www.risoe.dk/business_relations/Products_Services/Dosimetri/NUK_highdose_measurment_service.aspx?sc_lang=en.
4. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10098.
5. http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=33952.

About the Author

Oliver Vogt is the Director of Process and Equipment Engineering, providing global capital project delivery for Hospira, Inc. In that position, he is responsible for managing the corporate process, equipment, automation, and controls engineering functions supporting global capital projects for LVP, SVP, and device products, mainly barrier isolation, liquid and lyophilized manufacturing along with packaging and device assembly operations. His role involves partnering with Hospira operations plants to resolve capacity, new product and manufacturing line performance issues, and supporting initiatives involving engineering and manufacturing excellence. Vogt has more than 17 years of experience in project management, equipment engineering, and process design in the pharmaceutical industries. His career highlights include positions in plant engineering, EHS and maintenance management, high speed automation engineering, equipment development, design and fabrication. He is a member of ISPE and PDA. Vogt has been a speaker at several pharmaceutical industry symposia with a focus on manufacturing productivity and engineering excellence. Before joining Hospira in 2006, Vogt worked for TEVA Pharmaceuticals, Abbott Laboratories, and Optima Machinery Corporation. He received a BS in automation and equipment engineering from the State Academy in Mosbach, Germany and an MBA from Marquette University, Wisconsin. He can be contacted by telephone: 224-212-4847 or by email: oliver.vogt@hospira.com.

Hospira, Inc., Dept. 073W Bldg. H2-2, 275 N. Field Dr., Lake Forest, Illinois 60045, USA.

Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2010, Vol. 30 No. 1
www.ISPE.org

Microreactor Technology: Innovations in Production Processes

by Yukako Asano, Shigenori Togashi, Hidekazu Tsudome, and Sei Murakami

This article presents microreactor technology providing the effective numbering-up processes from R&D to plant construction, which enables facility and equipment installation times to be reduced and yields and product qualities to be improved.

Introduction

Micromachining technologies are being applied to the design of miniaturized devices for chemical synthetic applications, i.e., microreactors.[1,2,3] A microreactor is a device that has micro channels on the order of micrometers and that enables chemical reactions to be performed in reaction space several orders of magnitude smaller than conventional batch reactors.[4,5]

These downsizing effects bring a number of attractive features to microreactors. In this article, microreactor technology is introduced and the effective numbering-up processes from R&D to plant construction is explained using a microreactor system. Several examples of production process application for microreactors, including mixing, reactions, emulsification, and concentration of liquids are included.

Features of Microreactors

Figure 1 shows two mixing fields in typical Y-shaped microreactors obtained by fluid dynamics simulation. Figure 1 (a) shows a mixing field with a channel width of 1 mm corresponding to a batch mixing device, i.e., a batch reactor, and (b) shows another with a channel width of 0.1 mm corresponding to a microreactor. In the mixing field in batch mixing devices, the two kinds of fluid are barely mixed with each other, as shown in Figure 1 (a). In contrast, in the mixing field in a microreactor, the two kinds of fluid are mixed just after they are introduced into the field, as shown in Figure 1 (b).

These differences in mixing performance can be explained from the fact that the diffusion time of molecules, t, is proportional to the square of the channel width, L,

$$t \propto \frac{L^2}{D} \qquad (1)$$

where D is the diffusion coefficient of a molecule. As is apparent from Equation (1), when L is reduced to 1/10, the diffusion time is reduced to 1/100 and the two kinds of fluid can be mixed 100 times faster.

Table A shows examples of downsizing effects, including the above fast mixing.[6] In microreactors, the effects of parameters associated with surface, diffusion, heat transfer, viscosity, and surface tension become pronounced, while parameters associated with volume, mass, and inertia force have small effects. This gives microreactors several advantages. In a small reaction space with a high surface-to-volume

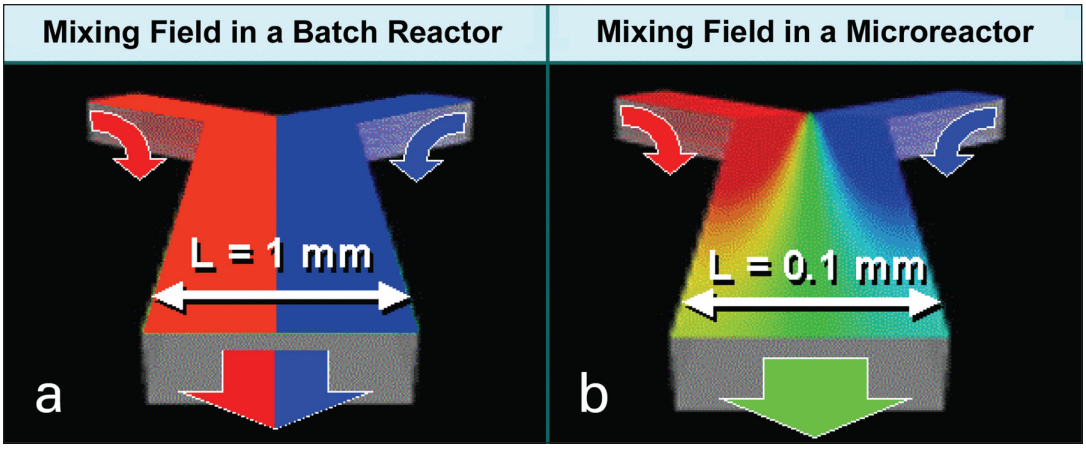


Figure 1. Two mixing fields in typical Y-shaped microreactors obtained by fluid dynamics simulation. (a) shows a mixing field with a channel width of 1 mm corresponding to a batch mixing device, i.e., a batch reactor, and (b) shows another with a channel width of 0.1 mm corresponding to a microreactor.

"These numbering-up processes enable facility and equipment installation times to be reduced, and yields and product qualities to be improved. Furthermore, it is possible to conserve space and energy with these processes."

Parameter	Symbol or Relation	Scaling Factor (size:1/ε)
Length	L	$1/\varepsilon$
Surface Area	S	$1/\varepsilon^2$
Volume	V	$1/\varepsilon^3$
Mass	$\rho \cdot V (= M)$	$1/\varepsilon^3$
Inertia Force	$M \cdot \alpha$	$1/\varepsilon^3$
Gravity	$M \cdot g$	$1/\varepsilon^3$
Pressure	-----	$\sim 1/\varepsilon^3$
Pressure Loss	-----	$\sim \varepsilon^3$
Surface Tension	$\sigma \cdot L$	$1/\varepsilon$
Molecular Diffusion	-----	$\sim 1/\varepsilon^3$
Heat Transfer	-----	$\sim 1/\varepsilon^3$

Table A. Examples of downsizing effects (L = length, S = surface area, V = volume, ρ = density, M = mass, α = acceleration, g = acceleration of gravity, σ = surface tension).

ratio, microreactors provide fast mixing and have accurate thermal and reaction time control.[1,2,3,6]

Because of these features, microreactors enable chemical reactions to be controlled, which accelerate reaction rates and improve yields. This has been reported in various reactions, including a Friedel-Crafts monoalkylation reaction,[7] a nitration reaction,[8] a Grignard reaction,[8] and a Sonogashira coupling reaction,[9] among others.

Moreover, continuous flow in microreactors enables reaction processes to be monitored, controlled, and analyzed and intermediate storage to be reduced. Process risks may be reduced, because there is small amount of substances in a microreactor.[6]

The time taken from R&D to plant construction also can be shortened by "numbering-up," i.e., parallel arrays of the same kinds of microreactors developed in the R&D stage for production increase. Figure 2 shows the processes from R&D to plant construction using the batch method and a microreactor.[6] In the batch method, a number of scale-up processes are necessary from R&D, through pilot plants, to plants for mass production. It is difficult to keep each stage equivalent under regulation during these scale-up processes. In contrast, in a microreactor, once a microreactor is optimized in the R&D stage, the same kinds of microreactors are arranged in parallel arrays in order to increase production.

These numbering-up processes enable facility and equipment installation times to be reduced, and yields and product qualities to be improved. Furthermore, it is possible to conserve space and energy with these processes.

From Product Development to Plant Construction with Microreactors

As explained before, the downsizing effects in microreactors give several advantages, such as fast mixing, accurate thermal control, and reaction time control. Basically, the reactions

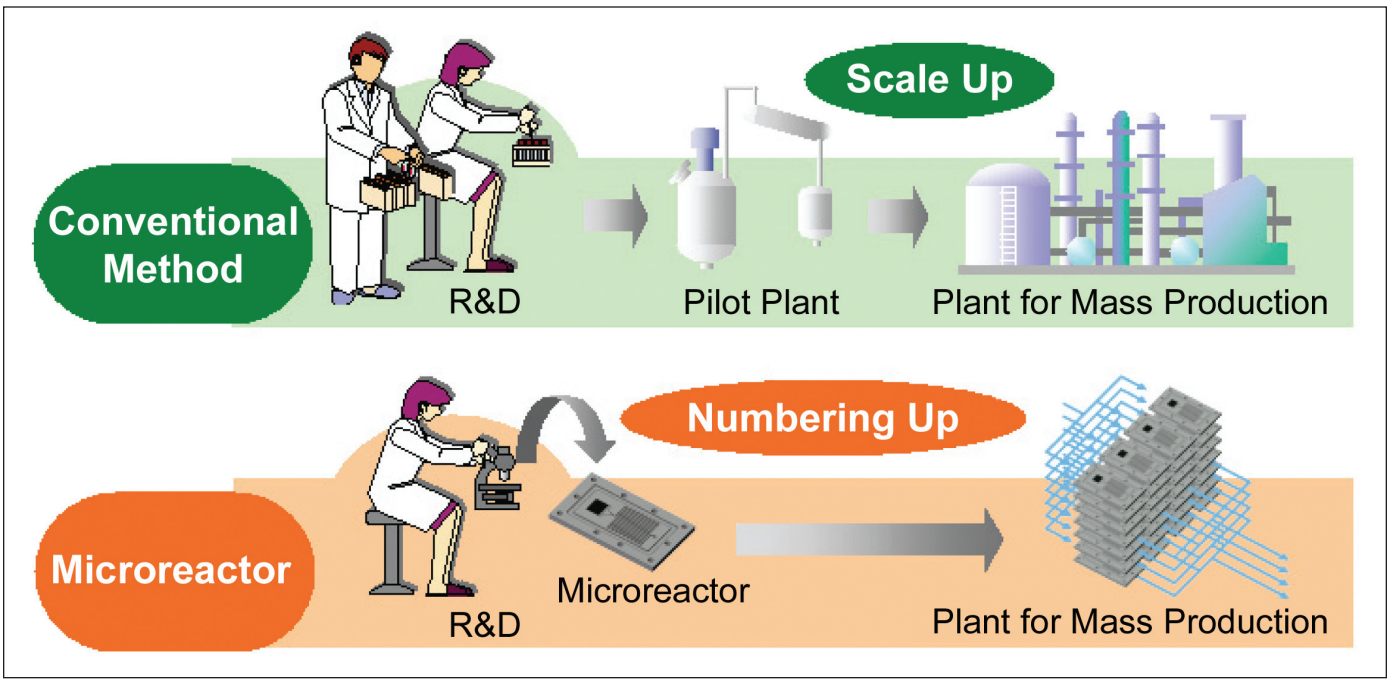


Figure 2. Processes from R&D to plant construction using the batch method and a microreactor.[6]

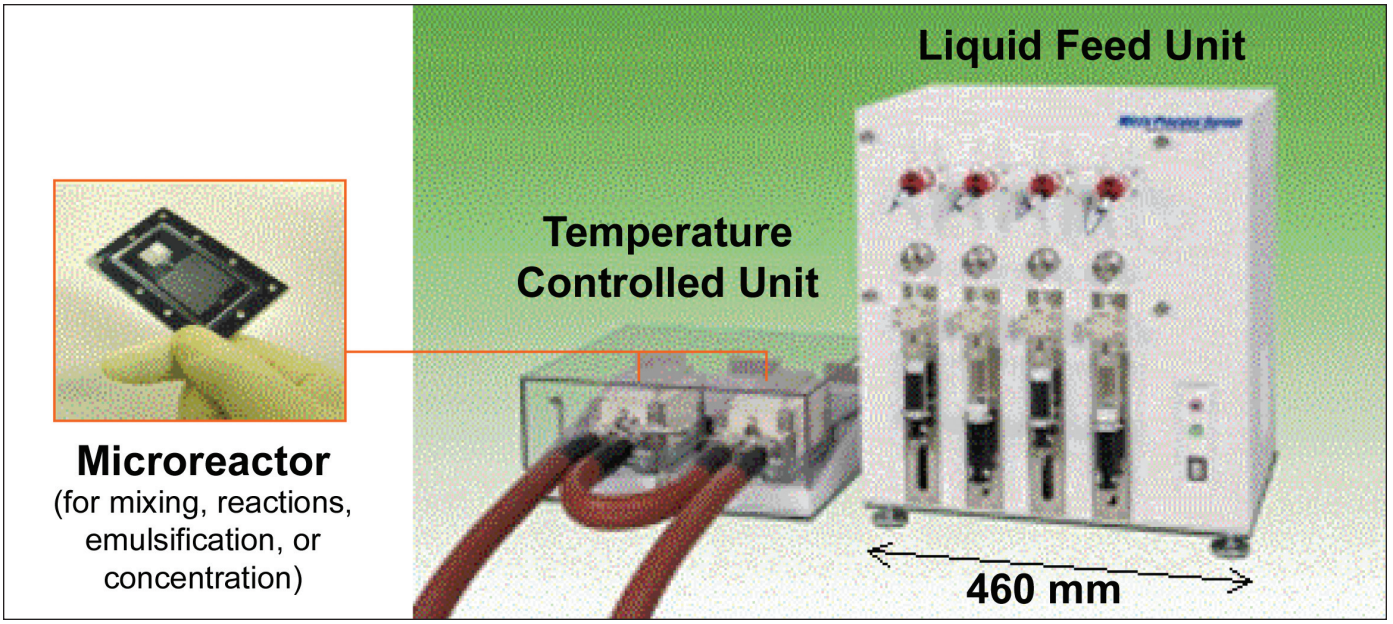


Figure 3. Micro Process Server for small volume production or R&D (460 mm (W) × 451 mm (D) × 536 mm (H)). The capacity is 30 mL/min.

with diffusion-controlled processes can benefit from the above features.[1,2,3,6] Microreactors and reaction conditions have to be optimized for the selected production process to obtain the maximum downsizing effects.

A flow of the numbering-up processes using a microreactor system is explained in the following. At first, a production process is selected for a microreactor (Step 1), and the process is analyzed using laboratory equipment (Step 2). Then, a microreactor is customized for the process (Step 3), and the production process is optimized (Step 4). Finally, a plant for mass production is constructed (Step 5). In what follows, the numbering-up processes with a microreactor system are introduced in the same order as these steps.

Step 1: Process Selection

A production process, i.e., mixing, a reaction, emulsification, or concentration of liquids is selected for a microreactor. Whether this selected process is appropriate for microreactors or not is clarified at Step 2 and Step 3.

Step 2: Process Analyzation

In this step, the process selected at Step 1 is analyzed via a microreactor system. Figure 3 shows a microreactor system for small volume production or R&D used at Step 2. This equipment is 460 mm (W) × 451 mm (D) × 536 mm (H) and consists of a liquid feed unit and a temperature controlled unit, which are controlled by a monitoring unit.

External Dimensions	460 mm (W) × 451 mm (D) × 536 mm (H)
Weight	35 kg (main unit)
Liquid Feed System	Electronically controlled syringe pump for continuous feeding
Capacity	30 mL/min
Settable Temperature Range	-20 to 120°C
Number of Microreactors Mounted	2 (available for two-stage reaction)

Table B. Equipment specifications of the Micro Process Server for small volume production or R&D.

The equipment specifications are shown in Table B. The liquid feed unit can store up to four syringes and electronically controlled syringe pumps for continuous feeding within the flow rate of 30 mL/min. The temperature controlled unit can have up to two microreactors mounted. Therefore, this system can be used in a two-stage reaction. The temperature controlled unit also can set temperatures over a range of -20 to 120°C by introducing the circulated fluid from the temperature controlled bath.

The process is applied to a microreactor with the standard channel structures and it is judged whether any downsizing effects appear or not. When there are any effects with a microreactor, it may be possible to maximize the effects with the customized microreactor for the process.

In some cases, some simulation technologies are introduced in order to make this step shorter. For example, reaction rates or reaction yields in reaction processes can be predicted with experimental results or quantum chemical calculations.[6,10] Emulsification processes also are predicted depending on

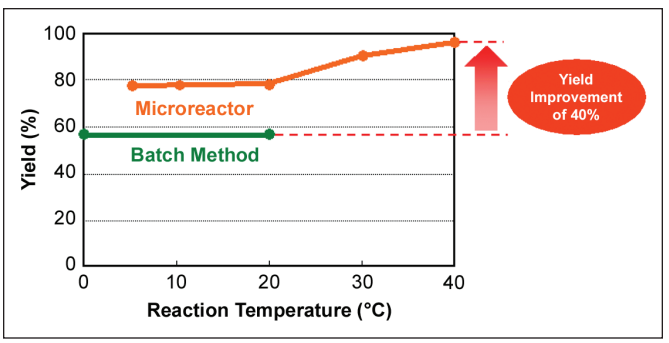


Figure 4. Dependence of the yields on the reaction temperature in the bromination reaction.[6]

Reaction	Reactants		Objective Product(s)	Byproduct
	A	B	P_1	P_2
Bromination	3,5-Dimethylphenol	Bromine	4-Bromo-3,5-dimethylphenol	2,4-Dibromo-3,5-dimethylphenol
Nitration	Phenol	Nitric acid	2-Nitrophenol and 4-nitrophenol	2,4-Dinitrophenol
Ester reduction	Isopropyl benzoate	Diisobutylalminium hydride (DIBAL)	Benzaldehyde	Benzyl alcohol

Table C. Three consecutive reactions applied to microreactors.[6,12]

the volume ratio of oil to water and the property of oil using a fluid dynamics simulation.[11]

Step 3: Microreactor Customization

Microreactors may be customized for the selected process in order to obtain the maximum downsizing effects. Step 3 and Step 2 can be repeated if necessary.

Figure 3 also shows an example of microreactors for mixing or reactions. The Micro Electro Mechanical Systems (MEMS) technology is used to miniaturize channels for the combined flow of liquids, which enables uniform mixing of liquids on the micrometer order.

Our fluid dynamics simulation technique is performed to figure out the best fluid channel structures, such as channel widths and channel lengths for the best mixture. For example, it can be simulated that the two liquids are introduced into multilayer channels and mixed uniformly in the microreactor in Figure 3, just after they have flowed together and contracted. The experimental results at Step 2, such as the reaction time and change in the reaction temperature, also are useful for the optimization of the channel structures.

The materials of microreactors also have to be selected depending on properties of liquids. Microreactors are made from metals, such as stainless steel or hastelloy alloy; resins, such as acrylic resin, silicon resin, or polyetheretherketone (PEEK); silicon; or quartz glass to name a few.

Step 4: Process Optimization

We have verified that microreactor technology enables faster and more accurate mixing, reactions, emulsification, and concentration of liquids, i.e., improves yields and product qualities. Several examples of production process applications for microreactors are introduced here.

1. Liquid Phase Mixing/Reaction Processes

In mixing/reaction processes, two different types of solutions mix homogenously. We applied consecutive reactions in Equations (2) and (3) to microreactors.

$$A + B \rightarrow P_1 \quad (2)$$

$$P_1 + B \rightarrow P_2 \quad (3)$$

where the molecules A and B are the reactants, the molecule P_1 is the monosubstitution in the first step reaction, and the molecule P_2 is the disubstitution in the second step reaction. Here, P_1 is the objective product and P_2 is the byproduct. However, P_2 in addition to P_1 are formed in the batch method.

We applied the following three consecutive reactions to microreactors, as shown in Table C: the bromination reaction of 3,5-dimethylphenol with bromine, the nitration reaction of phenol with nitric acid, and the ester reduction reaction of isopropyl benzoate with diisobutylalminium hydride (DIBAL).[6,12] In the bromination reaction, the 3,5-dimethylphenol solution in dichloromethane and bromine solution in dichloromethane were prepared with a molarity of 0.82 mol/L. These solutions were introduced into a microreactor and mixed with the identical equivalent at the reaction temperatures from 5 to 40°C. In the nitration reaction, the phenol solution in water and nitric acid solution in water were prepared with molarities of 0.90 mol/L and 15.78 mol/L, respectively. These solutions were mixed under the condition of excess nitric acid (the equivalent ratio of nitric acid to phenol was 7) at 25°C using a microreactor. In the ester reduction reaction, the isopropyl benzoate solution in toluene and DIBAL solution in toluene were prepared with a molarity of 0.1 mol/L. These solutions were introduced into a microreactor and mixed with the identical equivalent at the reaction temperatures from -70 to -10°C. These processes were performed in a nitrogen atmosphere to prevent the deactivation of DIBAL. Moreover, we performed experiments with the conventional batch method for comparison.

Table D shows the yields of the objective products, monosubstitutions by using the batch method and a microreactor.[6,12] As is apparent from Table D, the yields of objective products were improved by using a microreactor. In particular, the yield for the bromination reaction was improved by about 40 percent, from 58.6 to 98.6 percent.

Figure 4 shows the dependence of the yields on the reaction temperature in the bromination reaction.[6] Homogenous mixing using a microreactor provides larger yield at all reaction temperatures. Moreover, the dichloromethane solvent used limits the reaction temperature to about 20°C in the batch method with the open reaction system because this solvent is a volatile liquid and the boiling point is low (around 40°C). In contrast, a microreactor with the closed reaction system enables experiments even at the reaction temperature near 40°C because the system is under pressure and prevents

Reaction	Batch Method	Microreactor
Bromination	58.6	98.6
Nitration	77.0	86.3
Ester Reduction	25.2	38.1

Table D. Yields (%) of the objective products, monosubstitutions by using the batch method and a microreactor.[6,12]

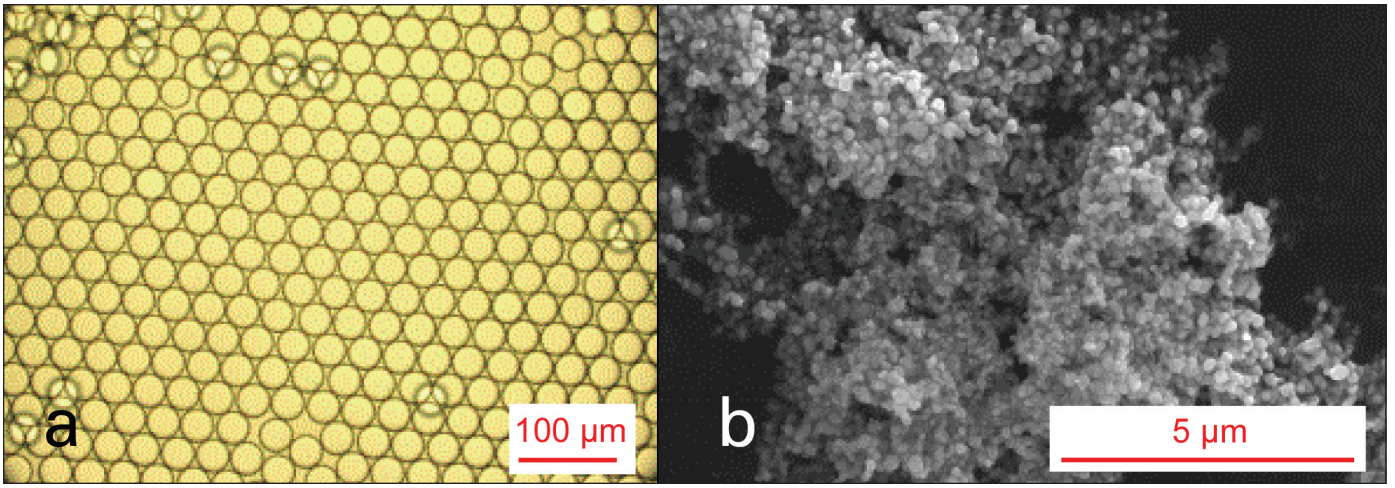


Figure 5. Photos of (a) emulsified droplets in water-in-oil emulsification using a microreactor and (b) nanoparticles of silver chloride generated by a microreactor.[11]

the solvent from vaporizing, and the yield reached 98.6%. Furthermore, the reaction time was less than one second and reduced to about 1/2000 when using a microreactor.[6]

2. Emulsification Processes

In emulsification processes, two different types of solutions make a heterogeneous system. One solution is dispersed, and emulsified droplets are formed in the other solution. A microreactor is expected to disperse emulsified droplets uniformly due to uniform mixing.

Figure 5 (a) shows a photo of emulsified droplets in water-in-oil emulsification using a microreactor.[11] The volume ratio of water to oil was 4. Uniformity of emulsified droplets was achieved with a maximum variation of 6.3 percent. Moreover, this emulsification process using a microreactor was performed under low pressures of 0.5 MPa or less and minimized a rise in temperature, which prevented thermal deterioration.

3. Nanoparticle Generation Processes

Nanoparticles have attracted attention, because properties on the nanometer order are quite different from those on larger orders. Nanoparticles are expected to be applied to a wide range of regions, such as catalysts, electronics, and photonics, among others. We applied the silver chloride generation reaction in Equation (4) to microreactors.

$$AgNO_3 + NaCl \rightarrow AgCl + Na^+ + NO_3^- \quad \textbf{(4)}$$

The 0.05 mol/L silver nitrate solution in water and the 0.05 mol/L sodium chloride and 0.05 mol/L polyvinylpyrrolidone (PVP) solution in water were prepared. PVP was added in order to prevent the generated nanoparticles from being aggregated. These solutions were introduced into a microreactor and mixed with the identical equivalent at 20°C. Moreover, we performed experiments with the conventional batch method for comparison.

In the batch method, the generated nanoparticles were widely distributed. In contrast, nanoparticle uniformity was obtained using a microreactor, as shown in Figure 5 (b). This comes from the fact that a microreactor enables uniform mixing of two reactants and accurate reaction time control.

4. Concentration Processes

The efficiency of concentration processes depends on the surface-to-volume ratio, thermal controllability, and degrees of vacuum, as typified by evaporators. Figure 6 shows a microreactors system for concentration on the basis of the principle of vacuum concentration. This system is 3400 mm (W) × 900 mm (D) × 2500 mm (H), and consists of a liquid feed unit and three concentration units, i.e., micro-evaporators with micro flow channels that form thin layers of liquids to the limit and provide accurate thermal control, which are controlled by a monitoring unit. The liquid feed unit also introduces hot water

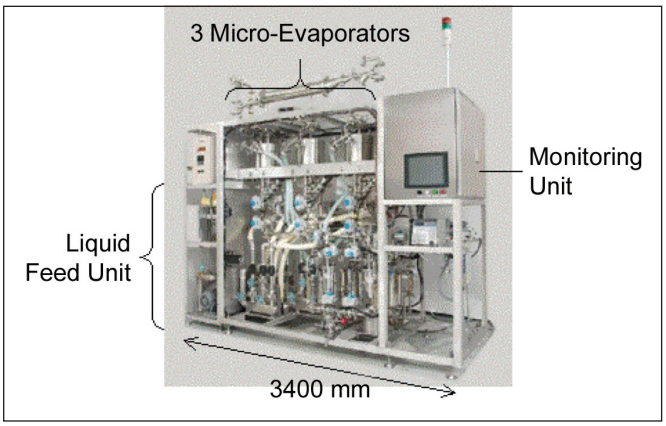


Figure 6. Micro Process Server for concentration (3400 mm (W) × 900 mm (D) × 2500 mm (H)).

External Dimensions	3400 mm (W) × 900 mm (D) × 2500 mm (H)
Weight	1300 kg
Liquid Feed System	Continuous double plunger pump
Capacity	600 mL/min (72,000 kg/year)
Numbering Up	3 micro-evaporators mounted in parallel

Table E. Equipment specifications of the Micro Process Server for concentration.

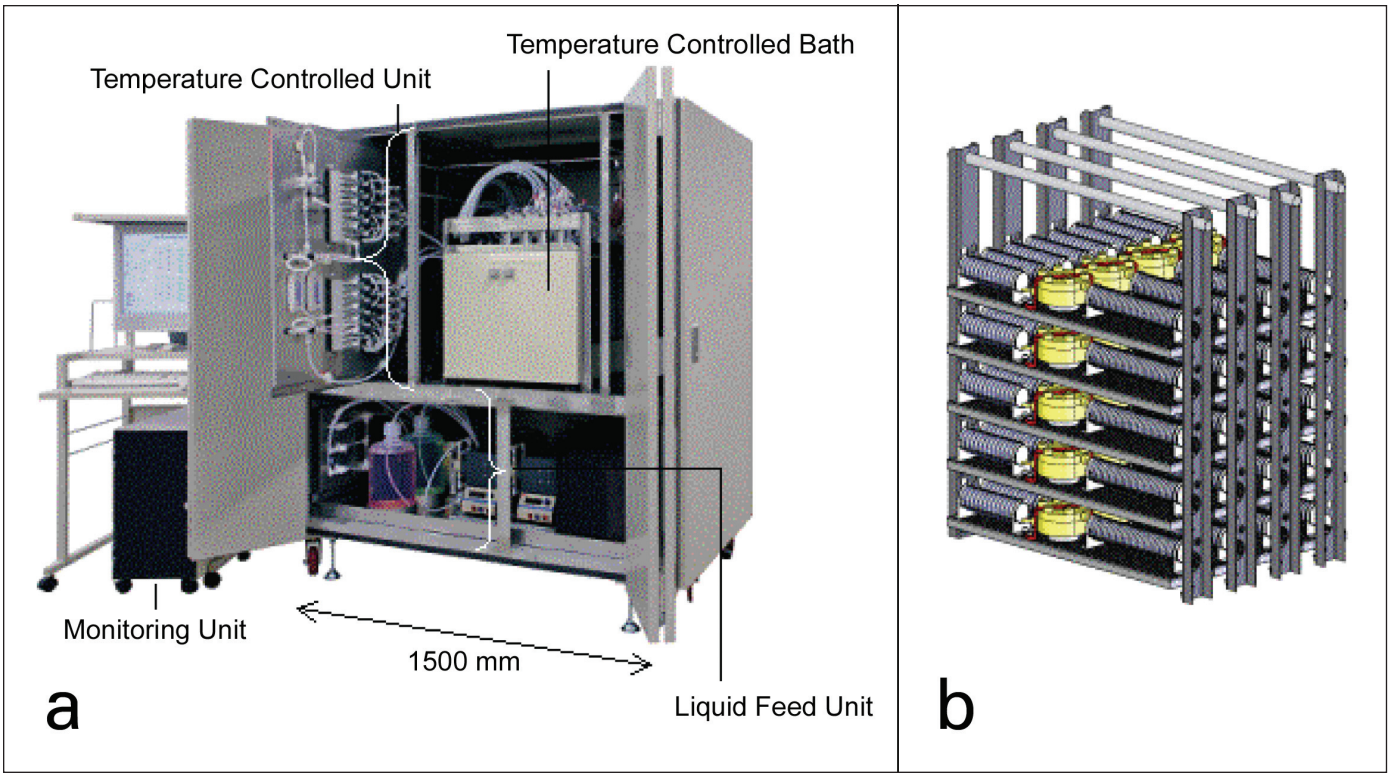


Figure 7. Prototype microreactor plant (1500 mm (W) × 900 mm (D) × 1500 mm (H)).[12] (a) shows the internal configuration, and (b) shows the numbering-up configuration of 20 microreactors installed in the temperature controlled bath.

into the channels of micro-evaporators under vacuum. The use of these micro-evaporators reduces the size of a production plant and minimizes any rise in temperature, preventing thermal deterioration.

The equipment specifications are shown in Table E. Fluid manipulation enables continuous flow rates of 600 mL/min (72,000 L/year) when the concentration rate of black vinegar is about eight. The concentration rate of black vinegar was up to 20. The micro-evaporators have no rotary components for easier maintenance and management. This Micro Process Server for concentration has successfully been in stable operation for 10 months as of March 2009 for the production of vinegar tablets.

Step 5: Plant Construction

At first, the prototype microreactor plant is shown in Figure 7.[12] Figure 7 (a) shows the internal configuration, and (b) shows the numbering-up configuration of 20 microreactors installed in a temperature controlled bath. This prototype plant is 1500 mm (W) × 900 mm (D) × 1500 mm (H). As shown in Figure 7 (a), this plant consists of a liquid feed unit and a temperature controlled unit that includes a temperature controlled bath, which are controlled by a monitoring unit.

These equipment specifications are shown in Table F.[12] Twenty microreactors are arranged in parallel like a computer blade server and are stacked five deep and in four rows, as shown in Figure 7 (b). The capacity is 600 mL/min, which corresponds to the production of 72,000 L/year. The reaction temperature is controlled over a range of -15 to 80°C with the temperature controlled bath. The monitoring unit monitors the flow rates of two reactants, the pressure on the uppermost and lowermost streamsides, and the temperatures of each microreactor and the circulated fluid in a temperature controlled bath.

The nitration reaction in Table C was performed in order to evaluate the performance of this prototype microreactor plant. Table G shows the yield using this microreactor plant (20 microreactors used) compared with the batch method and a microreactor (shown in Table D) in the nitration reaction.[12] Compared with the batch method, the yields of the objective products were increased, and at the same time, the yields of the byproducts were decreased by using microreactors. Moreover, the result using this microreactor plant was almost the same as when using one microreactor. Therefore, it was confirmed that this prototype microreactor plant with 20 numbering-up microreactors was able to increase the production scale without decreasing the yield of the products.

A microreactor system for large-volume production with double diaphragm pumps is shown in Figure 8 (a). This system is for mixing, reactions, and emulsification and is 1600 mm (W) × 900 mm (D) × 1400 mm (H). It consists of a liquid feed unit and a reaction unit, which are controlled by a monitoring unit. However, the system does not have a temperature controlled unit mounted to control temperatures.

The equipment specifications are shown in Table H (a). Two diaphragm pumps are installed and five microreactors are mounted in parallel. The capacity is 2,400 L/day (2 L/min) and is mostly equivalent to a sizing frame of a typical batch plant,

External Dimensions	1500 mm (W) × 900 mm (D) × 1500 mm (H)
Weight	450 kg (main unit)
Liquid Feed System	Continuous dual plunger pump
Capacity	600 mL/min (72,000 L/year)
Settable Temperature Range	-15 to 80°C
Numbering Up	20 microreactors mounted in parallel

Table F. Equipment specifications of a prototype microreactor plant.[12]

	Objective Products (2-Nitrophenol and 4-Nitrophenol)	Byproduct (2,4-Dinitrophenol)
Batch Method	77.0	7.7
One Microreactor	86.3	2.3
Prototype Microreactor Plant (20 microreactors used)	88.1	1.7

Table G. Yields (%) using the prototype microreactor plant (20 microreactors used) compared with the batch method and one microreactor in the nitration reaction.[12]

(a) Double Diaphragm Pumps	
External Dimensions	1600 mm (W) × 900 mm (D) × 1400 mm (H)
Weight	300 kg
Liquid Feed System	Continuous double diaphragm pump
Capacity	2,400 L/day (2 L/min)
Numbering Up	5 micoreactors mounted in parallel
(b) Double Syringe Pumps	
External Dimensions	1560 mm (W) × 1500 mm (D) × 1800 mm (H)
Weight	450 kg
Liquid Feed System for continuous feeding	Electronically controlled double syringe pump
Capacity	1,200 L/day (1 L/min)
Settable Temperature Range	5 to 80°C
Numbering Up	10 micoreactors mounted in parallel

Table H. Equipment specifications of the Micro Process Servers for large volume production with (a) double diaphragm pumps and with (b) double syringe pumps.

i.e., a 1,000 L vessel. It is possible to monitor the pressure and flow rates on the upstream sides of five microreactors.

Figure 8 (b) shows a microreactor system for large-volume production with double syringe pumps. This system is for mixing, reactions, and emulsification and is 1560 mm (W) ×1500 mm (D) × 1800 mm (H). It consists of a liquid feed unit and a temperature controlled unit, which are controlled by a monitoring unit. The temperature controlled unit includes a temperature controlled bath.

The equipment specifications are shown in Table H (b). Ten double syringe pumps are mounted, and 10 microreactors are installed in parallel in the temperature controlled bath. The capacity is 1,200 L/day (1 L/min) and is just equivalent to a sizing frame of a typical batch plant. The double syringe pumps enable accurate feed control. The reaction temperature is controlled over a range of 5 to 80°C with the temperature controlled bath. The monitoring unit monitors the pressure on the upstream side of 10 microreactors and the circulated fluid in the temperature controlled bath.

Summary

In this article, microreactor technology was introduced, including the features of microreactors, and the effective numbering-up processes were explained from R&D to plant construction using a microreactor system.

Several examples were shown of production process applications for microreactors: mixing, reactions, emulsification, and concentration of liquids. It was verified that microreactors enabled facility and equipment installation times to be reduced and yields and product qualities to be improved.

In liquid phase mixing/reaction processes, there appeared the yield improvements of objective products. In particular,

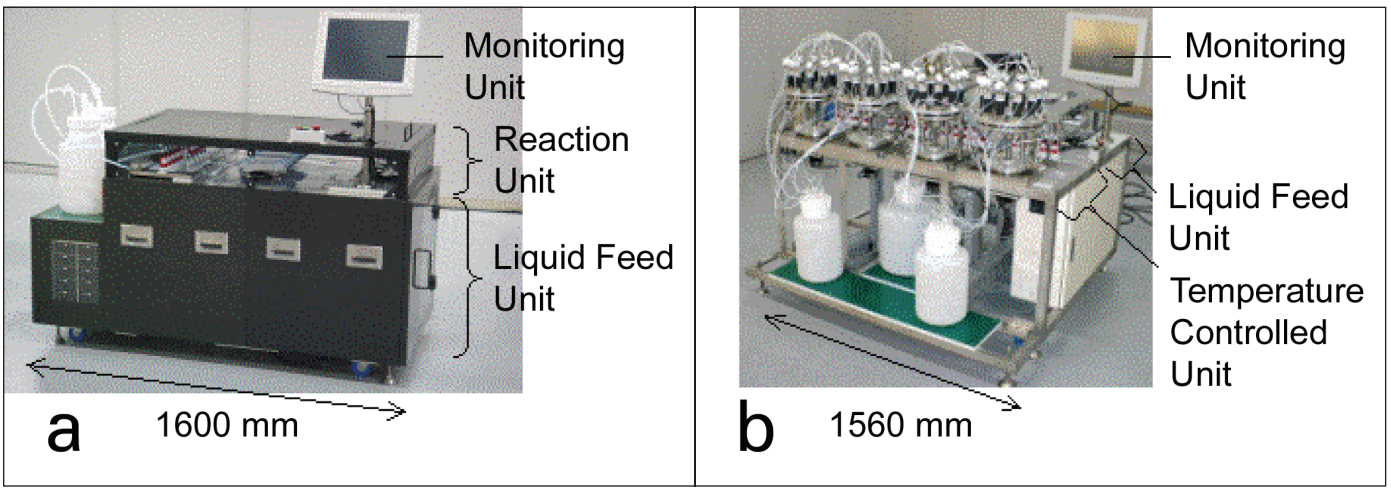


Figure 8. Micro Process Servers for large-volume production with (a) double diaphragm pumps (1600 mm (W) × 900 mm (D) × 1400 mm (H)) and with (b) double syringe pumps (1560 mm (W) × 1500 mm (D) × 1800 mm (H)).

"It is known that it takes about 11 years from the preclinical testing to the approval in pharmaceutical fields.[13] We have had experience of going through Steps 1 through 5, i.e., from R&D to plant construction in one year."

the yield for the bromination reaction was improved by about 40 percent. Uniform emulsified droplets were generated in the emulsification process. Similarly, uniform nanoparticles were generated in a nanoparticle generation process. In the concentration process, the concentration rate of black vinegar, a functional food, was up to 20. The system for concentration has successfully been in stable operation for 10 months as of March 2009 for the production of vinegar tablets.

As explained before, microreactor processes are quite different from the conventional batch processes. The larger surface-to-volume ratios of microreactors can bring more easy corrosion. Crystal precipitation can block small micro channels. However, these challenges may be solved by increased experiences of using microreactors.

In the batch method, a number of the scale-up processes are necessary from R&D to plant construction. It is known that it takes about 11 years from the preclinical testing to the approval in pharmaceutical fields.[13] We have had experience of going through Steps 1 through 5, i.e., from R&D to plant construction in one year. The time for scale-up can be shortened with microreactors. Microreactors can contribute to more efficient volume production.

References

1. Benson, R.S. and Ponton, J.W., "Process Miniaturization – A Route to Total Environmental Acceptability?", *Trans. Inst. Chem. Eng.*, Vol. A71, 1993, pp. 160-168.
2. Schubert, K., Bier, W., Keller, W., Linder, G., and Seidel, D., "Gas to Gas Heat Transfer in Micro Heat Exchangers," *Chem. Eng. Process.*, Vol. 32, No. 1, 1993, pp. 33-43.
3. Ehrfeld, W., Golbig, K., Hessel, V., Löwe, H., and Richter, T., "Characterization of Mixing in Micromixers by a Test Reaction: Single Mixing Units and Mixer Arrays," *Ind. Eng. Chem. Res.*, Vol. 38, 1999, pp. 1075-1082.
4. Hessel, V., Hardt, S., and Löwe, H. (eds.), **Chemical Micro Process Engineering: Fundamentals, Modeling and Reactions**, Wiley-VCH, 2004.
5. Hessel, V., Löwe, H., Müller, A., and Kolb, G. (eds.), **Chemical Micro Process Engineering: Processing and Plants**, Wiley-VCH, 2005.
6. Asano, Y., Togashi, S., Shiraishi T., Kawamura, T., and Oda, M., "Challenges and Benefits of Microreactor Technology in API Manufacturing," 2005 ISPE Annual Meeting.
7. Suga, S., Nagaki, A., and Yoshida, J., "Highly Selective Friedel–Crafts monoalkylation using Micromixing," *Chem. Commun.*, Vol. 3, 2003, pp. 354-355.
8. Taghavi-Moghadam, S., Kleemann, A., and Golbig, K.G., "Microreaction Technology as a Novel Approach to Drug Design, Process Development and Reliability," *Org. Proc. Res. Dev.*, Vol. 5, No. 6, 2001, pp. 652-658.
9. Fukuyama, T., Shinmen, M., Nishitani, S., Sato, M., and Ryu, I., "A Copper-Free Sonogashira Coupling Reaction in Ionic Liquids and its Application to a Microflow System for Efficient Catalyst Recycling," *Org. Lett.*, Vol. 4, No. 10, 2002, pp. 1691-1694.
10. Asano, Y. and Togashi, S., "A Study on Solvent Effects using a Microreactor," submitted to *J. Chem. Eng. J.*
11. Katayama, E., Miyamoto, T., Togashi, S., and Endo, Y., "Computational Fluid Dynamics of Water-in-Oil Emulsion using Microreactor," International Symposium on Micro Chemical Process and Synthesis (MiPS2008), Extended Abstract, 2008, pp. 14.
12. Hessel, V., Schouten, J.C., Renken, A., and Yoshida, J.I. (eds.), **Micro Process Engineering: A Comprehensive Handbook**, Wiley-VCH, 2009.
13. The Pharmaceutical Research and Manufacturers of America (PhRMA), "Research and Development," http://www.phrma.org/, 2005.

About the Authors

Yukako Asano, PhD is a Researcher at the Mechanical Engineering Research Laboratory, Hitachi, Ltd., Tokyo, Japan. She focused her doctoral program on chemistry and obtained a PhD in science from Keio University, Japan. She has engaged in the research and development of pharmaceutical plants, particularly microreactors and microreactor systems. She is a member of ISPE, the Society of Chemical Engineers, Japan, the Theoretical Chemistry Society, the Society for Chemistry and Micro-Nano Systems, and the Chem-Bio Informatics Society. She can be contacted by e-mail: yukako.asano.dp@hitachi.com.

Shigenori Togashi, PhD is a Senior Researcher and Deputy Department Manager of the Mechanical Engineering Research Laboratory, Hitachi, Ltd., Tokyo, Japan. He focused his doctoral program on mechanical engineering and obtained a PhD in engineering from the University of Tokyo, Japan. He has mainly engaged in fluid system controls and fluid dynamics simulations for home appliances, cell culture apparatus, cell detectors, biochemical analyzers, microreactors, and microreactor systems, among others. He is a member of the Society of Chemical Engineers, Japan, the Chemical Society of Japan, the Japan Society of Fluid Mechanics, the Society for Chemistry and Micro-Nano Systems, and the Chem-Bio Informatics Society. He can be contacted by e-mail: shigenori.togashi.gf@hitachi.com.

Mechanical Engineering Research Laboratory, Hitachi, Ltd., 832-2, Horiguchi, Hitachinaka, Ibaraki, 312-0034, Japan.

Hidekazu Tsudome is a Senior Researcher at the Tsuchiura Research Laboratory, Hitachi Plant Technologies, Ltd., Tokyo, Japan. He has developed a new micro-reaction device: a high speed micro-evaporator (concentrator) with extremely low thermal damage to sample ingredients for the food industry. This system was commercialized and has successfully been in stable operation for 10 months as of March 2009 for the production of vinegar tablets. He is a member of the Institute of Electrical Engineers of Japan and the Society for Chemistry and Micro-Nano Systems. He can be contacted by e-mail: hidekazu.tsudome.ju@hitachi-pt.com.

Social Infrastructure and Industrial Machinery Systems Group, Hitachi Plant Technologies, Ltd., 603 Kandatsu-machi, Tsuchiura, Ibaraki, 300-0013, Japan.

Sei Murakami, PhD is a General Manager of Industrial Plant Systems Group, Hitachi Plant Technologies, Ltd., Tokyo, Japan. He is a BS graduate of Osaka University, Japan, and holds a PhD in engineering from Yamaguchi University, Japan. His job responsibilities include pharmaceutical manufacturing plant development, engineering, design, and construction. He joined the mammalian cell culture research project at MIT, 1989. He is a member of ISPE, PDA, ASME, the Japanese Association for Animal Cell Technology, and the Institution of Professional Engineers, Japan. He can be contacted by e-mail: sei.murakami.dg@hitachi-pt.com.

Industrial Plant Systems Group, Hitachi Plant Technologies, Ltd., Rise Arena Bldg. 5-2 Higashi-Ikebukuro 4-chome, Toshima-ku, Tokyo, 170-8466, Japan.

Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2010, Vol. 30 No. 1
www.ISPE.org

Wesley P. Wheeler discusses the current state of contract manufacturing in a challenging economic environment and how Patheon strives for efficiency and service excellence under his leadership.

PHARMACEUTICAL ENGINEERING Interviews
Wesley P. Wheeler, CEO and President, Patheon

by Gloria N. Hall, Editor, *Pharmaceutical Engineering*

Wesley P. Wheeler is CEO and President of Patheon Inc., a leading global provider of drug development and manufacturing services to the international pharmaceutical industry. Wheeler's 30-year career includes multinational experience in pharmaceutical manufacturing, sales and marketing, R&D, and engineering with three global pharmaceutical companies. He joined Patheon from Valeant Pharmaceuticals International, a California-based global specialty pharmaceutical company, where he served most recently as President, North America, R&D, and Global Manufacturing. Prior to joining Valeant in 2003, Wheeler served as President and Chief Executive Officer of DSM Pharmaceuticals Inc., a contract pharmaceutical manufacturer, where he led the organization through a business turnaround, significantly increasing new business, compliance, and profitability in approximately 13 months. Prior to DSM, Wheeler was Senior Vice-President of Logistics and Strategy for GlaxoSmithKline plc. In this role, Wheeler was responsible for managing the manufacturing rationalization of Glaxo Wellcome and SmithKline Beecham, which included a supply network of over 100 plants in 41 countries. Previous to his manufacturing role, Wheeler was Vice President of Marketing for Glaxo Wellcome, responsible for antibiotic, antiviral, gastrointestinal, and metabolic products. In addition to brand marketing, he was instrumental in developing the marketing services infrastructure for Glaxo Wellcome. Wheeler joined Glaxo in 1989 after a 12-year career at Exxon Research & Engineering Co. Wheeler holds a BS degree in mechanical engineering from Worcester Polytechnic Institute and an MBA degree from California Lutheran University.

Q In 2008, Patheon moved its headquarters from Ontario, Canada to Research Triangle Park, North Carolina. How does this relocation fit into the company's strategic growth plan?

A Relocating the headquarters to the US was a decision we made in early 2008, just after I joined the company. We evaluated multiple cities and the Research Triangle Park area provided us the best combination of proximity to customers, talent, and effective cost of living.

Q How long has Patheon been restructuring itself and what have been the major changes within the company to date?

A The company has struggled since its acquisition of MOVA Pharmaceuticals in Puerto Rico almost five years ago. The main issue was reduction of revenue while maintaining three sites. The cost of multiple staff, high cost of energy and reduced revenue combined to turn our P&L upside down. We are turning the situation in Puerto Rico around. We are now stabilizing our revenue base and consolidating all of our resources into one site at Manati.

The biggest challenge in the past year has been the impact of the global economic downturn on our customer base. Our Pharma-

ceutical Development Services (PDS) customers have experienced some cash constraints, which has led to development programs being placed on hold or cancelled, particularly early phase development projects. On the Commercial Manufacturing side of our business, we're still working with our clients to make the in-source vs. outsource decision, particularly as our industry is flush with unused capacity. The economic situation has placed even more stress on our clients to watch costs and limit the scope of their own re-structuring programs.

Q What is the company's strategy in dealing with loss revenue from scaled-back or cancelled projects? As a contract manufacturer, how is Patheon surviving?

A We feel that we are well positioned for growth. We have a very lean structure and have improved on all 18 of our operating metrics. Our PatheonAdvantage program is driving incredible results at all sites. We have a diversified portfolio of business which allows us to weather downsides. We are very diverse in our offering and can turn capital projects quickly through the use of ePM and aggressive project management. We can move equipment from site to site, and we are taking advantage of the extensive used equipment market when necessary. We have weathered the storm well and look forward to growing both in terms of volume and market share.

Q Do you think that pharmaceutical and biotechnology companies are adopting outsourcing strategies for cost, for access to new technology, or for a quicker time to market?

A Cost is a driver for manufacturing outsourcing, but we don't see it as the biggest driver. Efficiency and service excellence are the biggest drivers. Companies are evaluating their cost-basis overall and analyzing if it strategically and economically makes sense to have internal Manufacturing. Historically, companies have built factories to assure security of supply and mitigate risk; this is where our new performance guarantee comes in. As far as I know, we're the only company in our industry offering guaranteed on-time delivery in every new Commercial Contract we sign. We need to make it clear to our clients that they don't need to build a factory to have security of supply.

Q How does Patheon achieve the "4-6-8 Promise" of its Quick to Market program? What are some of the elements or tools of your program that allows the company to rapidly develop or transfer commercial products to manufacturing facilities within Patheon's network?

A The 4-6-8 and Quick to Market programs are in place to emphasize that we can move as fast, or at times faster, than our clients. Many times clients will fear that they will lose time working with their partners and third-parties on very time sensitive projects, particularly commercial launch projects. We have a very robust set of project management tools and resources that enable us to be in lock-step with our customers.

Q What Lean Manufacturing or Operational Excellence tools has Patheon employed?

A We have a comprehensive Global Program we launched when I arrived called Patheon Advantage (PA). We're making great progress. It's all about culture change, on both fronts. The fundamentals of Lean Six Sigma support the fundamentals of Quality by Design (QbD): customer focus, data-based decisions, and statistical analyses – not instinct – to manage risk. Some tools, particularly Quality Function Deployment, Design for Six Sigma, and Design of Experiments are particularly well-matched with QBD. We're finding that the methods we're developing and the culture change we're building with PA fully support our move to QbD.

Q What have been your most significant achievements within your Technical Excellence Program?

A Patheon Advantage is successful for us because it is based on the principles of Lean Six Sigma: focus on customer value, make decisions based on data, eliminate waste and variation, and engage our people to make change. One of the most valuable Lean Six Sigma tools for us has been value stream mapping. It helps us understand our business "door-to-door," so we can eliminate the bottlenecks and waste that inhibit responsiveness and increase cost.

Q How does Patheon respond to the volatility of the US versus Canadian dollar?

A The company's debt is US dollars and Euros, which is most of our revenue currencies so that creates a natural hedge. In Canada, we have a few Canadian plants (costs in Canadian dollars); however, a majority of those contracts are in US dollars business (revenue) so we do basic currency hedging to prevent surprises driven by currency fluctuation.

Q How does Patheon manage changing international regulations since some areas are conflicting?

A Over the past 10 years, the major regulatory agencies (FDA, EMEA, and Japan) have made significant progress in harmonization. In our sites where we supply multiple countries and regions, which is most of our facilities, we have specific process and procedures to deal with any nuances or conflicts. However, it is still very clear to me that the US and European inspections standards and styles are quite different, and we do our best to work with all of them.

Q Are there any plans for Patheon to generate their own products?

"All of us, contractor and owner alike, are struggling with many of the same issues, such as regulatory harmonization, counterfeiting, inspection standards, RFID, technology transfer requirements, etc."

A We're a services company and have no plans to become a product company. Having said that, we're constantly acquiring or developing technologies and solutions that can be value added for our customers. Our model will be to gain more annuity revenues from these technologies or to develop creative deals with customers, rather than to develop our own products.

Q What are challenges in technology transfer?

A Although technology transfers are never easy, we have a pretty well developed process for "on-boarding" new products into facilities. Many of the challenges arise if you didn't get enough data from the customer up front in doing the contract and you get "surprises" as you're starting the transfer. We've learned from this in the past and have strong contacting procedures to guard against this.

Q How can ISPE serve contract manufacturers better?

A I have recommended to ISPE in the past that they become the voice of manufacturing in our industry. The Society has had an excellent run in the engineering and validation spaces, and has made a huge contribution to manufacturing vis a vis the Baseline Guides. I think it is time for ISPE to 'own' the manufacturing space as well. All of us, contractor and owner alike, are struggling with many of the same issues, such as regulatory harmonization, counterfeiting, inspection standards, RFID, technology transfer requirements, etc. I think we should take another run at SUPAC, for example, in an effort to allow faster and easier movement of products from one site to another.

Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2010, Vol. 30 No. 1
www.ISPE.org

This article covers the methods, technologies, and case studies for the automated testing of an installed system.

Test Automation in GxP Regulated Environments

by Radha Ramesh

Introduction

Automated test tools can bring many benefits to testing of systems in GxP regulated environments, including:

- increased repeatability and consistency
- faster identification of defects
- more comprehensive regression testing
- more efficient compliance
- wider test coverage
- deeper and more thorough testing

There is no reason why appropriate test automation should not be applied in a GxP regulated environment, as long as the approach is documented and justified and provides adequate and secure objective evidence.

Automated test tools can be applied throughout the software development life cycle, including business modeling, requirements management, configuration management, defect tracking, syntax checking, coverage analysis, and unit testing.

The intent of this article is to focus on methods and technologies for the automated testing of an installed product, application, or system. It does not consider methods or tools used for other purposes. Here, testing can be considered from three key points-of-view:

1. The "how" – mechanisms used to drive a test.

2. The "what" – aspects of the software specifically being tested.

3. The "needs" – those business or operation requirements that motivate the need for testing (for example, as part of a migration or infrastructure qualification effort).

Testing Mechanisms

Generally, software testing tools and technologies provide users with either a Graphical User Interface (GUI) for configuration or a command-line for inputs needed to apply their functionality and services. Application Programming Interface (API) testing, which directly drives the system beneath the business or application logic layer, is another approach. However, this requires access to the underlying code and is most often used in software development rather than test environments.

Graphical Test Interfaces

An attractive feature of typical GUI-based software testing is that it can be relatively simple to create tests through a so-called "capture/playback" feature. Here, while operating the system under test, its services and functionality are exercised while in "record" mode and a desired sequence of events is captured. This ease-of-use provides significant benefits. A problem with this approach is that even the smallest change to the user interface will cause the tests to fail. Tool vendors overcome this by providing some kind of scripting language. Taking advantage of this requires some level of technical expertise although diminishing some of the value provided by the GUI.

Command-Line Scripting

If the system under test can be invoked and pass parameters from a DOS/Windows or UNIX command line, then testing can be automated by generating input strings. Results can be assessed by looking for specific messages or by comparing outputs with known, expected results. The ability to compare files, messages, or even graphic images will require either the coding of custom scripts or the use of an

Benefits of Automated Software Testing

The advantages to automating a system, especially when it is custom built, requiring multiple versions or third party software that gets regularly updated, are innumerable.

- Testing and automation provide increased consistency in the organization's deployed systems through consistent application with increased quality results. There is a faster execution with more defects found earlier, thereby improving quality.
- Automation technology can mean faster test execution that saves both time and money, while allowing the involvement of non-technical personnel in the validation process. Can run a larger number of tests in more situations (i.e., run a more complete suite of regression tests on patches or upgrades).
- With automated test technology, organizations can test whenever changes occur or as often as they like to verify that they are in compliance, reducing worry and risk.
- Deeper and more thorough testing: with data-driven testing, it becomes easy to execute multiple test iterations using different data sets, allowing coverage of more data permutations than would be possible using traditional manual methods.
- The ability to test applications under load with multiple users is very difficult, ineffective, and costly if done manually, while automated performance testing tools allow stress testing of the application in a repeatable fashion against large numbers of virtual users.
- Testing can run unattended.
- The process used to automate a software test also lends itself to making a "movie" of a specific process – and that "movie" can subsequently be an extremely useful training tool.
- Reducing compliance risk through electronic pre and post approvals. Rather than being part of a specific phase within validation, the traceability matrix is a tool that can be used to assure the completeness of validation. The electronic signature workflows for pre and post approval testing; fully electronic reviews and approvals that can be completed anywhere at anytime with internet access allows for flexibility during test execution, review, and approvals.
- Electronic traceability of requirements to testing as well as the clear and concise reporting on testing activities reduces paper work and improves efficiency.
- During test automation, using integrated data tables to pump large volumes of data or using parameters to call business rules that can be maintained separately assists in normalizing the testing effort and increasing the coverage of tests executed.

accompanying comparison tool. An important advantage of command-line scripting is that one or more languages, such as Perl, can provide a powerful environment for generating files – especially large files – for program inputs or for comparison with program outputs.

API Test Harnesses

Where the system under test adheres to layered design with a thin (shallow layers on top of the program) GUI that communicates with a business logic layer, which in turn interacts with a data layer, simple and highly effective tests can be created using tools designed to exercise the business logic layer directly with only a few syntax requirements. Here, tests are created as inputs paired with expected outputs that can be employed by users whose interest is to verify that the requirements for a given custom built application are satisfied.

Testing Specific Aspects of Software

Exercising and evaluating specific characteristics of a software implementation – the "what" realm – testing generally focuses on one or more capabilities as defined by the requirements and specification used to design and build an application. Identifying the purpose for a particular test and the benchmarks needed for an evaluation is essential to the proper formulation of the test itself. Apart from common examples, such as functional testing, load, stress, and performance testing, compatibility, safety/hazard, and security testing, other automated testing types include:

- content and data migrations
- infrastructure
- web-based applications
- manufacturing

These are considered separately below.

Automated Testing of Content and Data Migrations

Automated migration testing can be used efficiently to extend sampling to larger data sets, increasing the precision of measurement and the overall accuracy of the data migration process. For any target GxP instance, it is essential to validate each migration so that sufficient evidence is collected to ensure a high degree of confidence that the system will meet its intended use.

Automated testing provides significant benefits when compared to the more common approach of manual sampling. These include:

- tight integration with the migration specification where all source to destination mappings must be defined
- ability to test 100% of the migrated data and/or content
- verification of the mapping rules[1] that define the required transformations of the legacy data and/or unstructured content to a destination system
- testing of the mapping rules must be performed independent of the migration process (do not use the migration

tool configured with the mappings to perform this test)
- report deviations identified and tie those deviations to the source and target records
- report all migration results inclusive of deviations and fields migrated "as expected" for destination system support and auditing
- rapid production execution[2] and time-to-deployment of target (recipient) systems

Automated Testing for Infrastructure

Large IT departments often deal with complex infrastructures of networks, firewalls, switches, routers, and servers. As a result, it can be quite cumbersome and difficult to ensure that all infrastructure components subject to compliance are in fact maintained in a compliant state.

For example, in a Linux environment where hundreds of servers are regularly updated with security patches, the process of manually verifying configurations can become nearly unmanageable in many cases.

Automating the infrastructure testing processes can effectively address this challenge. If a baseline configuration can be defined for an infrastructure component, an automated tool can rapidly and accurately verify which component adheres to that configuration and which does not.

The way in which these tools are primarily used is to conduct an Installation Qualification (IQ) when the server is installed and configured. Subsequently, the operational level checks (such as security, Sarbanes Oxley (SOX) compliance, etc.) are conducted periodically (i.e., once a month).

Since this whole process is automated and tied to a database, compliance becomes a more manageable task and allows the organization to scale to the growing business needs.

Automating Testing for Web-Based Applications

Automated web testing tools can play a crucial role in the definition and usage of quality models. They are important for reasons that are very similar – in fact echo – those associated with other test domains as previously discussed, such as non-web software and infrastructure, because they:

- can implement to objective metrics
- are systematic and mostly error free
- are much more cost-effective than manual approaches

These tools are available in a number of types, including:

- accessibility testing and repair
- usability
- performance testing
- security testing
- analyzing web server logs
- classifying a site based on criteria acquired from other web sites

There are certain drawbacks with the use of these tools – they are limited in their capacity to assess entire sets of properties and the results they generate often require manual intervention for proper review and interpretation.

Yet common quality models for web implementations often include testing attributes that are amenable to automated testing. Assessments can be calibrated through appropriate configuration and results weighed according to criteria defined within the application.

Automated Testing for Manufacturing

Automated testing in the manufacturing environment commonly addresses systems whose purpose is to automate the manufacturing process itself. These in turn are generally comprised of three functional system types:

1. process supervision
2. process information management
3. production scheduling

The above often include a mix of programmable logic controllers, distributed control systems, operator workstations, report printers, secure networks, and servers.

First, *process supervision*. These components read information from and produce outputs to physical equipment, such as agitators, valves, and pumps. Because of safety concerns, automated testing cannot be extensively applied to them. Instead, testing must be applied across several phases starting with a simulated environment.

Second, *process information management*. These systems commonly interface with other applications, such as warehouse inventory control, weighing and dispensing, and Laboratory Information Management Systems (LIMS) in order to complete the processing history and materials genealogy. Process information management implementations are good candidates for automated testing, because they are in effect read-only environments. Functional and performance testing of the Human-Machine Interface (HMI), report generators, and the programmatic interfaces to systems, such as LIMS, can present tedious work and benefit from automated testing tools and methods.

Finally, *production scheduling*. This component determines where a particular batch of product is to be made, the materials to be used, and the date and time when the batch should be run. Production scheduling also may be a good candidate, depending on the level of automation used here (in some facilities, there is extensive human involvement in scheduling). However, again for safety reasons, this component must be carefully controlled, so as to not initiate any inadvertent or hazardous physical activity on the manufacturing floor.

Therefore, manufacturing automation systems are typically not good candidates for test automation, but it has been applied successfully in some areas. Examples include LIMS and environments where simulations enable testing to avoid use of chemicals and materials that would otherwise be employed.

Case Study

Automated test tools can bring many benefits to testing of systems in GxP regulated environments, as long as the ap-

proach is documented and justified and provides adequate and secure objective evidence. This case study shows how faster and more efficient testing is possible through the appropriate application of test automation tools.

Application

During the development of a regulated system, a determination is made on the scope and type of validation. Manual testing is performed if the test involves verification of reports or if testing is limited to a single iteration with no accompanying patches/version upgrades.

If automated testing is considered, a proof of concept is conducted.

The testing described in this article involved a version upgrade of a custom developed order management system.

Situation

One of the first tasks was to perform an assessment on test automation tools and benchmark the appropriate tool for use within the organization. A decision was made to evaluate several alternative test automation products, select one based on appropriate criteria, apply it, and then evaluate the results in order to measure and confirm its benefits.

Tool Selection: Criteria

The integrity of this exercise depended not only on the efficacy of the automated test technology, but also its organizational relevance. To this end, a review was made of the firm's existing and planned systems and applications that are or will be subject to regulatory compliance.

The main criterion that determined our tool selection was the predominance of multiple versions of one particular database as our backend in our regulated applications. The tool was selected primarily because of its widely recognized best-of-breed fit with the company's de facto database standard. Along with the primary testing tool, a companion workflow and process control product was chosen.

Procedures and Processes

The concomitant needs for test automation to work included the need for Standard Operating Procedures (SOPs) and electronic workflows. SOPs were created for both the test automation tool and the administrative tool that was used for managing requirements and defects. These described how they were to be used and managed. The tool also supports a workflow that has electronic signature to capture test reviews, approvals, post execution reviews and QA approvals.

Because the test automation and workflow tools were to be used to validate the firm's regulated applications, each required its own validation prior to deployment. A decision was made to perform these validations in-house applying existing standard procedures and a rigorous application testing process, inclusive of the formulation and execution of detailed testing requirements and plans. A vendor audit was not performed because it had been adequately demonstrated that both tools were fit for their intended use.

Administration and Security for Test Automation

One of the primary methods through which test automation can be effectively and uniformly administered throughout the company is through the use of Standard Operating Procedures (SOPs) and training. These SOPs define how the administrative tool and the test automation tool would be used by the testers.

The security and authenticity of the test scripts was ensured through the following methods:

- A workflow with eSignature approvals during test development and test execution. This included approvals by the technical team member and Quality Assurance during test script review and after test execution.
- Once a release was completed, the entire sets of tests were locked and no new test could be added or changed within the test set.
- New runs may be executed, but no test could be purged.

Application	Results
The testing approach involved development and support of off-the shelf software with custom interfaces with: • 1000 Requirements (Approx.) • 10 Modules • 67 RICE Elements	On an average, executing these scripts manually would take eight weeks for one iteration costing $320,000 with 14 offshore testers and 15 US testers. Test Automation, by using modular testing framework, reduced the development cycle to 90 days and execution to five days costing $40,000. (Modular testing framework: the test script modularity framework requires the creation of small, independent scripts that represent modules, sections, and functions of the application-under-test. These small scripts are then used in a hierarchical fashion to construct larger tests, realizing a particular test case.)
Load testing of an enterprise system uncovered issues requiring patches and system tweaking on: • capacity configuration • connection problems • clustered environment • interface testing • response times at remote locations	Failure to launch for each day would have resulted in a loss of about one million to business.
An automation tool used to perform functional test, load test, monitor the IVR production system on a 24/7 basis, and identify environmental differences Functional tests involved developing and executing around 150 test scripts.	Developing these scripts manually cost $84,000 as opposed to $17,000 for automation. Executing these scripts manually cost $17,000 as opposed to $6,000 for automation. This is more than $75,000 in savings for one iteration of Interactive Voice Response (IVR) system.

Table A. Case Study – application and results.

- After the completion of the testing effort, the database that stored the actual test scripts and screenshots were archived and an additional copy maintained within the project repository.

Initial Tasks

The test automation program began with manual tests, evaluated for commonality between the scripts and separated those that could and could not be automated. In some cases, when scripts were created to address common requirements, there would be a single script - for instance, 200 surveys now just have one test to check 600 different combinations of questions and answers. As part of initial activities, all the data is maintained in the Excel spreadsheet and parameters in the form of XML files. The coding standards when developing the test automation scripts include not having 'go-tos' and more importantly, developing detailed comments within the scripts.

Effective Management and Leadership

The importance of a team lead who also can act as an administrator of the system will determine the success of the automation effort. Knowledge of the tool and the ability to assign work appropriately is very important.

Recognizing the pitfalls for custom software that was re-engineered, the test lead should be able to shift resources at a moment's notice. Some of the common areas that hinder proper test automation development include requirements that do not have detailed workflows, incomplete requirements, or lack of developer assistance for the system.

Different styles of developing test scripts could result in problems with maintenance, but this can be preempted with detailed procedures for developing test scripts. The team should be built carefully with a strict interview process that brings in the best of talent.

Common Pitfalls

Some of the pitfalls in test automation include object recognition, attempting to automate a legacy system or early versions of software. Most challenging of all is the concept of 'Testing the Tester.' This was mostly addressed during the technical review of one tester's work by his/her peer.

The Results

Clearly, the savings from the use of automated testing were considerable. Beyond that, the thoroughness of the testing and its associated documentation significantly enhanced the validation task, while minimizing net compliance risk.

Summary

"Computerized test management tools can significantly reduce the amount of paper used during testing and can provide helpful test management support. This includes the ability to report on the status of test activities and facilitate test activities by the use of workflow. In most large testing projects, the use of such a tool can reduce testing time scales."[3]

Conclusion

Automated test tools can be used to improve test execution efficiency and effectiveness in a GxP regulated environment and provide many other benefits if selected, managed, and used appropriately.

Further information on efficient and effective testing practice may be found in GAMP® 5.[4] Further detailed information on Automated Test Tools may be found in the GAMP® Good Practice Guide: Testing of GxP Systems.

References

1. Mapping rules define the source to destination system translation often required, including arithmetic, logical and string manipulation.

2. Production execution of the data migrations process often requires some level of manual sampling that will need to verify the production run. For example, where the business may require weekend turnaround, only an automated testing process can deliver the necessary level of qualification in this timeframe.

3. *GAMP® Good Practice Guide: Testing of GxP Systems,* International Society for Pharmaceutical Engineering (ISPE), First Edition, December 2005, www.ispe.org.

4. *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems,* International Society for Pharmaceutical Engineering (ISPE), Fifth Edition, February 2008, www.ispe.org.

About the Author

Radha Ramesh has more than 22 years of experience in the IT industry in areas of development, business analysis, quality assurance, compliance, and computer system validation; the last 12 years were in the pharma industry. In her latest role as Assistant Director in a biotech company, Ramesh has built a world class team for test automation, audit, and SOX IT controls, and has managerial and executive expertise. Ramesh has significant global experience in the startup and functioning of offshore and new sites globally. She has built offshore teams of more than 20 people that provide test automation services, resulting in a service that is similar to 'follow the sun approach.' In addition, she also has been in charge of international software and CRO audits with participation in GMP audits, and has personally executed them in America, Asia, and Europe. She can be contacted by telephone: +1-908-673-9000 or by email: rramesh@celgene.com.

US Corporate Headquarters, Celgene Corporate Headquarters, 86 Morris Avenue, Summit, New Jersey 07901, USA.

Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2010, Vol. 30 No. 1
www.ISPE.org

A Synopsis of Explosion Hazards During the Transfer of Powders into Flammable Solvents and Explosion Preventative Measures

by Martin Glor

This article presents the explosion hazards associated with powder transfer into vessels, which may contain flammable solvent vapors. The formation of explosive atmospheres and occurrence of ignition sources such as static electricity are described. Preventive measures and technical equipment are outlined and discussed.

Introduction

Explosion prevention must be a primary objective of employers wherever the process of transferring powders into flammable solvents is utilized, regardless of the industry and existing practices. In Europe, the ATEX directives[1] and Directive 1999/92/EC[2] provide guidance for manufacturers of equipment and manufacturers of good sound explosion prevention and protection. In the US, this topic is addressed within the NFPA standards 69[3] and 77.[4]

The addition of powders such as catalysts, pigments, and other reactants into a reactor, hopper or large container is a common operation within the process industry. Frequently, the vessel into which the powder is being added will already be charged with flammable solvents. These solvents can create an explosion environment both within the vessel and in the surrounding atmosphere. This potential hazard is dependent on the flashpoint of the solvent, the temperature of the solvent and the ambient temperature of the surrounding atmosphere.

Equally significant is the nature of the powder and the act of transferring it. The combustibility of the powder, combined with the characteristics of the powder in addition to the transfer process, increases the potential for formation of an explosive dust/air mixture both in the container and in the immediate surroundings. The amalgamation of flammable solvent vapors and explosive dust/air mixtures can form a volatile hybrid mixture.

The presence of such types of explosive atmospheres corroborates the fact that this type of operation is clearly one of the most hazardous within the process industry if exclusion of effective ignition sources is the only basis of safety. If all those effective ignition sources generally considered common and insignificant, including those ignition sources related to electrical equipment, mechanical load, open flames, cutting, welding and smoking etc., have been excluded through the introduction of precautionary measures, the hazard of electrostatic ignition inherent in the powder transfer remains a viable possibility for causing an explosion.

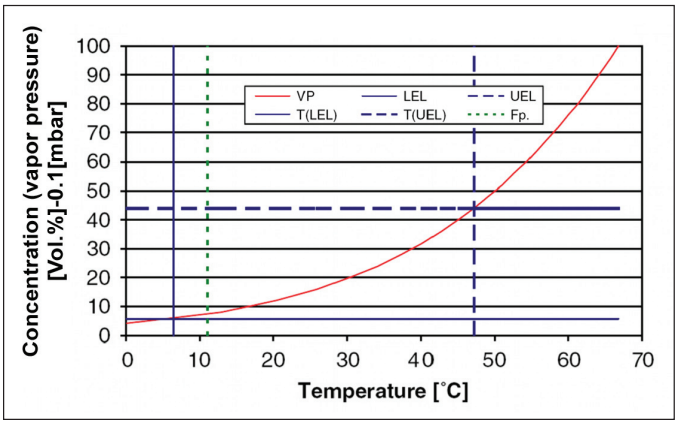


Figure 1. Relationship between the vapor pressure curve, the explosive range, and the flashpoint of methanol.

Considering the facts above, the probability of an explosion occurring during the transfer process is high because the probability of a coincidence in space and time of an explosive atmosphere and the activation of an effective ignition source, such as static electricity, is high. Furthermore, the severity of such an explosion could be disastrous, especially when taken into consideration the number of operators that would be directly exposed to the initial blast wave and

subsequent fireball. Serious if not life threatening burns are likely, especially in the presence of a dust cloud or hybrid mixture explosion.

Therefore, it is an employer's responsibility to ensure the appropriate organizational, operational, and technical preventative measures are in place. Organizationally, at a minimum, this can be addressed by assigning hazardous areas and issuing fire permits, combined with the adequate training of operators. Operational and technical measures are addressed through standardized, documented, and approved operating instructions, earthing, dissipative shoes, an adequate and appropriate repair and maintenance program, in addition to appropriate ventilation, temperature control, nitrogen blanketing, and in the case of an emergency, adequate and appropriate explosion suppression systems.

Procedures relating to the process and the materials of use are implemented utilizing the following basic principles given in the relevant standards and codes of practice:

- Prevent the formation of explosive atmospheres.
- Where prevention due to the nature of the process and materials is precluded, then:
  - Ignition sources must be avoided.
  - Mitigation of the detrimental effects of an explosion must be a priority to ensure the health and safety of operators.

According to the author's experience, most pharmaceutical companies are well aware of the explosion hazards and make appropriate efforts to minimize the explosion risk (explosion probability as well as explosion severity). However, experience also shows that management of changes is not always dealt with in a prospective way in the field of explosion prevention. The cumulative effect of small single changes of the process, operation, or product may lead to a substantial increase of the explosion hazard. In addition, increasing turnover of personnel may lead to a lack of knowledge, which can only be compensated with increased training.

Even with the characteristics of explosions well known and comprehensively investigated in the past, explosion issues have not gone away, even with modern techniques. This was recently demonstrated by the sugar dust explosion on 8 February 2008 in Georgia, USA.[5]

Formation of Explosive Atmospheres: The Probability and Causes of Explosions

Determining the risk of an explosion is important in assessing how a process should be carried out and if adequate safety measures are in place. Explosion risk is defined as the product of the explosion severity multiplied by the explosion probability. The explosion severity has to be classified high since fatalities can hardly be ruled out in manual transfer operations. In order to assess the explosion probability associated with charging powder into a reactor already containing flammable solvents, the following two main criteria need to be established:

1. the ignition sensitivity of the atmosphere which is categorized by the Minimum Ignition Energy (MIE)
2. the probability of an explosion occurring at different locations

Once these criteria have been established, the hazard of a specific ignition source, e.g., static electricity creating an explosion also can be determined.

For most commonly used solvents, the relationship between their vapor pressure curve, explosive range of their vapor, and their flashpoints are well recognized - *Figure 1*. The majority of universal solvents, including white spirit, toluene, acetone, ethyl acetate, ethanol, methanol, isopropanol etc., have flashpoints below room temperature. Explosive range of solvents tends also to increase with increasing temperature.

Explosive dust clouds formed during the transfer of powders can be located within the reactor or at the point of entry into the reactor, i.e., the manhole and its surrounding area. Particle size and distribution, moisture content, concentration, and explosibility of the powder in its tumultuous state when being charged to the reactor, make up the powder characteristics which can then be expressed in terms of the Lower Explosion Limit (LEL), Minimum Ignition Energy (MIE), and Minimum Ignition Temperature (MIT), etc.

When a dust cloud mixes with flammable solvent vapors, either within the reactor or at the manhole, a hybrid mixture is formed. The explosion hazards of hybrid mixtures have been extensively reported; however, the most relevant points regarding their characteristics are listed below:[6]

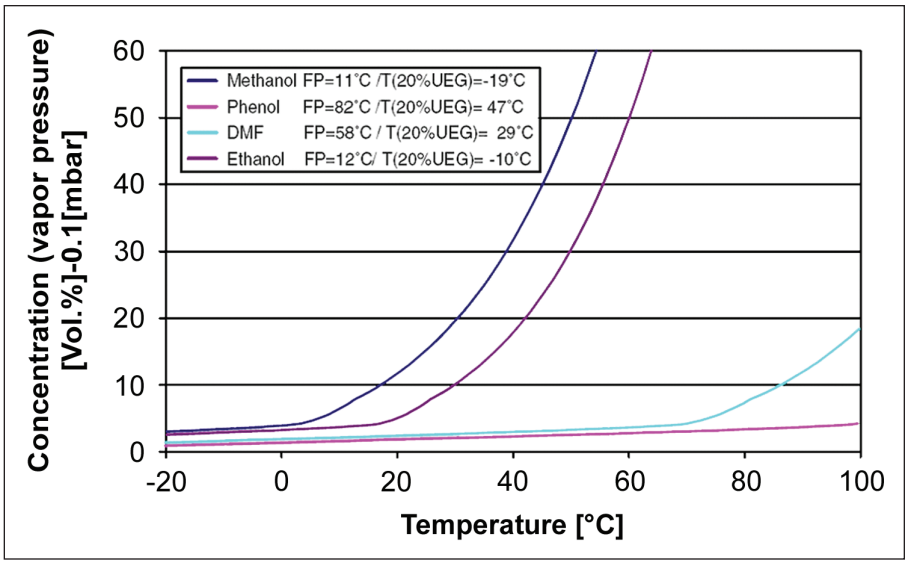


Figure 2. Vapor pressure curve for different solvents at concentrations below the lower explosion limit.

- A solvent's MIE is generally much lower than that of a pure powder. Therefore, when a hybrid mixture is formed, its MIE will be somewhere between the two and tends to veer toward the lower range, even if the flashpoint of the solvent is above ambient temperature.
- Regardless of whether the concentrations of the dust cloud and solvent vapor are below their own LELs, a hybrid mixture is an entirely separate entity that may well be within the explosion range.

There are exceptions regarding the explosive properties of a hybrid mixture, specifically the MIE. If the vapor concentration is below 20% of the LEL of the solvent, the MIE of the pure powder would then be representative of the explosion hazard for the hybrid mixture.[7] The vapor pressure, temperature, LEL, and flashpoint of solvents are used in conjunction with each other to determine the probability of a hybrid mixture forming under specific environmental conditions. The "30 to 40 K" rule applies to this calculation, i.e., the vapor pressure reaches a concentration of 20% of the LEL at temperatures 30 to 40 K below the flashpoint of most commonly used solvents - *Figure 2*.

Vapor atmospheres also can be created by charging powder where solvents or solvent residue and therefore vapors are not already present in the reactor, as the powder itself may contain solvent residue capable of creating a vapor atmosphere. If solvent residue in a powder is present at less than 0.5% (by weight), the probability of a hybrid mixture being formed can be negated as a rule,[7] the exception being when the powder is ground up allowing the desorption of vapors creating a vapor atmosphere.

In the case of toluene or methanol, which are solvents with flashpoints only slightly below ambient temperature, the entire gas phase within the reactor, i.e., from the liquid surface to the point of entry (manhole), can be filled with an explosive atmosphere. In their gas phase, solvents are at their most ignition sensitive concentration; this is especially the case for toluene.

Conversely, if a solvent has a low flashpoint (high vapor pressure at room temperature), the environment within the reactor will tend to be saturated. In this instance, the most explosive range will occur around the manhole. However, if large amounts of powder are conveyed into a reactor containing a solvent with a low flashpoint, the entrainment of air associated with the operation also may cause the atmosphere within the reactor to become explosive.

Potential Process Induced Ignition Sources

Static Electricity

The occurrence of static electrical discharges at different locations and during distinct phases of the process of powder transfer are dependent on the methods used for transferring the powder into the reactor. Electrostatic ignition associated with packaging, equipment, and operators can in theory be removed with the use of conductive materials, reliable earthing, and other such measures. Discharges associated with the products remain. Substantial changes to the product properties would be required in order to remove the electrostatic ignition sources within specific products. Details regarding the incendiary properties of the electrostatic discharges related to gases, vapors, dusts, and hybrid mixtures are given in the literature.[7,8]

Typical potential discharges when transferring powders are listed below:

- spark from any conductive, but not earthed bag, bin, drum, container, etc.
- brush discharges from any non-conductive bag, bin, drum, container, etc.
- spark discharges from any conductive, but not earthed auxiliary device used in the transfer procedure, e.g., shovel, funnel, chute, pipe, etc.
- spark discharges from the operator if he is not reliably earthed
- brush discharges from any non-conductive auxiliary devices, e.g., shovel, funnel, chute, pipe, etc.
- brush discharge from the dust cloud formed within the reactor during transfer of the powder
- spark discharges from any conductive, but not earthed fixtures and fittings within the reactor
- brush discharges from the charged solvent, suspension, or emulsion preloaded in the reactor
- brush discharges from the powder heap formed on top of the liquid phase within the reactor
- cone discharges from the powder heap formed on top of the liquid phase

Mechanical Sparks and Hot Surfaces

During the transfer of powders into a liquid, an agitator is normally running in the reactor. The rotating mechanical seal on the agitators shaft is a potential ignition source that cannot be ruled out because the hot surfaces potentially present on the shaft can induce a reaction. Additionally, mechanical faults of the agitator, such as mechanical sparks caused by the operation of the agitator, also are potential ignition sources.

The addition of the powder prior to the solvent, in an effort to reduce risk, is commonly not possible due to the formation of lumps and problems with the homogeneity of the mixture.

Practices, Techniques, and Equipment: Avoidance of the Creation of Explosive Atmospheres

If an explosion occurs, it is likely to cause significant damage to equipment and the infrastructure of the plant. More importantly, jeopardizing personnel and exposing them to possible injury or even death is unacceptable. Therefore, it is clear that operations where the transfer of powder into reactors containing flammable solvents or even where very sensitive powders with MIE's below a few Millijoules are being transferred into solvent free vessels, the transfer should not be carried out using open methods.

As previous sections have outlined, it is nigh on impossible to prevent the formation of explosive atmospheres. Additionally, the exclusion of effective ignition sources from a process is not simple and can in no way be a guaranteed measure against explosion risks.[6,9,10] It

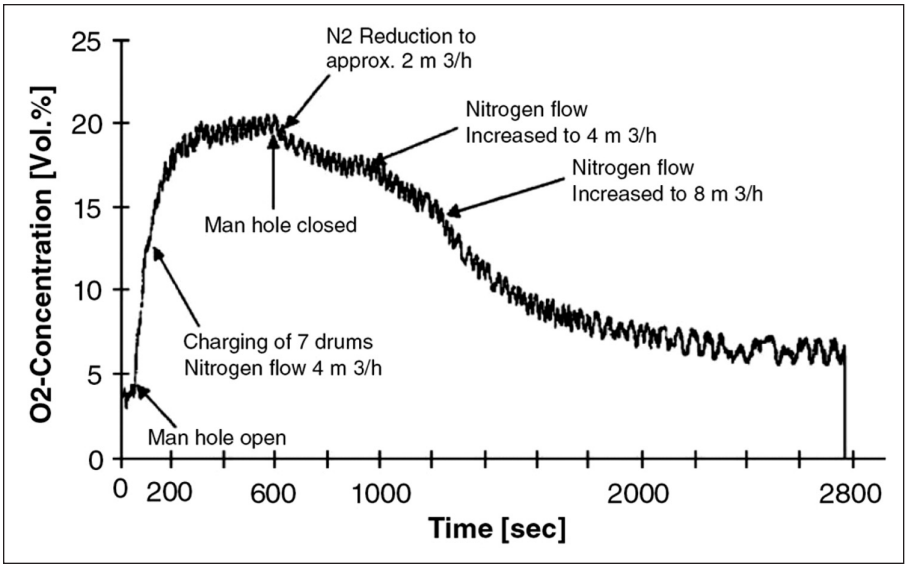


Figure 3. Oxygen concentration in a preinerted reactor after opening the man hole and addition of powder.[9]

is necessary for employers to utilize every possible precaution to prevent explosions from happening and protect both their personnel and their plant.

In order to attain the required level of safety for such transfer operations, powders must be conveyed under inert conditions, especially when the recipient vessel is preloaded with flammable solvents. Inert conditions exist where the oxygen content of the reactor is at a level below the Limiting Oxygen Concentration (LOC), where explosions are no longer possible.[6]

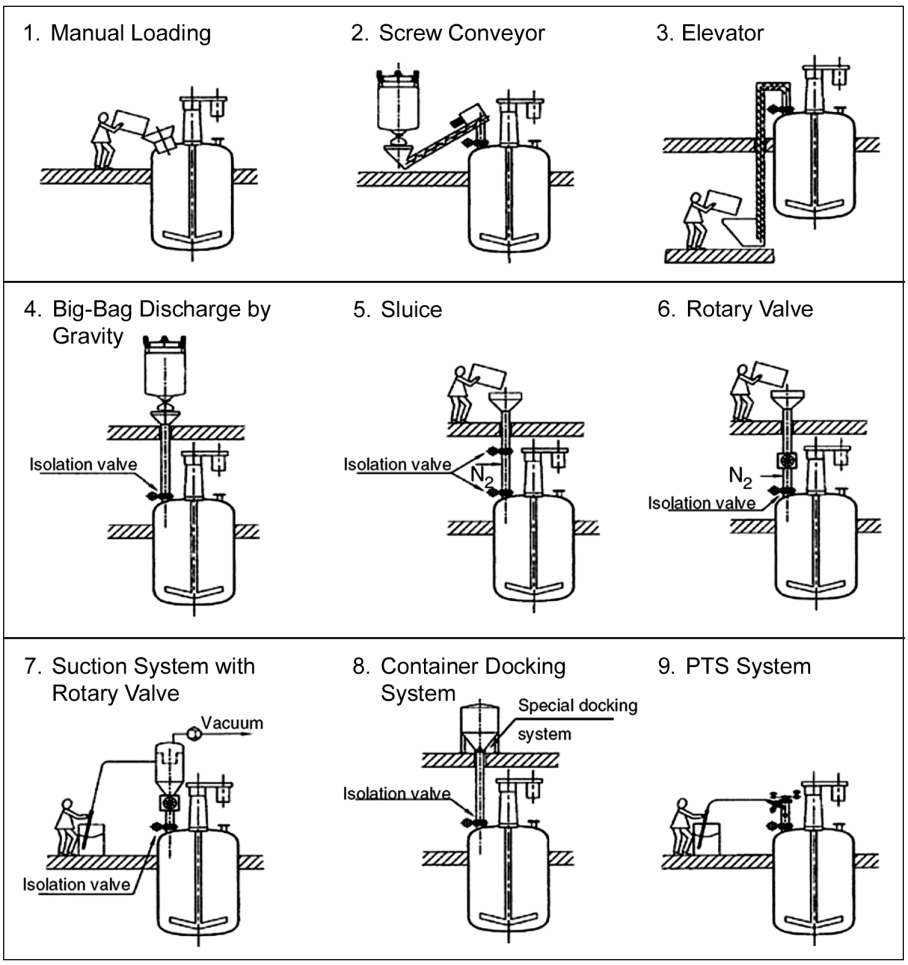


Figure 4. Different methods of powder transfer into a reactor.

Reducing the oxygen content of a vessel is achieved with the addition of carbon dioxide, nitrogen, or any other inert gas.[11] However, as illustrated in Figure 3, the opening of any access port and the addition of the powder itself will cause the previously inerted reactor atmosphere to be lost. The opening of the manhole allows the inert atmosphere within the reactor to diffuse into the surrounding environment, thus increasing the level of oxygen. The addition of powder also increases the oxygen level within the reactor due to the entrains of oxygen within the powder resulting from the turbulence created by the powder swirling around in the oxygen rich atmosphere outside and at the manhole of the reactor. The LOC within the reactor is compromised and the hazard of explosion is again present. Modern technology provides the solution to these problems; using any type of lock to transfer the powder into an inerted or reduced oxygen containing reactor is a method of choice.

Figure 4 illustrates some of the more common lock systems available today demonstrating the different methods of powder transfer into a reactor. Table A compares some of the existing lock systems against criteria for prevention of an explosive atmosphere. Notably, oxygen enrichment within the reactor is a fundamental problem associated with all the lock systems, with the exception of the PTS system, as more powder is transferred into the reactor. Oxygen enrichment is increasingly highlighted when low bulk density products (apparent density as opposed to skeletal density) and/or large volumes of powders are being transferred. Figure 5 illustrates the effect of oxygen enrichment in the reactor due to the oxygen entrained within the powder.

Explosion Protection and Containment: The Practicalities Examined

Consideration of the safety aspects

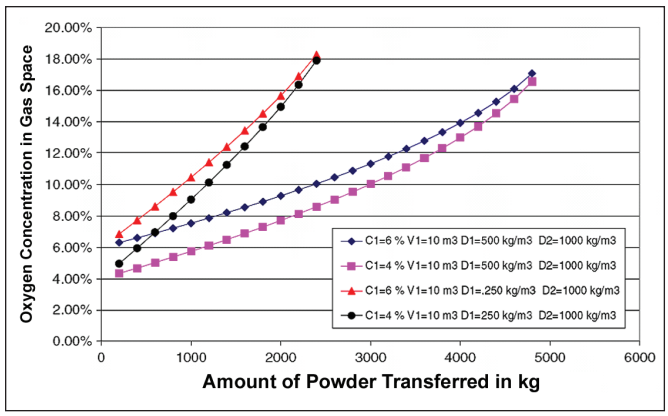


Figure 5. Oxygen enrichment during transfer of powder into a preinerted vessel. C1: Oxygen concentration in the reactor before the transfer, V1: volume of the gas phase in the reactor before the transfer, D1: bulk density of the powder transferred, D2: skeletal density of the powder transferred.

associated with the transfer of powders into flammable atmospheres must incorporate measures taking into account the toxicity and the reactivity of the powder being transferred. This is especially true within the pharmaceutical industry. These factors, in addition to the evermore stringent quality control and production standards, make containment inevitable and also should make manual handling obsolete.

The addition of powders into reactors through open manholes is still practiced in the process industry. The introduction of alternatives to this method (Figure 6) tend to be more focused on the containment aspect and do not incorporate the added need for improving the safety of the process with regard to explosion hazards.

Most contemporary methods for contained transfer of powders use gravity as the impetus to charge the powder into a reactor. This requires multi-story facilities to be built. The powder is delivered to a higher floor and falls through a chute directly into the production equipment. The problem of containment around the loading zone is addressed by incorporating a laminar flow booth, for example, into the area and a drum lifting system within it to eliminate manual handling. In these instances, operators must still wear personal protective equipment, including full body suits, masks, and depending on the toxicity of the powder, external respiratory apparatus.

Alternatively, containers may be equipped with automatic connecting valves (active and/or passive) or Flexible Intermediate Bulk Containers (FIBC – Figure 7) fitted with docking devices that enable a receiver to be connected or disconnected

	Manual Transfer	Screw Conveyor	Bucket/Chain Conveyor	FIBC Discharge	2 Valve System	Rotary Valve	Vacuum Transfer with Lock	Docking Station for Containers	PTS- System
Prevention of Explosive Atmosphere									
Transfer to closed reactor, inerting possible	-	+	++	++	++	++	+	++	+++
Entrainment of air with powder transfer highly improbable	-	++	-	+	+	+	+	+	+++
Entrainment of air within bulked product excluded	-	-	-	-	-	-	-	+	+++
Repeated inerting not required for transfer of large quantities	-	++	-	+	+	+	+	+	+++
Inert atmosphere maintained after transfer	-	+	-	+	+	+	+	+	+++
Diffusion of flammable gases or vapors to surroundings excluded	-	+	+	+	+	+	+	+	+++
Formation of dust cloud in surroundings not expected	-	+	-	+	-	+	+++	+++	+++
Other Advantages									
Required space (particularly above the reactor) low	+	+++	.	-	.	-	++	-	+++
Easy to clean	++	+	-	++	+	+	+	+	++
Mobile transfer system	+++	++	-	-	-	-	-	-	++
Transfer into pressurized systems	-	-	-	-	-	-	-	-	+++
Not depending on flow properties of powder	+++	-	+++	+	+	+	+	++	+++
GMP (good manufacturing practice) Conformity	-	+	-	+	+	+	+	+++	+++
Transfer over large distances	-	+	++	-	-	-	++	-	++
Investments	+++	+	-	+	+	-	-	-	+
Charge Moist or Solvent Wet Powder	+++	+	++	++	+	+	+	+	+++
For Multipurpose Applications	+	-	-	++	+	+	++	+	+++
Provides Manufacturing Flexibility	+	+	-	++	-	+	+	-	+++
Automated Operation	-	+	+	+	+	++	++	++	++
Environmental Health & Safety	-	+	+	+++	+	+	+	+	+++
Key: - (No); + (Sometimes); ++ (Usually); +++ (Yes)									

Table A. Characteristics of the different powder transfer methods as shown in Figure 4.

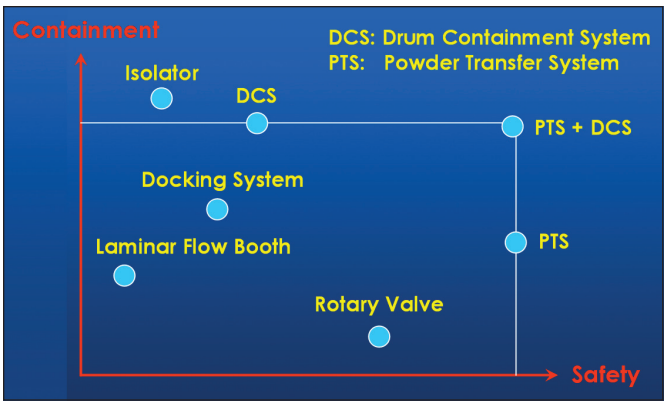


Figure 6. Improved gravity charging mechanisms.

in an *almost* airtight manner. These systems enable large quantities of powder to be transferred, in excess of 100kg, and reduce the requirement for manual handling. This method also would be suitable for processes where intermediate products are used in a process that requires storage or isolation between phases.

A product with high toxicity will require more containment. Glove boxes offer one of the only solutions and protect the operator, product, and environment - *Figure 8*. However, the cost of this solution can often be prohibitive in that most glove boxes are rigidly designed for a specific use, require a large dedicated area within the plant and are not ergonomically designed, causing operators' discomfort.

The chutes used for charging the powder into the reactors can get clogged and bridging may occur, especially if the powder has poor flow characteristics or high moisture content. Cleaning and validation is an inherent problem and increases proportionately with the length of the chute.

Gravity charging as a process itself can be a safety issue. The process cannot be rendered completely inert and the problems associated with increasing the oxygen concentration within the reactor is, as previously discussed, a significant issue. The use of inert gases to reduce the oxygen content introduced to the reactor via the powder is costly as large volumes of such gases, i.e., Nitrogen is required with this system. To counterbalance these inadequacies, solutions are required, convoluted instrumentation may need to be incorporated to monitor oxygen levels, etc. These in turn increase the cost, affect the reliability of the process by requiring calibration, maintenance, and other repairs that necessitate down time. Or the system itself may have to be modified, e.g., charging the powder into an empty reactor, this may address most of the safety issues, but the efficiency of the process will be compromised. The following points listed below illustrate the detrimental effects of charging powder into a reactor in the absence of solvents:

- production of static electricity as powder is introduced under dry conditions
- damage to the reactor lining due to abrasion or corrosion
- damage of agitator seal or the agitator itself by the large amounts of solids at the bottom of the reactor
- increased mixing cycle and problematic product homogenization due to the formation of agglomerates

ATEX standards determine the delineation of zones within a process environment. The choice of equipment, its configuration, and the methodology employed within a plant can directly impact the determination of zones. Therefore, certain zones may be downgraded, for example, where the plant would then benefit from operational advantages and associated economic benefits.

Common to the majority of powder handling systems is the lack of a physical barrier between the reactor and other production equipment, thus rendering them neither pressure nor explosion proof. The operating pressure of the recipient vessel, temperature, and presence of flammable atmosphere are serious hazard risks, especially when charging powder and even more so when powder is charged in a open way by gravity. The powder loading area must be classified as a hazardous area where explosive dust and/or solvent vapor atmospheres may be formed.

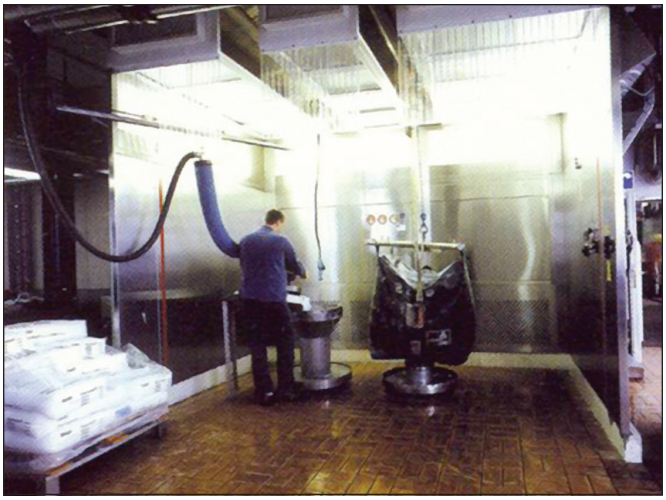


Figure 7. Charging from FIBC in a laminar air flow booth on the upper floor.

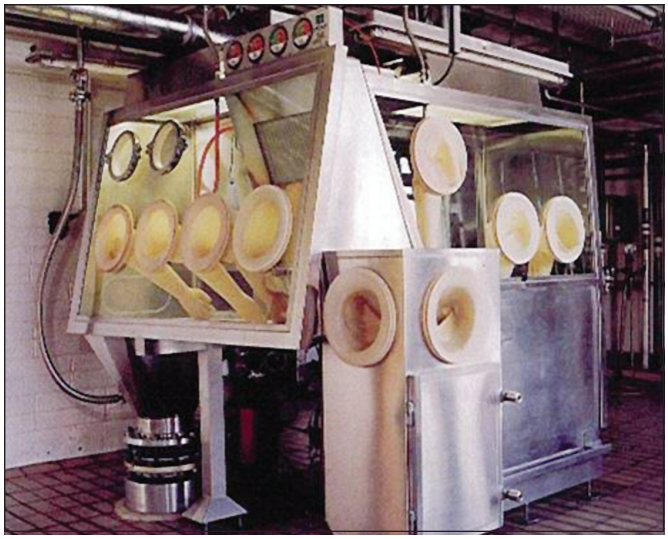


Figure 8. Charging through a glove box isolator.

Economic constraints within the process industry create a diversity of challenges. From the conception and implementation of a flexible production unit which complies with current quality control and safety legislation, also capable of adapting to changing demands in the marketplace and future changes in policies, to maintaining the lowest possible overheads. Existing process systems which may need updating to comply with legislation and increase productivity face even tougher fiscal dilemmas as the nature of such systems do not lend themselves to modification and often entirely new systems are required.

Having established that gravity charging systems are fundamentally unsafe, manufacturers face the predicament of a loss of productivity versus significant costs associated with addressing the inherent operative hazards. The solution for manufacturers is to use a system capable of isolating process equipment during the filling stage and transfers powder in a contained way.

The patented Powder Transfer System (PTS) - *Figure 9*, is a technology which provides a total solution to the problems faced by manufacturers including safety, containment, and productivity. The concept of the PTS is to actively convey a powder of any characteristic without using gravity, effectively in the same way liquids can be handled. Vacuum and pressure are combined to allow the transfer of powder from any receptacle (container, drum, big bag, silo, process equipment, etc.) over long distances (horizontally and vertically). The problems of designing new plants or processes are solved.

The simple, yet effective operation of the PTS works as the product is sucked into the main body/chamber by vacuum.

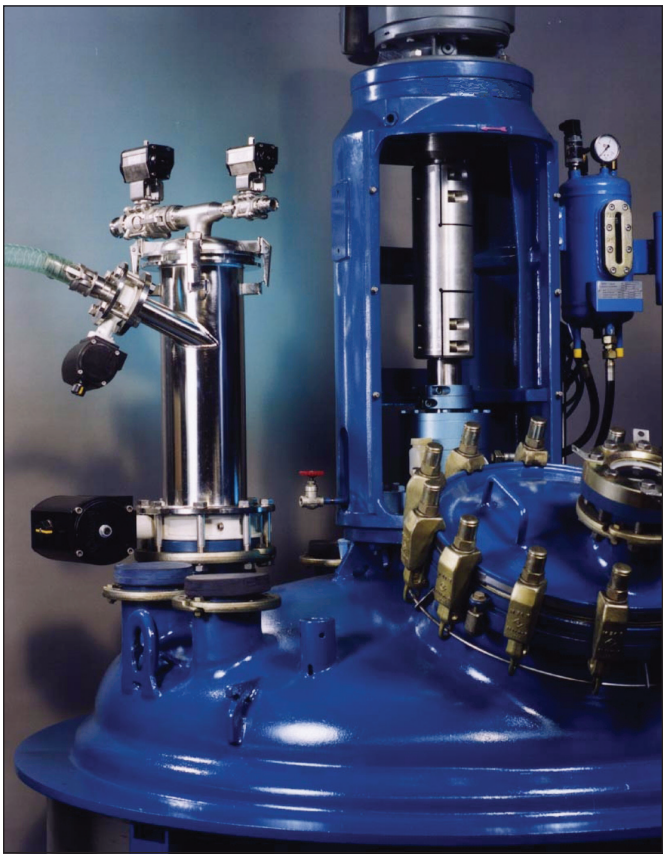


Figure 9. Powder Transfer System.

A filtration membrane fitted inside the PTS at the top of the chamber acts to ensure no powder escapes or enters the vacuum line. Once the chamber is full, the vacuum remains on to eliminate excess oxygen that has been entrained in the powder during its transfer and then the cycle is reversed. The powder is discharged into the recipient vessel under pressure by using compressed gas (i.e., nitrogen), the compressed gas also is used to clean the internal membrane and prevents it from clogging up before the whole operation is repeated.

The PTS installed directly onto the reactor (or other process equipment) is designed to operate under pressure and when in use, isolates the two systems from each other. The technology not only acts to reduce the oxygen content of the powder before it is discharged into the reactor, but also keeps the atmosphere within the reactor inert while powder is being charged into it by using nitrogen or other inert gas to pressurize and empty the PTS chamber. This equipment allows powder to be safely charged in to a reactor, even one that contains solvents or operates under pressure without the hazard of explosions or gas leaks.

Conclusions

Historically, operations where powders are transferred into reactors have resulted most conspicuously in fires and explosions. This risk is increased significantly where flammable solvents are present within the process.[13] A large proportion of such operations are still carried out manually, thus exposing personnel to safety hazards.

Either in the presence or absence of flammable gases or vapors, the MIE of the powder and the method of transfer affect the probability of occurrence of an explosion. In order to assure the safety of these processes, the transfer of powders should be carried out:

- in closed systems
- utilizing every precaution during and after the transfer to maintain the lowest possible oxygen concentration within the reactor
- separated by a physical barrier

Most gravity based transfer systems offer overall poor levels of safety and explosion hazards are further compounded by the nature of the material being transferred and the process conditions. An operation that is considered safe under one set of parameters can be de-stabilized by changing one small aspect of the system. Systems which do not use gravity, like the PTS system, provide the features listed below:

- eliminate oxygen from the powder
- have a physical barrier between the powder and the reactor during loading
- provide a safe solution for powder transfer regardless of the characteristics of the powder and the process parameters

The importance of process optimization in conjunction with ever changing safety and quality criteria means that in order

for manufacturers to effectively function in a competitive marketplace, the process technology they choose must be flexible and guarantee full safety of their personnel, product, and equipment regardless of the process parameters and powder characteristics.

References

1. Directive 94/9/EC of the European Parliament and of the Council of 23 March 1994 on the approximation of the laws of the Member States concerning equipment and protective systems intended for use in potentially explosive atmospheres. Also known as ATEX 95, (1994).
2. Directive 1999/92/EC of the European Parliament and of the Council of 16 December 1999 on minimum requirements for improving the safety and health protection of workers potentially at risk from explosive atmospheres (15th individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC). Also known as ATEX 137, (1999).
3. NFPA 69: Standard on Explosion Prevention Systems, Current Edition: 2008.
4. NFPA 77: Recommended Practice on Static Electricity, Current Edition: 2007.
5. Insurance Journal, "Imperial Sugar Company Reports Explosion at Georgia Refinery," http://www.insurancejournal.com/news/southeast/2008/02/08/87189.htm.
6. Bartknecht, W., "Explosionsschutz, Grundlagen und Anwendung," Springer Verlag Berlin, Heidelberg, New York, (1993).
7. BGR 132, "Avoidance of Ignition Hazards Due to Static Electricity," Hauptverband der gewerblichen Berufsgenossenschaften, Fachausschuss Chemie der BGZ, (March 2003).
8. CENELEC: Technical Report CLC/TR 50404 "Electrostatics - Code of Practice for the Avoidance of Hazards Due to Static Electricity," (June 2003).
9. Glor, M., Journal of Loss Prevention in the Process Industries 14, 123-128, (2001).
10. Glor, M., Proceedings of the 11th Symposium Loss Prevention 2004, Praha, Congress Centre, 31 May to 3 June 2004, 2233-2241, (2004).
11. Expert Commission for Safety in the Swiss Chemical Industry (ESCIS): Booklet 8, "Inerting – Methods and Measures for the Avoidance of Ignitable Substance-Air Mixtures in Chemical Production Equipment and Plants," (1993).
12. Hoppe, T., and Jaeger, N., Proceedings of 39th Loss Prevention Symposium of the American Institute of Chemical Engineers, 10-14 April 2005, Atlanta, Georgia, (2005)
13. Fishwick, T., Loss Prevention Bulletin, 171, 7,(2003).

About the Author

Martin Glor, PhD is Member of the Executive Committee of the Swiss Institute for the Promotion of Safety and Security in Basel (Switzerland), an institute specialized in process safety consulting, testing, and training. Glor is an internationally acknowledged expert in explosion technology and particularly in static electricity with more than 30 years of experience in the pharmaceutical industry. He is the author of several books and numerous publications. He received the ESCIS-award from the Expert Commission of the Swiss Chemical Industry and the Helmut Krämer award from the working party "Static Electricity in the Process Industries" of the European Federation of Chemical Engineering (EFCE). He is Chairman and Member of several national and international committees. Glor obtained his PhD in experimental physics from Basel University, Switzerland. He can be contacted by telephone: +41(0)61-696-2501 or by email: martin.glor@swissi.ch.

Swiss Institute for the Promotion of Safety & Security, WRO-1055.5.23, P.O. Box CH-4002 Basel, Switzerland

Architects, Engineers – Constructors

CRB Consulting Engineers, 7410 N.W. Tiffany Springs Pkwy., Suite 100, Kansas City, MO 64153. (816) 880-9800. See our ad in this issue.

Cleanroom Products/Services

AES Clean Technology, 422 Stump Rd., Montgomeryville, PA 18936. (215) 393-6810. See our ad in this issue.

Dust Collectors

Farr APC, 3505 S. Airport Dr., Jonesboro, AR 72401. (866) 530-5474. See our ad in this issue.

Employment Search Firms

Jim Crumpley & Associates, 1200 E. Woodhurst Dr., Bldg. B-400, Springfield, MO 65804. (417) 882-7555. See our ad in this issue.

Life Science Solutions

Telstar, Josep Tapiolas 120, 3 Bajo, 08223 Terrassa Barcelona, Spain. +34 0937361600. See our ad in this issue.

Passivation and Contract Cleaning Services

Active Chemical Corp., 4520 Old Lincoln Hwy., Oakford, PA 19053. (215) 676-1111. See our ad in this issue.

Passivation and Contract Cleaning Services (cont.)

Cal-Chem Corp., 2102 Merced Ave., South El Monte, CA 91733. (800) 444-6786. See our ad in this issue.

Processing Systems

GEA Process Engineering, 9165 Rumsey Rd., Columbia, MD 21045. See our ad in this issue.

Intelligen, 2326 Morse Avenue, Scotch Plains, NJ 07076. (908) 654-0088. See our ad in this issue.

Pharmaceutical Online, 5340 Fryling Road, Suite 101, Erie, PA 16510. (814) 897-7700. See our ad in this issue.

Pumps

Watson-Marlow Pumps Group, 37 Upton Drive, Wilmington, MA 01887. (978) 988-5325.

Wilden Pump & Engineering, LLC, 22069 Van Buren St, Grand Terrace, CA 92313. (909) 422-1730. See our ad in this issue.

Sterile Products Manufacturing

Process Tek - *Sterility by Design*
INNOVATION, RELIABILITY & PROFESSIONALISM
R&D, Validation, GMP Auditing,
HACCP, Problem Solving and Training
for sterile products, packages & processes
Kailash S. Purohit, PhD
www.processtek.net • kaipurohit@processtek.net

Tanks/Vessels

Murray Company, 2919 E. Victoria Street, Rancho Dominguez, CA 90221. See our ad in this issue.

Validation Services

Commissioning Agents, Inc., 1515 N. Girls School Rd., Indianapolis, IN 46214. (317) 710-1530. See our ad in this issue.

Validatool, 74 Rue de Bonnel, 69003 Lyon, France. +33 042610810. See our ad in this issue.

Valves

Gemu GmbH & Co., Fritz-Mueller-Str. 6-8, D-74653 Ingelfingen, Germany. +49 7940123-0. See our ad in this issue.

Water Treatment

Elettracqua Srl, Via Adamoli 513, 16141 Genova, Italy. +39 0108300014. See our ad in this issue.

MECO, 12505 Reed Rd., Suite 100, Sugar Land, TX 77478. (800) 421-1798. See our ad in this issue.

Siemens, 10 Technology Dr., Lowell, MA 01851. (978) 934-9349. See our ad in this issue.

Advertiser's Index

On-Line Exclusive Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2010, Vol. 30 No. 1

Streamlining of Raw Material and Culture Media Testing and Release for Clinical Manufacturing

This article presents a Lean/Kaizen team effort to improve raw material and culture media testing and release cycle times for clinical manufacturing campaigns.

by Beth H. Junker, Susan Gibbons, Jocelyn Lazor, Monica Storz, Vicky Griffin, Kelli Pardue, Marshall Gayton, and Raymond Kaiser

Introduction

Product development pipeline portfolios change frequently, requiring re-evaluation of existing workflows and systems to streamline efforts to satisfy changed business and technical requirements. Non-platform and non-animal cell-based product candidates currently undergoing clinical manufacturing require significantly more (~2-fold) individually-purchased Raw Material (RM) and Culture Media (CM) items compared with prior platform, animal cell-based product candidates, such as monoclonal antibodies from Chinese Hamster Ovary (CHO) cells. This increase is largely because products based on animal cell culture typically utilize pre-prepared liquid or powder medium formulations released as a single entity by vendors and not because the actual number of individual ingredient components is lower. As a result, larger numbers of required release tests are performed by the material user that then require review, approval, and investigation of any Out-Of-Specification (OOS) results obtained.

Overall, the supply chain for RMs and CM has simple requirements, including: 1. provide the right material of the proper type, amount, quality, and release status in the right place at the right time, 2. minimize lot-to-lot variability by demonstrating controllability and repeatability, and 3. reliable notification of vendor manufacturing changes. Key components of this supply chain are vendors, both manufacturers and distributors, as well as internal and external contract laboratories that test RM and CM samples for release. External contract laboratories minimize the need for internal laboratories to remain ready to perform a wide variety of infrequently required tests.[1]

Project Goals

The goals of this efficiency project were to 1. reduce the number of individual analytical tests conducted externally by up to 50% or replace some of them with internal, at-line Process Analytical Technologies (PAT), translating into **external release testing spend** reductions for contract release testing laboratories, 2. reduce the total number of **internal release hours** by up to 25%, specifically reducing Out-Of-Specifications (OOSs) per year by 30% through appropriate release plan requirements and fewer tests and minimizing new items introduced/year from process development efforts, which require authoring new release plans and developing new release tests by creating a decision framework and approval process, and 3. improve material **release cycle time** from item identification through item release by 10%.

The project's focus was on RMs and CMs used in the clinical manufacturing of therapeutic proteins. Its initial emphasis was on CDER- rather than CBER-regulated products, specifically therapeutic proteins rather than vaccines. The project avoided revisiting GMP testing regulations (but attempted to benchmark their implementation where possible), established licensed manufacturing RM/CM release plans, previously implemented efforts to reduce testing on certain CMs, and batch record review for CMs, which are constituted in-house from released RMs. It also avoided bulk release and stability testing and consumables, such as filters, which sometimes are considered RMs by other organizations.

Key Definitions and Regulations

Raw materials are defined as chemicals, biological materials, specialty chemicals, and

vendor-prepared solutions that are used in the manufacturing process and/or development of biological products. Specifically, cultivation media or buffer solutions were defined as RMs if purchased from a vendor, but CMs if prepared in-house. Consequently, there was a batch preparation document for each CM that required approval before its release. Compendial RMs possessed monographs in at least one of the major compendia[2,3,4] which described testing requirements. Owing to their higher quality and documented release assays, compendial conformance was a desired attribute for RMs destined for clinical and eventual licensed manufacturing. Very few early phase clinical raw materials possessed published harmonized compendial tests and undertaking additional compendial harmonization efforts for these early phase clinical materials was cumbersome.[1,5,6] It was challenging to release only for a specific compendia and then to track subsequent usage in clinical trials. Consequently, complete multi-compendial testing had been implemented for those RMs where multiple monographs existed. Non-compendial raw materials obviously did not have monographs in the major compendia.

Raw material testing requirements were explicit [US CFR Title 21 Part 211.84(d)(2)]: "Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality." A component is defined as [US CFR Title 21 Part 210.3(b)(3)] "any ingredient intended for use in the manufacture of a drug product." Excipients were a special class of RMs, which included the bulk protein plus any RM that was used in solutions to prepare the bulk for formulation (e.g., alum adjuvant, bulk formulation buffer, or other stabilizers).[7] Excipient testing expectations also were explicit [Annex 8 of EU EudreLex Vol 4 (Part 1)] and were not replaceable by additional procedures to manage suppliers: "The identity……..can normally only be ensured if individual samples are taken from all of the containers and an identity test performed on each sample."

A critical RM was defined as any material having direct product contact and possessing at least one of the following characteristics: single-source supplier, new technology, excipient, animal-derived, not well characterized, or impacting product performance/stability. Critical RMs were evaluated on a process-specific basis, based on their intended use[8] and their effect on the production process.[9]

Culture Media (CM) were constituted internally in-house, one to four weeks ahead of use, in a facility that was governed by an internal quality group. Each CM was sterile filtered into pre-sterilized bags and most CMs were tested for key component ID/composition, sterility, and endotoxin to supplement other available manufacturing controls (e.g., batch sheets, material use logs). In addition, there was a "make and use" CM designation, requiring use at-risk within a shortened one to three day expiration period and parallel testing of retains. Examples included CM that were unstable or unable to be filtered.

Challenges for Clinical Manufacturing

Owing to the large number of different product campaigns each year, RM vendors for early phase clinical material manufacturing were more numerous and often not overlapping those utilized for late-phase clinical and licensed product manufacturing. In addition, RMs were likely to change during the early development phase,[8] particularly RMs whose variability was demonstrated to adversely affect the process during testing of multiple lots. This pattern was especially true for non-platform and non-cell culture products. Often RMs used for one product were not used for subsequent products, making it risky to devote valued quality auditing resources to vendor auditing during early clinical phases where the probability of success was ~25 to 50%. Consequently, the number of approved suppliers that underwent an audit (attaining either a "needs improvement" or "satisfactory" status) was substantially lower for clinical campaigns, heightening the quality risk associated with accepting RMs based solely on vendor Certificate of Analysis (COA).

Non-compendial RMs from vendors with satisfactory quality questionnaire status were accepted based on review of COA against specifications and re-performing at least one other relevant quality test, which was typically identity and color/appearance. Compendial RMs were re-tested according to available compendial tests, based on compendia representing a minimum set of published available quality expectations.[2,3,4]

Few RMs used in clinical manufacturing were ordered more than once or twice per year. Thus, resources to maintain an audited vendor status, typically requiring at least one audit plus multi-lot experience of at least three lots, far outweighed by ~10-fold prospective reduced testing benefits. One alternative way to gather RM manufacturing and quality information was through satisfactory completion of quality questionnaires relating to BSE/TSE controls, antibiotic/potent compound segregation, overall quality systems, and business financial soundness. However, there was additional complexity obtaining the vendor information required to complete these questionnaires if the vendor was a distributor and not the RM manufacturer itself.[5] All questionnaire responses were evaluated for acceptable responses before the RM contacted in-house equipment and insufficient or unclear responses were considered a significant risk to proceeding.

Three additional factors affected RM/CM testing and release resources significantly, including: 1. since the BSE/TSE control questionnaire typically was focused around a specific RM or specific lot, approved, satisfactory manufacturers were not necessarily approved for other RMs manufactured at the same site or even in the same building; 2. composite sampling was not permitted for excipient RMs, which required that 100% of the lot containers utilized undergo individual ID testing; and 3. preferred RM manufacturers were suppliers known to be reliable based on past experience of receiving prompt notification of RM manufacturing changes and thus, were desirable vendors for concentrated business at the preferred site.

Problem Definition and its High Level Causes

Key voice of the customer requirements were rated according

to their impact on the three measurable project goals of **external release testing spend, internal release hours, and identification-to-release cycle time. Controlled new RM/CM identification, streamlined release execution,** and **identification of testing requirements** (e.g., test type and specifications) scored highest, followed by reduced number of release plans/revisions, reduced OOSs, and clarified roles and responsibilities. These customer requirements had significant impact on all three project goals: the highest impact was on internal release hours, followed by external release testing costs, followed by identification-to-release cycle time.

Testing and release **inefficiency** was caused by 1. process development's selection of new, non-compendial, and/or animal-derived RMs, particularly late relative to when required for clinical material campaigns, 2. long release assay development cycle times for new RMs/CM, 3. timing and comprehensiveness of vendor responses, particularly when completing quality questionnaires, 4. unclear roles and responsibilities along with missing workflows especially for identification of new RMs/CM, and 5. corporate procurement preferences for buying materials from distributors (e.g., warehouses) to obtain consolidated business discounts, which made it challenging to identify a consistent manufacturer.

In contrast, testing and release **efficiency** was caused by 1. implementation of process platforms utilizing similar RMs for subsequent campaigns (driven primarily by the pipeline product portfolio), 2. use of existing RMs/CM and vendors, preferably internal vendors followed by external material manufacturers, along with internal guidance to steer selection away from potentially problematic materials and vendors, and 3. early and robust execution of process development efforts to ensure RMs/CM were selected promptly relative to when needed for clinical material campaigns. Some authors have given guidance on selecting RMs/CM to avoid negative impact to clinical and ultimately commercial manufacturing efforts.[8,9,10]

Process Demand Analysis

RM/CM testing and release for clinical manufacturing was desired to be structured for timely release of all items for a single campaign so bulk product could be released and associated paperwork closed out for the campaign. Release was preferred to be completed before clinical manufacturing use although some materials (particularly CM) frequently were used "at risk." A release delay for even one material was undesirable. In addition, since more than 75% of the items were identified concurrently with the initial process definition, an unavoidable workload bolus was generated. Consequently, the underlying project goal was to increase release testing speed and efficiency to minimize "at risk" material use, avoiding usage delays until risks can be minimized.

A process lead time of 3.3 months was established from a previous clinical manufacturing efficiency project,[11] based on a facility throughput of one campaign per month. Each campaign was assumed to have ~68 RM/CMs (~40 RMs and ~28 CMs, ~36 upstream and ~32 downstream), excluding cleaning solutions. Using ~19 available working days per month, the estimated takt time (overall required rate/available working time) for sequential RM/CM release was ~0.28 day/item. Current release times ranged from 15 to 80 days with an average of 16 to 19 items released per month (~1 day/item) or just below 30% of target. Generally, individual item release testing was bundled together (two to five items/bundle) based on when samples were obtained from received materials.

Test Type	Mean	Standard Deviation	Median	Inter-quartile Range
Non-compendial RM	3.3	1.4	3	2
Compendial RM	19.1	5.2	20	5
CM	4.5	1.2	5	1
RM test numbers exclude label claim and certificate of analysis reviews.				

Table A. Tests per item for RMs and CM over an 18 month period.

Selected Background Data

Selected background data has been summarized below to quantitatively illustrate the current state of RM/CM testing and release in the clinical manufacturing area.

Numbers of Tests

Typical numbers of tests per item are shown in Table A. The most common tests for non-compendial RMs (over 10%) were color/appearance and general identification via Infra-Red (IR). The most common tests for CMs (over 33%) were sterility and LAL, in addition to identity and composition. About 30% of all RMs types utilized compendial testing, but over an 18 month period, the number of RM items ordered that were compendial was slightly lower at 21%.

Testing Turnaround Time

Over the past two years, turnaround times from the sample submission to data approval from two external testing labs averaged 1.1 (±0.77) months and 2.1 (±0.81) months.

Repeated and New RM/CMs

About 100 to150 different types of RMs/CMs were ordered each year with about 140 RMs types maintained in inventory for in-house CM preparation and other clinical manufacturing uses. The percentage of unique RM/CM items (i.e., only one lot ordered per year) rose steadily from 37% in 2005 to 70% through the first three quarters of 2008. Few RMs (20%) and CM (9%) had more than three lots released over an 18 month period, indicating lack of consistent and substantial experience with most RM/CMs and associated RM vendors. This situation was a direct result of process development's selection of new RMs/CMs for suitably productive process scale-up for different types of products/production platforms.

The percentage of new RMs/CMs types was about 50% (range of 40 to 70%) over the past three years. Higher percentages of new RMs/CMs types occurred in years when new clinical manufacturing processes were introduced from novel processes being development to support new products entering the portfolio. About 15 to 25% of RM/CM types were excipients

with an average of 3.8 (±1.5) per project (~20 excipients, ~2.5 containers/excipient). Thus, a significant number of RM/CMs types were subject to the excipient requirement of 100% ID testing of containers.

Use at Risk

About 40% of all RM/CM items typically were used before release and thus, "at risk" in clinical manufacturing campaigns (i.e., all testing results not received back). Most (~95%) of these risk memos were for CM. About 25% of all CM typically were used at risk, rising to 60 to 100% when campaign timelines became compressed. The number of risk memos written quadrupled from 3.2/months to 13.5/months over the past three years and ~75% of the risk memos were for CM testing status. These data suggested that current timing for release was insufficient to match process needs, particularly when unexpected campaigns were undertaken or timelines accelerated.

Out-Of-Specification (OOSs) Results

Over the past three years, about 4% of all individual lots tested generated an OOS which translated to a rate of ~10/year. Specifically, there were typically about 2.5-fold more OOSs for CM than RMs. About 20 to 35% of the OOSs listed as their resolution revising the release plan which suggested initially inadequate setting of testing specifications.

Types of RMs/CMs

Many of the RMs/CM utilized possessed chemically simple compositions. About 23% of RM release plans and 32% of CM release plans were for simple inorganic salts. Over an 18 month period, the frequency of the type of RM lot released by chemical classification was as follows: chromatography resin (15%), inorganic salt (14%), gas (13%), inorganic base (6%), and inorganic acid (3%). Based on release plans, about 72% of CMs had ingredients in either one or two classifications; about 83% of these plans were for downstream media ingredients. Similarly, over an 18 month period, the frequency of the type of CM lot released by chemical classification was inorganic salt (25%), inorganic salt with an organic buffering molecule (18%), inorganic base (13%), and organic buffering molecules (10%). Excipients commonly were inorganic salts (35%), amino acids (15%), and inorganic bases (11.5%). These data suggested that switching one or two test methodologies to an at-line format would impact a large fraction of release testing for chemically simple RMs and CM.

Vendors

The composition of the RM vendors was primarily internal vendors (i.e., procured and released elsewhere within the company) and external distributors. About 24% of RM items were procured from internal vendors. About 34% of all vendors (45% of external vendors) were distributors (i.e., not the material manufacturer). Three key distributors accounted for 31% of the external vendors and 69% of the distributors. It was considerably more challenging to obtain quality information from distributors since contact with the material manufacturer was often only indirect and manufacturers frequently changed.

Areas of Identified Pain

Three major areas of pain were identified qualitatively when Subject Matter Experts (SMEs) evaluated overall process flow charts, including: 1. lead time for new RM/CM identification by process development personnel, which required a minimum of three to four weeks for running the upstream and downstream experimentation and demonstrating analytical acceptability, 2. assay development and establishment of specifications for subsequent release testing, and 3. determination of GMP suitability, specifically obtaining and evaluating vendor responses to quality questionnaires (e.g., BSE/TSE control).

Various root causes were brainstormed according to established fishbone categories, then the most impactful ones were selected by the team (bold type), including: 1. measurement – repeating selected vendor release tests owing to insufficient business benefit of a vendor audit; setting specifications based on a single lot or sample; using only educated guesses about test specification relationship to incompletely defined process requirements early in the process development cycle; 2. materials – **difficulty extending expiry** without vendor data resulting in discard and re-supply especially for critical or expensive RMs; long process development lead time and insufficient line of sight to eventual release requirements when identifying RMs/CM; 3. methods – **lack of non-overlapping compendial standards** with limited and slow success of efforts to resolve differences; **competing priorities** for both internal and external testing laboratories which lead to long queues and turnaround times; insufficient release test robustness; time consuming requirements to mitigate quality risks associated with reduced testing requirements; 4. machines – **lack of an allocation tool** to manage restricted release leading to additional testing to cover all possible uses; 5. people – **difficulty finalizing quality questionnaires** that are slow to be returned and often have missing information (often because the vendor's fraction of its business with the biopharmaceutical industry was small;[1] **too few resources** to conduct necessary steps when new RMs/CM are identified; **insufficient definition of roles and responsibilities** (e.g., workflow for new RM/CM definition by process development personnel; meaning of approval signatures on release plans and CM preparation batch sheets); 6. mother nature – externally-located (e.g., different state) release testing laboratories; changing worldwide quality regulations.

The key areas of pain and associated root causes noted above were directly related to the previously high scoring categories of **controlled new RM/CM identification, streamlined release execution, and identifying testing requirements** (e.g., test type and specifications) - *Table B*.

Current States

Next, root causes and areas of pain were explored further by developing and analyzing using current state value stream maps.

The process for RM identification to release had up to four

sequential key steps depending on whether the RM was new, the RM was compendial, the vendor was new, or the vendor was external, including: 1. RM identification by process development, 2. procurement, delivery, release plan authoring, release assay development, sampling and submission, solicitation of vendor questionnaires, 3. release plan approval, sample testing, release package assembly, quality questionnaire response evaluation (including obtaining missing TSE/BSE information and clarifying vendor responses), and 4. quality approval/release. The simplest case was an existing material from an internal vendor and the most complex case was a new RM from a new, external vendor. Based on associated requirements, five scenario groups were developed from 12 different scenarios and the most complex case was selected for rigorous evaluation - *Figure 1.*

The process for CM identification to release had up to four sequential steps depending on whether the CM was new, including: 1. CM identification by process development, 2. scheduling and constituting the CM in-house from purchased RMs, authoring/approving the batch document, cleanability testing, release plan authoring, release assay development, sampling and submission, 3. release plan approval, sample testing, release package assembly, and 4. quality approval/release. Two scenario groups were developed for two different scenarios, existing and new CMs, and the most complex case (new CM) was selected for rigorous evaluation - *Figure 2.*

High Scoring Requirements (VOC)	**Key Root Causes (Fishbone Diagram)** Bold = key item	**Kaizen Observations (current state VSM)**	**Potential Solutions** Bold = key item
Controlled New RMs/CMs Identification	**Insufficient definition of roles and responsibilities**	Variable approver responsiveness and unclear commitment	**Inform and train on relevant SOPs;** clarify importance (e.g., development samples, specs)
	Long process development lead time to identify new RMs/CMs	Process sample analysis queue time	**Workflow for new RM/CM identification and implementation;** improved analytical support cycle time for process development samples
	Insufficient line of sight to RM/CM release and S&E approval	GMP suitability established late in process; pre-approval procedures rigorous and time-consuming	**Set up approved and accessible RM/CM and vendor listing;** identify contacts for feedback to process development (1-2 day turnaround)
Streamlined Release Execution	**Difficulty finalizing quality questionnaires (GMP suitability)**	Second handling of questionnaires to obtain/clarify missing/unclear information	**Start effort at-risk w/top three proposed new RM/CMs; utilize existing COE**
	Two few resources (internal and external)	New RM/CM disrupts workloads for existing RM/CMs	Cross-train staff to redeploy to peak loads
	Long queues/**competing priorities**	Test lab turnaround times for testing and assay development (same people and equipment); bundling of customer tests by lab/sequential execution of several compendial tests; variability in timely RM order receipt; variability in CM preparation cycle time	**Develop release assays at-risk w/ top 3 proposed new RM/CMs; reduce testing lab queue through clear expectations;** conduct sterility/LAL using faster research division lab only; use of buffer distribution system; reduced cleaning cycle between buffers to improve throughput
	External communication	Multiple contacts at multiple vendors; samples shipped to 4 locations; sample volume sometimes insufficient	Consolidate to a few preferred distributors, **reduce external samples shipped**
	Internal communication	Combined RM/CM orders for new/existing items	**Individual RM/CM order designation in header**
Identifying Testing Requirements (e.g., test type and specifications)	**Difficulty extending expiry**	No sample retained Vendors would rather sell new lots	Re-test expired RMs using saved samples; request vendors extend expiry
	Lack of non-overlapping standards	Repeat testing of similar tests from multiple compendia	**Eliminate redundant compendial tests especially for non-critical items;** leverage manufacturing and industry harmonization efforts
	Insufficient release assay development timeliness and specification robustness	Sample from process development needed for several steps; buffer complexity interferes with existing release assays	**Clear roles for specification setting for process development; develop release assays at-risk with selected proposed RM/CMs**
	Requirements for reduced testing time-consuming	Little difference between internal CM testing (made in-house) and external liquid RM testing (made by vendor)	Implement seven day read for sterility to avoid risk memo; **alternate ID and composition testing for CMs**
Composite release plans not feasible since expiry and storage conditions different for each item. **Lack of allocation tool** to be addressed as a separate IT project.			

Table B. Relationship of requirements to root causes/Kaizen observations and potential solutions.

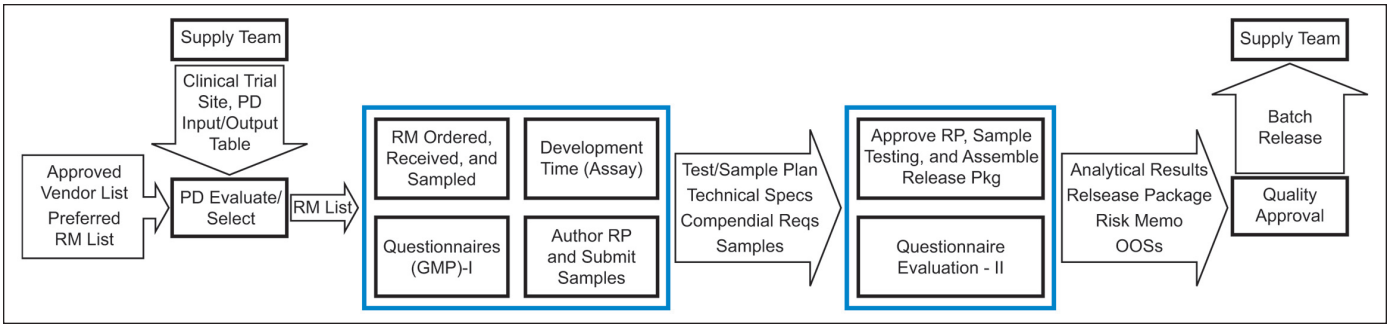


Figure 1. Current state RM value stream map (new RM from an existing or new external vendor).

Overall, the new RM/CM identification to release process required satisfactory quality questionnaires from the vendor (RM only), analytical comparability of product, possibly development of a clearance assay in the final product, release plan, release assay, and solution preparation batch sheets (CM only). Using subject matter expert estimates, current state durations for RMs were 1.75 months (range of one to six months) for existing RMs from internal vendors and five months (range of three to 9.5 months) for new RMs from new, external vendors. Reuse of a vendor for a new RM decreased this time only slightly by up to about 0.5 month. Current state durations for CMs were four months (range of one to 5.5 months) for existing CMs and five months (range of 2.5 to 8.5 months) for new CMs. In some cases, release of an existing buffer for a CDER-regulated process was permitted based on manufacturing documents and at-line conductivity and pH testing, reducing the duration to up to 1.5 months (range of 0.5 to 2.5 months). Available data was collected to validate key parts of the current state duration estimates: release assay development, questionnaire solicitation, and sample testing.

Future States

Redesigning and Reorienting Workflow Solutions

By addressing the root causes previously outlined, a potential future state value stream map was developed for RMs (Figure 3) and then applied to CMs (map not shown), which reduced overall cycle time by mitigating large differences in cycle vs. process (touch time), and in some steps, raised complete and accurate percentages.

The following assumptions for target cycle times and complete and accurate percentages were linked with specific root causes from Table B, including: 1. long queues/competing priorities (e.g., assay development, sample testing, quality questionnaires): a typical delay of one week was assumed for external lags and one-half week for internal lags. Specifically, maximum sample testing and release assay development cycle times became < 0.75 months (target 0.5 month at testing lab). 2. Finalizing GMP suitability: it was assumed that quality questionnaire procedures (e.g., content of acceptable responses, focused follow-up to obtain missing information) could be developed such that 90% of them were complete and accurate within one week for existing vendors and 80% for new vendors. 3. Long lead time for RM/CM identification by process development: the new RM/CM workflow was assumed to be implemented, which permitted advance at-risk steps to be executed for the top three leading candidates being tested for process performance. This pre-investment permitted identification of RM/CMs substantially closer to the date of clinical manufacturing.

In addition, steps were rearranged to increase the amount of RM/CM testing and release activities conducted in parallel rather than in series, a key method to reduce overall cycle time - *Figure 3*. Specifically, the questionnaire solicitation and release assay development steps were to be conducted at risk. Thus, if a proposed new RM/CM material was tested by process development and not ultimately incorporated into the process, these completed tasks might be used to enhance the supermarket listing of desirable approved RMs/vendors. Key to avoid clogging the system with "at risk" activities was to

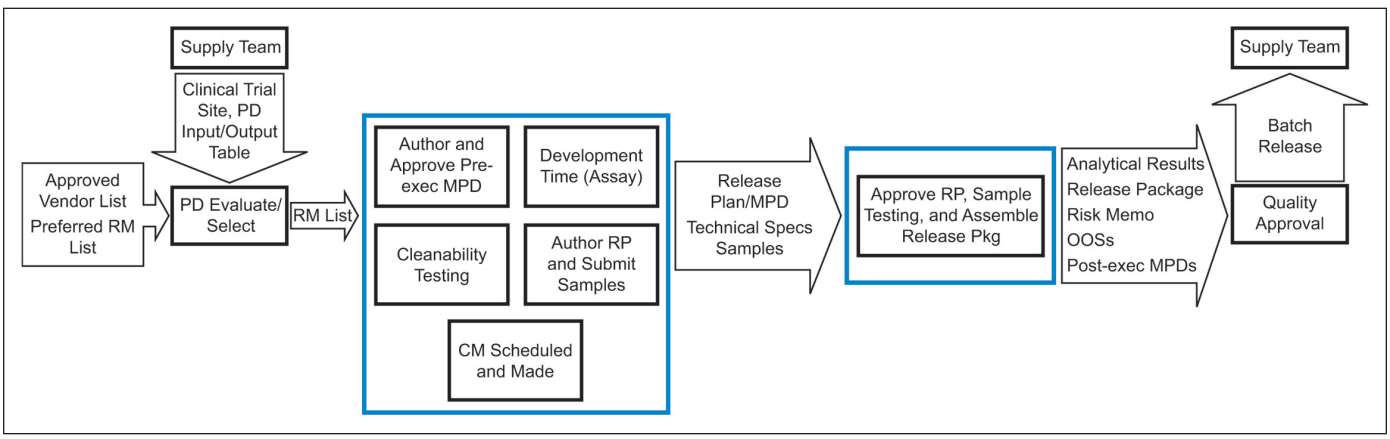


Figure 2. Current state CM value stream map (new CM constituted in-house).

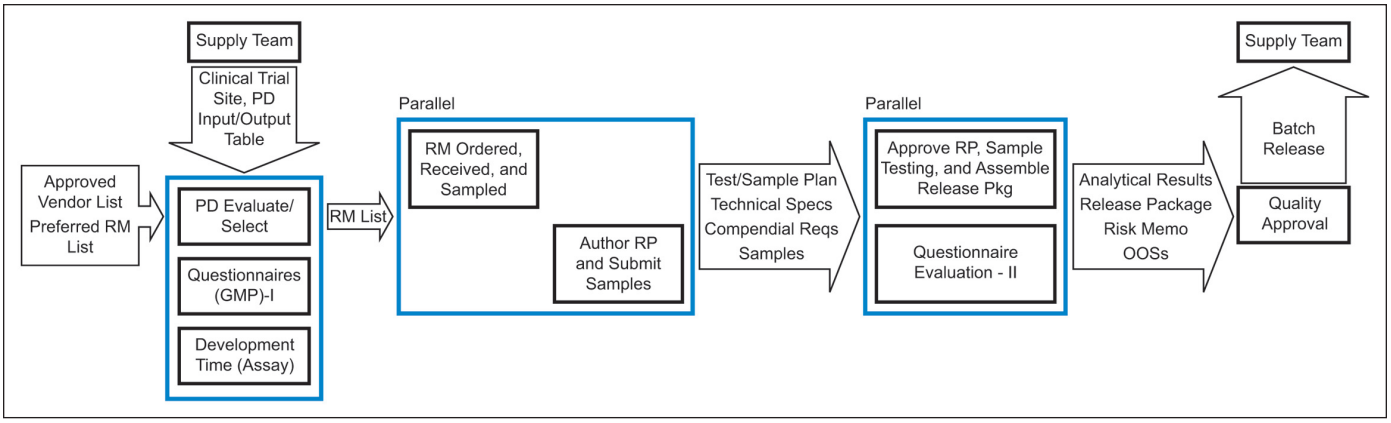


Figure 3. Future state RM value stream map (new RMs from an existing or new external vendor).

ensure that (1) only a few (~3) proposed RM/CM candidates underwent "at risk" steps and (2) the "at risk" steps (i.e., quality questionnaires and release assay development) ran efficiently.

Incorporating the above changes, cycle time reductions based on the future state were calculated. For a new RM from a new vendor (Figure 3), cycle times were reduced from five (three to 9.5) months to 2.5 (two to five) months and complete and accurate percentages rose from 5.5 to 23%. For a new CM constituted in-house, cycle times were reduced from 5 (2.5 to 8.5) months to 3.25 (2.5 to 4.2) months and complete and accurate percentages raised from 5.5 to 24.9%. These changes translated into about a 50% reduction in cycle time, a four-fold improvement in complete and accurate percentages, and nearly a doubling of the touch time/cycle time ratio (process cycle efficiency) from 35 to 40% to 60 to 70%. A breakdown of the expected cycle time improvements is shown in Table C.

Alignment ("Out of the Box") Areas

Further efficiencies likely were possible **if quality risks were able to be sufficiently minimized** via current or improved controls. Since each of these ideas required substantial discussion to ensure acceptable quality risk levels, Pugh ratings were used to select the future states with greatest impact on this particular efficiency project's goals. Next, an assessment of benefits, risks, and mitigations to achieve acceptable risk was conducted and Probability of implementation Success (POS) estimates assigned. Those ideas with acceptable risk/mitigation were evaluated using FMEA to generate workable solutions for implementation. Specifically, there was potential for the following: 1. using at-line methods (e.g., handheld Raman spectroscopy, laboratory osmometer) for conducting the required ID testing for RM solids as well as ID and potentially composition testing for CM liquids and 2. reducing compendial testing overlap. It was considered highly challenging at this time to mitigate risk 1. for extending RM expiry, 2. reducing the rigor of BSE/TSE questionnaires, 3. accepting RMs based solely based on the vendor's COA, or 4. releasing in-house constituted buffers based only on review of CM preparation batch sheets.

Step	Current State (range)	Future State (range)	Solution	Potential Reduction (%)
Total	5.0 (3.0-9.5)	2.5 (2.0-5.0)	Overview: New RM/CM ID workflow (at-risk questionnaires and release assay development), manufacturing Center of Excellence (COE) for BSE/TSE, contract testing lab turnaround expectations	50%
Process Development Evaluate and Select	1 (0.5-2.0)	0.75 (0.5-1.0)	Faster in process analytical turnaround time (already pursued via project integrators/coordinators)	25%
RM Ordered, Received, and Sampled	0.5 (0.25-3.0)	0.5 (0.25-1.0)	Consolidate using preferred vendors and RM/CM lists (new RM/CM ID workflow and prior efforts)	0% (reduce variability only)
Release Assay Developed	1.5 (1.0-3.0)	0.75 (0.5-1.0)	Contract testing lab turnaround time expectations, perform at-risk for new RMs based on new RM/CM ID workflow submittal sheets	25%
Questionnaires Solicited	1.0 (0.3-4.0)	0.75 (0.5-1.0)	Use of manufacturing COE for focused effort	25%
Release Plan Authored and Samples Submitted	1.0 (0.75-3.0)	0.25 (1.0-0.5)	At-risk assay development avoids waiting at this step	75%
Release Plan Approved, **Samples Tested** and Release Pkg Assembled	1.5 (0.5-2.5)	1.0 (0.8-1.2)	Contract testing lab turnaround time expectations	33%
Questionnaires Evaluated (if required)	2.0 (1.0-3.0)	1.0 (0.5-1.5)	Use of manufacturing COE for focused effort	50%
Quality Approval	0.5	0.25	Prioritize since review effort is minimal	50%

Table C. RM/CM identification to release average and range step cycle times (bold type indicates steps for future data collection).

Solution Selection

Additional solutions were brainstormed by the team and linked to high scoring voice of customer attributes, key root causes, and Kaizen observations from current state process steps - *Table B.* In most, but not all instances, the selected and feasible solutions matched the root causes with perceived higher severities. Solutions then were sorted according to effort (high, low) and impact (high, low). Pugh matrices were used to evaluate ideas with the greatest expected impact on this particular efficiency project's goals according to previously identified and rated voice of customer attributes: **controlled new RM/CM identification, streamlined release execution, identifying testing requirements** (e.g., test type and specifications), reduced number of release plans/revisions, reduced OOSs, and clarified roles and responsibilities. Top ideas in each solution category underwent an FMEA (severity, probability, and detection) analysis in two ways - *Table D*, including: 1. current state root causes were analyzed before and after applying solutions and 2. solutions were analyzed before and after applying additional measures to correct defective aspects. Thus, solutions selected generally had a low residual FMEA score with the highest remaining contribution owing to severity which typically was not able to be mitigated. Table E shows a summary of the key solutions and their projected benefits linked to each CTQ. Each solution is explained in more detail below:

New RM/CM Identification Workflow

A new RM/CM identification (ID) workflow was drafted, incorporating additional front-end structure around new RM/CM selection to permit front-loading longer cycle time steps to minimize overall cycle time - *Figure 4*, including: 1. process development (including upstream, downstream, or formulation) personnel identified the need for a new RM/CM, 2. approval was obtained from the ranking scientist or group manager according to pre-defined documented criteria (i.e., experimental due diligence to eliminate reasonable and timely alternative solutions, identification of potential collateral impacts to other parts of the process, generation of a comprehensive and ranked list of alternative RM/CM candidates along with pros and cons), 3. candidate RM/CMs were researched, proposed, and checked for presence on approved, posted RM/CM clinical and manufacturing listings, 4. RM/CMs not on approved listings were vetted for quality, analytical, or procurement concerns, 5. top-ranked, proposed RM/CMs (typically ~3) were use-tested in the process for improved performance with comparable product quality and simultaneously questionnaire solicitation and assay development commenced at-risk, 6. if needed, a clearance assay was developed, and 7. completed approval criteria charts were filed with the area's raw material planner for quarterly review by stakeholders.

CTQ	Process Step	Current State FMEA	Solution	Future State FMEA	Mitigation State FMEA	Projected
Control for New/Changed RMs	Several	294	New RM/CM identification workflow	84	Add to developmentability assessment, include in SOP/guideline, training	42
Streamlined Release Execution	Sample Testing	N/A	a. Handheld RM testing unit (ID) b. Visual RM testing (color and appearance)	144	Pilot period (do both), involve vendor	96
	Sample Testing	N/A	Alternate buffer ID testing (avoid samples for ID and composition)	240/192	Prospective review of solubility and make-up issues, robust finger-printing	144
	Sample Testing	252	Compendial overlap reduction	12	None	12
	Questionnaires	392	a. Use of existing COE/questionnaire at-risk solicitation b. Solicit and act on vendor feedback regarding questionnaires	126	COE priority (add to objectives, pay for services outside division), back-up plan (outside consultant)	105
	Several	504	Leverage RM/CM expertise (manufacturing, clinical)	75	COE priority (e.g., add to objectives, pay for services outside division)	45
	Develop Assay/Sample Testing	280	Contract testing lab turnaround/at-risk assay development	120	Involve procurement, budget additional funds, link to area priorities	90
Reduction of RM/CM OOS	Assemble Release Package	N/A	Linked to compendial harmonization, RM/CM analytical expertise, and Process Development roles and responsibilities	N/A	N/A	N/A
Clear Roles and Responsibilities	Author/Approve Release Plans and Mfg Docs	315	Roles and responsibilities/best practices docs for Process Development	24	Include in SOP/guideline, training	12
Reduced Number of Test Plans/Revisions	Author/Approve Release Plans	N/A	None	N/A	N/A	N/A

Table D. FMEA of current and future states.

CTQ	Solution	Projected Benefit/Measure
Control for New/Changed RMs	New RM/CM identification workflow	95% follow process
Streamlined Testing	a. Handheld RM testing unit (ID) b. Visual RM testing (color and appearance)	Up to 50% reduction in external samples sent
	Alternate buffer ID testing (avoid samples for ID and composition)	Up to 50% reduction in external samples sent
	Compendial overlap reduction	Up to 35% reduction in compendial tests
	a. Use of existing COE/ questionnaire at-risk solicitation b. Solicit and act on vendor feedback regarding questionnaires	Up to 25% reduction in effort Up to 25/50% reduction in cycle time for solicitation/evaluation
	Leverage RM/CM expertise (manufacturing, clinical)	Linked to other benefits
	Contract testing lab turnaround/at-risk assay development	Up to 30/50% reduction in cycle time Up to 40% reduction in risk memos
Reduction of RM/CM OOS	Linked to compendial harmonization, RM/CM analytical expertise, and PD roles and responsibilities	Up to 30% reduction in OOS
Clear Roles and Responsibilities	Roles and responsibilities/best practices docs for PD	Linked to other benefits
Reduced Number of Test Plans/ Revisions	None	N/A

Table E. List of key solutions, status, and projected benefits for each CTQ.

It was desired by process development for steps one to four to occur within one to two days (Figure 4) so as not to delay further process development progress, typically on the critical path to clinical studies. There also was considerable benefit from this procedure controlling early process development efforts for a project, even during screening of future production strains to avoid altered strain performance when strains were subsequently transferred to process development. Thus,

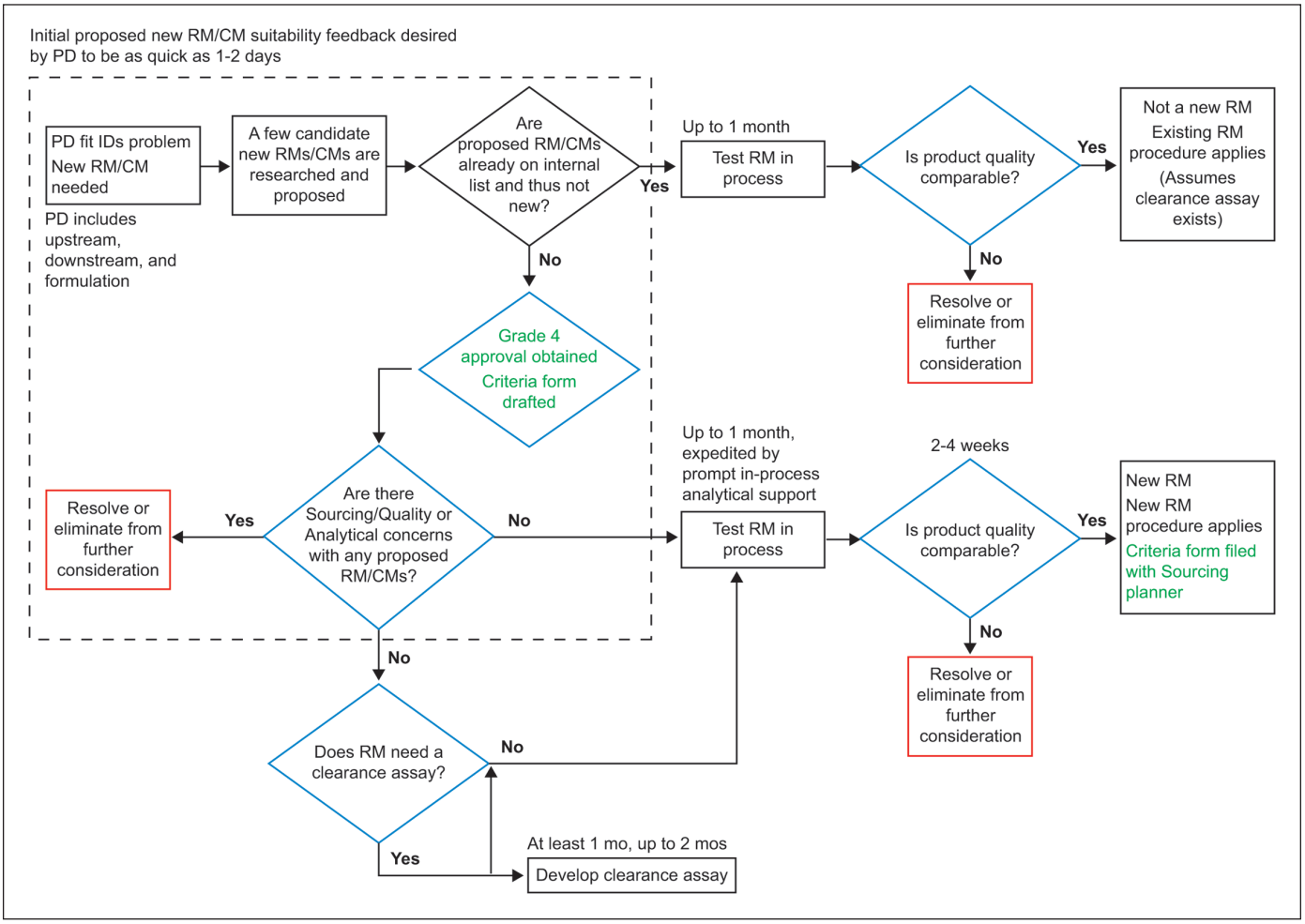


Figure 4. Proposed workflow for new RM/CM identification.

it was proposed to include an RM/CM evaluation within the developmentability assessment conducted for product candidates as a formal criteria for approval. In addition, line of sight sourcing for new and even existing RM/CMs used for process development experiments was considered important: similar grades, but not necessarily vendors, were used for simple items, such as salts, while the same grade and vendor were used for complex items, such as proteins unless equivalence was shown via use or release testing.

Alternate ID, Compositional, and Color/Appearance Testing

Sending of RM/CM samples to external contract testing labs was potentially replaceable by at-line, alternate ID, and color/appearance testing for RMs and alternate ID and composition testing for CM. The True-Scan Raman instrument (Ahura Scientific, Wilmington, MA) was selected as the leading contender for alternate ID and potentially compositional testing based on prior experience at Merck for tablet counterfeiting analysis. Raman was preferable over infra-red spectroscopy for several reasons, including: 1. plastic or glass had minimal interference, 2. typical analysis times typically were one to three minutes or less for simple items, 3. form and size did not interfere (e.g., crystal structure, moisture content), and 4. typically, only a single reference sample was required. This technology may not be suitable for fluorescent items (e.g., proteins, riboflavin) or dark or colored materials (e.g., soy peptone). It also cannot measure or distinguish between items having only monatomic ions (such as potassium or sodium hydroxide or sodium chloride) or items with multiple forms in solution such as ammonium hydroxide. Although unfortunate particularly since it was desired to avoid sampling concentrated acid or base solutions, these limitations were acceptable.

The calculation of spectral similarity was weighted to avoid indicating that the material was correctly identified when it was incorrect. The strategy was to protect against type two error/ß risk (i.e., avoid letting nonconforming items pass). Mismatches were able to be followed up with a library search of probable IDs. A Web-based application permitted download of spectra directly into existing LIMS applications.

Application of the True-Scan to CM analysis was based on the potential of Raman spectroscopy to detect components in a liquid mixture. It worked very well for buffers with component concentrations well over 100 mM, such as 400 mM phosphate buffer or 1 M Trizma base, and reasonable well for buffers with component concentrations at or around 100 mM. It could not detect the presence of sodium chloride at any concentration owing to it monatomic ions. Use of this technology (preferably performed on buffer solutions post-filling into disposable storage bags without removing an additional sample) was attractive to create a release test that was suitably discriminating.

An additional strategy for more quantitative compositional assessment was osmolality, which is based on freezing point depression. Changes are directly related to the ID (i.e., number of ions) and composition (i.e., solute concentration, non-ideality) of ions in a solution, which were somewhat predictable for simple CMs (i.e., particularly inorganic salts). In contrast to conductivity, which saturated at high component concentrations, osmolality increased directly up through about 1 M with the exception of highly concentrated organic buffers - *Figure 5*. At higher concentration solutions, particularly 2 M NaCl and above, it was limited since these solutions did not freeze. This approach was preferred over an in-process test (e.g., measurement after each successive component addition) that showed the correct "build" of the buffer, but was prone to errors of omission.

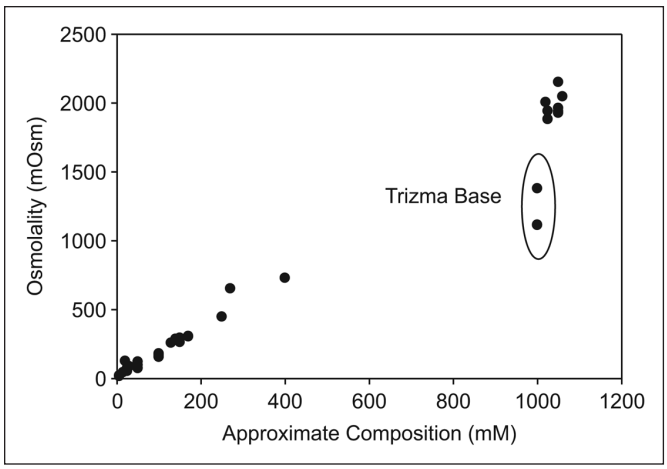


Figure 5. Increase of osmolality with composition.

To fully realize the benefit of handheld ID testing for RMs, it was necessary to conduct color/appearance assessments without taking and sending out samples for analysis. [Color/appearance was previously removed for CMs as part of a prior efficiency effort, but was felt necessary to retain for RMs as a regulatory expectation.] The laboratory procedure required placing a sample on white paper and then observing it. Typical color and appearance specifications were simple: specification of color (e.g., white) and format (e.g., powder). Only in rare cases, the specified format was a crystal geometry. There was potential for an "appropriately rigorous" visual check to be performed through clear plastic or glass containers when completing the receipt checklist, based on procedures in other regulated receiving areas on site. Results from this method then can be correlated with the laboratory procedure and evaluated for suitability.

Compendial Overlap Reduction

Past experience demonstrated that valid failures when repeating compendial tests already conducted by RM vendors were rare; typically failures were classified as invalid after investigation. Consequently, if the vendor already tested the item to multi-compendial standards, it was considered an appropriate risk for early phase clinical manufacturing to confirm testing for only one compendia for those tests that are present in more than one compendia (i.e., overlapping). Overlapping tests were defined as those tests which have similar designations (i.e., test titles) and not necessarily similar methodologies or specifications. It was assumed that vendor responses to quality questionnaires were reviewed and no gaps existed that would generate a significant quality

risk associated with applying these guidelines.

In the particular case of overlapping tests: 1. the preferred choice for overlapping tests was confirming to the European Pharmacopeia (EP) owing to broad applicability; the second choice was the Japanese Pharmacopeia (JP). 2. Any tests that were only present in a single compendia were repeated. 3. Full repetition of multi-compendial testing was recommended for materials from suppliers with a relevant questionnaire gap. Although less rigorous than some aspects of the available guidance for licensed raw materials, this approach was consistent with other key aspects, most notably for material destined for EU clinical trials.[12,13]

An analysis of testing change potential as a result of reducing compendial overlap, as well as instituting alternate testing for RM/CM Identification (ID), RM color and appearance, and CM composition was up to 53%. Individual breakdowns are shown in Table F. In the case of one external testing laboratory, nearly 75% of the sample tests potentially could be conducted in an alternate fashion "at-line."

Quality Questionnaire Workflow

Key aspects of the quality questionnaire workflow were targeted for improvement.

Preliminary data did not indicate an improvement in vendor response time and complete and accurate percentages when recently revised questionnaire forms aimed at clarifying requirements were implemented. To determine how to further improve vendor responses, feedback from selected vendor personnel who completed the questionnaires was solicited using the following questions: 1. Why does it take so long to return our questionnaires? 2. What can we do to speed up the process? 3. How fast is it for you to reach back to your suppliers and get feedback? 4. What questions or parts of the questionnaire may not be clear or require further clarification? 5. How would having information about how each question should be answered (i.e., an example of what information should be in the response) be helpful? Key feedback focused on permitting vendor statements in lieu of creating customized answers to the questionnaire. Based on these responses, there was benefit to instructing vendors to proactively evaluate their existing prepared statements against the questionnaire.

Effort to send initial questionnaires, obtain missing information, and evaluate subsequent responses was substantial and currently resided within the clinical manufacturing RM/CM planning and quality groups. There was no potential to utilize procurement for this task owing to workload and insufficient background knowledge. The ability to leverage an existing center of excellence located within a technical group in manufacturing for these BSE/TSE questionnaires and evaluations was negotiated. Target turnaround times and other expectations (i.e., consistency of response times, annual numbers of questionnaires) were developed guided by the future state value stream map. Utilization of this group was critical to the ability to initiate questionnaires at-risk based on new RM/CM workflow (up to 20/year). In case this group was overloaded, a back-up strategy to outsource these evaluations to an external quality consulting group also was undertaken.

Leverage RM/CM Expertise

Single points of contact were established to leverage expertise in both the laboratory technical support group within the manufacturing area and the analytical group within clinical manufacturing area. Target turnaround times and other expectations (i.e., consistency of response times, estimated numbers, and types of expected issues) were developed.

A mapped list of issues/contacts facilitated deployment:

Manufacturing technical support group requirements were based on a maximum of 12 campaigns per year with a target of six campaigns per year, including: 1. assist when necessary to define the analytical tests and specifications for new or revised RM/CM release protocols – approximately one per campaign, 2. assist in resolving problems/issues regarding novel assay needs with contract testing laboratories – approximately two per campaign, 3. provide technical input into RM/CM testing OOS investigations – approximately three per year (10/year total, but not all require input), 4. provide technical input into RM/CM Atypical Processing Report (APR) investigations – approximately one per year (APRs typically were related to RM/CM storage and CM manufacturing), 5. provide input into future analytical testing reduction initiatives (e.g., in-house buffer manufacturing testing reduction) ad-hoc/as needed.

Clinical manufacturing analytical group support requirements included: 1. evaluating external contract testing laboratory assay transfer qualification protocols – infrequent occurrence, 2. determining when review required for external contract laboratory methods and/or representative data to support determination of analytical test appropriateness – not typically necessary, but active determination desirable, 3. approving new and revised RM/CM release protocols with approval indicating agreement to analytical tests and specifications – ~50/year, and 4. evaluating resources for internal analytical testing support – rarely necessary.

Contracting Testing Lab	Initial Totals (current state)	Prior Elimination of Gen Color/ App for CMs	Estimated Compendial Overlap	Estimated RM Handheld ID	Estimated Alternate Color and Appearance	Estimated Alternate CM ID/Composition	Estimated Total Test Changes	Percent Changes %
A+B	1470	53	215	118	113	278	777	53.0
A	1164	N/A	215	114	113	112	554	48.0
B	306	53	N/A	4	0	166	223	72.9

Table F. Contract testing change potential. Basis: past two years (12/06 to 12/08)

Step	Current State (months)		Future State (months)					
	SME Estimate X (s)	Data X (s)	Projected X (s)	Min Difference δm	No. of Data Points for δ_m n_m	Target Difference δt	No. of Data Points for δ_t n_t	Estimated Time to Achieve n_t
Release Assay Developed	1.5 (1)	1.3 (0.4) (n = 6)	0.75 (0.25)	0.1	52	0.25	10	~6-12
Questionnaires Solicited	1.0 (1)	1.36 (1.13) (n = 5)	0.75 (0.25)	0.1	52	0.25	10	~4
RP Approved, Samples Tested and Release Pkg Assembled	1.5 (1)	1.1 (0.8) QCL 2.1 (0.8) QTI	1.0 (0.25)	0.1	45	0.5	4	~1.5

Table G. Estimate of data required to show significant improvement (one-sample T-test, power =0.8, α = 0.5).

Release Assay Development and Sample Testing Turnaround

Key aspects of the contract testing workflow were targeted for improvement.

Expedited service requirements were established by communicating to the contract testing laboratories, via the procurement and external sourcing groups. Turnaround times were 0.5 months target/0.75 months maximum each for sample testing, assay development, and occasional OOS investigations. The external testing labs then had the responsibility to cross train personnel or equip their laboratory to handle peak loads. In addition, testing lab personnel were given training and access to enter data directly into the Merck LIMS system remotely. The budget was extended to develop at-risk release assays (up to 20 at-risk/year) for those RM/CM types still requiring external contract lab release testing after implementation of alternative ID and composition testing methods.

Roles and Responsibilities

A review of recent OOSs revealed that ~20 to 35% were due to inadequate specifications or test method definition. To improve specification appropriateness, the following roles and responsibilities were established, including: 1. highlighting the need for additional care to properly prepare and document development sample preparation to ensure they were representative of RM/CM to be tested and then used in the clinical manufacturing process, 2. ensuring consistent level of oversight for setting/approving RM/CM testing specifications via appropriate consultation with scientific leaders to review that each specification had a meaningful impact on the process, and 3. instituting training on relevant SOP responsibilities for process development staff before sign-off on release plans (i.e., appropriate parameters measured for release testing, specifications acceptable to process capabilities, appropriate container closure, expiry information provided/reviewed) and CM preparation documents (i.e., verify bill of materials, calculations, specific gravity information, filter compatibility, and appropriate container closure for the material and intended process). On a semi-annual basis, OOSs (and associated RM/CM specs) were to be reviewed at the clinical manufacturing area's analytical steering committee.

Projected Achievement of Benefits

Three areas of the workflow were selected to quantify improvements in RM/CM identification-to-release cycle time: questionnaire solicitation response time (first step), release assay development, and sample testing. Using current state estimates for average and standard deviation, the number of data points, n_m or n_t (and thus, required time post-implementation) required to determine a significant minimum and target difference, δ_m and δ_t respectively, was estimated using a one-sample T-test (power = 0.8, α = 0.05) - *Table G*. Based on forecasted work initiation timing, the time estimated to obtain the target number of data points for δ_t = 0.25 months ranged from 1.5 to 12 months depending on the step.

Selected post-implementation data collection also was linked to the three initial project goals.

Internal release hours were evaluated through the metrics of the number OOS per year and indirectly through other metrics. **External release testing spend** was evaluated through the metrics of the number of compendial tests and the number of tests sent to external contract testing laboratories. Identification to **release cycle time** was evaluated based on 1. adherence to the new RM/CM selection criteria and associated pre-investment workflow (i.e., "at risk" quality questionnaire and release assay development), 2. sample testing, assay development, and questionnaire solicitation cycle times, and 3. indirectly by the percentage of risk memos per campaign.

Many of the changes outlined were able to be controlled by release plans. These documents specified the testing methods as well as specifications for each RM or CM. According to the test instrument vendors, these new testing methods were already in place at other companies in similar applications. Thus, once the new methodologies were developed and implemented in a release plan, it was a very high certainty they would be followed or else the RM or CM would not be released. Consequently, the probability of achieving the projected reductions was high based on solid business and technical foundations.

Despite the clear projected benefits, major factors challenging implementation of these somewhat modest changes center around workload prioritization and management sponsorship. As RM/CM testing and release delays continue

to increase, affected groups have begun requesting to speed up implementation. Until the majority of the changes have been implemented, it is difficult to demonstrate a significant overall performance improvement. However, the methodology presented, along with selected solutions, is applicable to other clinical and potentially even licensed manufacturing settings.

References

1. Kupp, G.D., Challenges, Considerations, and Benefits of Raw Material Testing, Pharmaceutical Technology, Analytical Chemistry and Testing, 1 February 2003, pp. 22-27.
2. US Pharmacopoeia 31, National Formulary 26, 2008.
3. Japanese Pharmacopoeia 15, 2006.
4. European Pharmacopoeia 6.0, 2008.
5. Wiggins, J., Compliance with Multi-Compendial Testing Requirements for Excipients: Challenges and Strategies, American Pharmaceutical Review 6(2): 10-14, 2003.
6. Wiggins, J., Skutnik, J.A., Shimek-Cox, J.L., Schwarzwalder, N.A., Compendial Issues: A Position Paper on the Ideal Pharmacopeia, Pharmaceutical Technology 32(11): 122-125, 2008.
7. Cundell, A.M., Managing Microbiological Quality of Pharmaceutical Excipients, PDA J Pharm Sci Technol, 59(6): 381-395, 2005.
8. Shadle, P.J., Qualification of Raw Materials for Biopharmaceutical Use, Biopharm 17(2): 28-41, 2004.
9. Mortellaro, S., Devine, M., Advances in Animal-Free Manufacturing of Biopharmaceuticals, Biopharm International Supplement, May, 2007, pp. 30-37.
10. Halsey, S., Ensuring Raw Material Quality, Pharmaceutical Technology Europe, 1 March 2009.
11. Junker, B.H., Hunsberger, K., Griffin, V., Hamaker, K., Holz, C., Caparoni, A., Kistler, K., Graczyk, J., Gayton, M., Clinical Manufacturing Efficiency, Pharmaceutical Engineering, 29(2): 48-58, 2009.
12. Committee for Medicinal Products for Human Use, "Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials," EMEA, London, 31 March 2006, www.emea.europa.eu/pdfs/human/qwp/18540104en.pdf, accessed 25 September 2008.
13. FDA Center for Drug Evaluation and Research (CDER), "Manual of Policies and Procedures: Acceptability of Standards from Alternative Compendia," (MAPP 5310.7), 3 November 2007, www.fda.gov/cder/mapp/5310.7R.pdf.

Acknowledgements

The authors would like to acknowledge the contributions of Jack Sinclair and Ralph Mancinelli.

About the Authors

Beth Junker is a Senior Scientific Director in the Bioprocess R&D department at Merck & Co., Inc. She is responsible for quality by design, knowledge management, operational excellence, as well as safety and environmental compliance. She obtained her black belt and currently is completing her master black belt certification. Previously, she was responsible for two non-GMP laboratory and pilot scale bioprocess operation areas, as well as rapid production of reagent proteins. She received her PhD in biochemical engineering from the Massachusetts Institute of Technology and her BSE in chemical engineering from Princeton University. She can be contacted by telephone: +1-732-594-7010 or by email: beth_junker@merck.com.

Susan Gibbons is a Manager in the GMP Quality Department at Merck & Co., Inc. She is responsible for quality oversight of clinical vaccines and biologics. This role includes providing quality guidance and support for the manufacture, testing and release of clinical supplies. Previously, she has held responsibilities for assay development and transfer, as well as technical support and oversight of release assays for marketed materials. She received her BS in biology from the University of Delaware. She can be contacted by telephone: +1-215-652-3802 or by email: susan_gibbons@merck.com.

Jocelyn Lazor is a Research Biologist in the Bioprocess Clinical Manufacturing and Technology department at Merck & Co., Inc. She is responsible for raw material planning and release. She received her BS in biology from Loyola College and an MS in quality assurance and regulatory affairs from Temple University. She can be contacted by telephone: +1-215-652-3236 or by email: jocelyn_lazor@merck.com.

Monica Storz is a Research Associate in the Bioprocess Analytical and Formulation Sciences department at Merck & Co., Inc. She is responsible for Equipment and Compliance in GMP/GLP Analytical Laboratories. Previously, she was responsible for GMP documentation and sample management for the release and stability of vaccines Phases I/II. She received her BS in biology from College Misericordia and a MS in biology from Villanova University. She can be contacted by telephone: +1-215-652-4105 or by email: monica_storz@merck.com.

Vicky Griffin is a Manager in the Bioprocess Clinical Manufacturing and Technology department at Merck & Co., Inc. She is responsible for raw material planning and release and GMP document management. She received her BS in biology/vertebrate physiology from Pennsylvania State University and an MS in quality assurance and regulatory affairs from Temple University. She can be contacted by telephone: +1-215-652-8883 or by email: vicky_griffin@merck.com.

Kelli Pardue is a Director in the GMP Quality department

at Merck & Co., Inc. She is responsible for quality oversight of clinical vaccines and biologics. This role includes oversight of a multi-product biologics pilot plant, external auditing, audits of regulatory submissions, and product release. She received her PhD in chemistry from the University of Rochester. She can be contacted by telephone: +1-215-652-5361 or by email: kelli_pardue@merck.com.

Marshall Gayton is Senior Director of the Bioprocess Clinical Manufacturing and Technology department at Merck, Inc. He is responsible for operations of a multi-product biologics pilot plant and the preparation of bulk clinical supplies for vaccines and therapeutic proteins. Gayton's experience in API and biopharmaceuticals spans more than 20 years, including manufacturing technical support, purification process development, and technology transfer to manufacturing for natural products and vaccines. He received his BS in chemical engineering from Rutgers University and an MS in chemical engineering from Rice University. He can be contacted by telephone: +1-215-652-1337 or by email: marshall_gayton@merck.com.

Raymond Kaiser is Executive Director in the Bioprocess R&D Department at Merck & Co., Inc. He is responsible for the process, formulation and analytical development of clinical vaccine candidates. Previously, he was at Wyeth, also in the development of vaccine candidates and at Eli Lilly & Company in the development and manufacture of therapeutic proteins. He received his PhD in analytical chemistry from Purdue University. He can be contacted by email: Raymond_Kaiser@merck.com.

Merck & Co., Bioprocess Research and Development, PO Box 2000 RY810-127, Rahway, New Jersey 07090, USA.

On-Line Exclusive Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2010, Vol. 30 No. 1

Life-Enhancing Biotherapeutics Company Nets Healthier Equipment

by Kevin Pait and Preston Ingalls

This case study shows the impact of an organized and focused continuous improvement effort using teamwork on equipment reliability.

Introduction

The following is a case study of the reliability improvement program utilized by a North Carolina biotherapeutics company in order to reduce equipment downtime thereby increasing the overall throughput of their products. This case study will define the equipment involved and its importance to the production process, identify equipment deficiencies, and explain the methodologies and tools used to achieve greater reliability and accountability.

The Company

The mission of Talecris Biotherapeutics, a global biotherapeutics and biotechnology company headquartered in Research Triangle Park, North Carolina, is "to be the recognized global leader in developing and providing vital protein therapeutics." Achieving this mission involves a firm commitment to customers, employees, and reliable equipment.

Because of the importance of equipment reliability, Kevin Pait, Director of Plant Engineering and Maintenance, implemented Total Process Reliability (ToPR). ToPR is a program developed in collaboration with TBR Strategies, a consulting firm based in Raleigh, North Carolina.

With the help of TBR Strategies, Pait identified two employees who would serve as ToPR Coordinators, and he also began to assemble an Implementation Team. The Coordinators, employees tasked with running the onsite ToPR program day-to-day, seek to identify the gaps between the current situation and the ideal situation. Next, they discern which ToPR methods and tools will most likely remove that gap. One Coordinator, Richie Hogg, is a Talecris veteran with nearly 17 years of production experience in operations, training, and performance development.

Hogg sees his position today as more theoretical than hands-on. "As ToPR coordinator, my main responsibility is to promote transformation through collaboration and partnership within the maintenance, operations, and engineering departments. I am a change agent."

Pre-Planning

The Implementation Team, responsible for initiating and guiding cross-functional teams, determines projects based on criticality and historical performance. Criticality is decided by the importance of a piece of equipment to the overall process, and performance is based on uptime or Mean Time Between Failure (MTBF).

Once the Implementation Team has identified the new project, a senior management sponsor meets with a coordinator and team leader to write a charter. The charter includes a description of the initiative, goals, scope, boundaries, and project deliverables. The team leader chooses a group of employees (consisting of representatives from maintenance, operations, and engineering) to serve

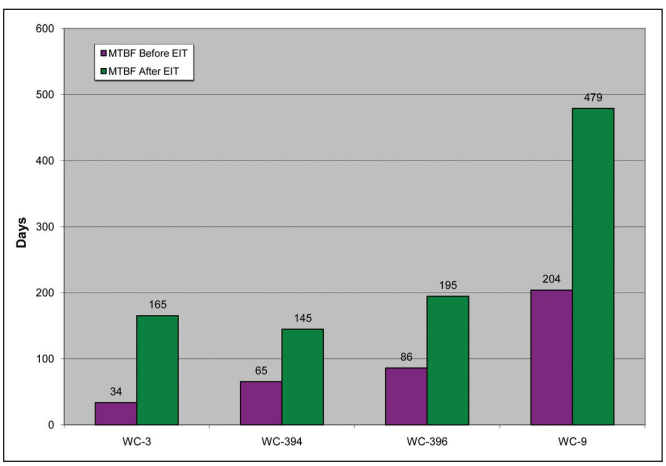


Figure 1. Westfalia centrifuge – MTBF.

on the Equipment Improvement Team (EIT).

The benefits of an EIT include creating and improving machine care standards, initiating and maintaining visual controls, restoring equipment to a like-new condition, developing action steps for machine improvements, and tracking and displaying progress of the equipment restoration efforts.

Determining the Issue

One of the main issues identified by the Implementation Team was the equipment reliability of the Westfalia centrifuges. The centrifuges are high speed solid-liquid separators which utilize the differences in density of solid particles to achieve separation. Centrifugal force, created at speeds of approximately 5500 rpm, causes the solid particles to separate and adhere to the bowl wall, while the lighter substances (liquid) pass through.

The centrifuges are used for multiple functions in the Fractionation method, including the process to remove intermediates used in the treatment of Hemophilia A. The centrifuges also are vital in the separation and recovery of proteins used to produce therapies to treat a rare and difficult to diagnose illness caused by genetic emphysema.

So, successful production of the company's life-enhancing therapies greatly depends on the availability of the 13 Westfalia centrifuges. In terms of performance, the centrifuges were requiring excessive maintenance. By examining each machine's failure report, the Coordinators identified the most problematic centrifuge.

The Process

The EIT process begins in a classroom format with a general safety review. The Coordinators then introduce the basic ToPR concepts to create an appreciation for the overall goals of the program.

The ToPR overview is followed by a discussion of the benefits ToPR can provide to the employee, the department, and the company as a whole. Team members learn equipment reliability principles, including the evolution of maintenance practices (World War II through today) and the theory of equipment operation.

The next step is viewing the equipment. During this time, the team identifies lock-out points and creates a plan of action. A list of cleaning needs and supplies is generated and an initial assessment is conducted on the equipment. The team reviews machine-specific safety information and identifies guard or cover removal points.

The next step of the EIT process takes place once again in a classroom setting. Discussion and lecture topics range from autonomous maintenance to cleaning and countermeasures. The team then moves back into a hands-on situation for a *Clean, Lubricate, Adjust, Inspect, Repair* (minor) and *Eliminate* (CLAIRE). This activity breeds a defect list that can be prioritized and corrected using countermeasures, steps taken to eliminate defects. Countermeasures include, but are not limited to job aids, modifications to reduce cleaning and lubrication time, best practices, and single-point lesson plans.

Equipment-Focused Improvement Techniques

One defect exposed by the EIT, seal damage, was the result of "flooding" the Westfalia housing during the cleaning cycle. A countermeasure, in the form of an operator care standard, was developed to eliminate seal failures due to inappropriate techniques.

Countermeasures can be implemented using many tools, such as job aids, which can sometimes be seen in the form of Single Point Lessons. This form of job aid is a one-page document clarifying a single point or task in an operation. Single Point Lessons provide a short, concise description of the task and utilize pictures to illustrate the proper techniques and methods to complete the task.

Some Single Point Lessons are preventive measures, not countermeasures. In the case of the Westfalia, a Single Point Lesson with six steps was developed to disassemble and inspect the centripetal pump to ensure that the inner parts were clean and the seals were in proper working condition.

Best Practice Standards are another type of Job Aid that identifies the "one best way" to complete a task. Best Practices can be used to eliminate defects as well as enhance techniques that improve equipment functionality. They may include, but are not limited to machine care, lubrication, and cleaning. In addition to best practices and operator care standards, the team creates an operator troubleshooting guide and a rebuild parts list.

Employee-Focused Improvement Techniques

Cross-departmental training is another tactic being used to ensure equipment reliability by amplifying the relationship between maintenance and operations. "In addition to participating in the EIT events, the Maintenance Department teamed up with trainers in the Purification Department to provide hands-on assembly training with each operator in the Production Department," explained Maintenance Technician Ronald Crocker. "The training helped improve operating equipment knowledge and resulted in a lower number of assembly errors."

Technician Julie Monteiro realized the value of the collaborative aspects of the ToPR implementation:

> "Having the operators and mechanics working together to refurbish the Westfalias bridged a gap between us. Operators are on the front-line of manufacturing, and now a ToPR trained operator understands how and why a piece of equipment works. Because of this program, operators and mechanics are speaking and understanding the same language."

Another component of the team's training involved "5S" events, which stands for *Sort, Set in order, Shine, Standardize, Sustain*. Through these events, team members make equipment and workplace upkeep a priority. Focusing on cosmetic and mechanical order helps establish an operational respect for the equipment and also creates a department-wide sense of ownership.

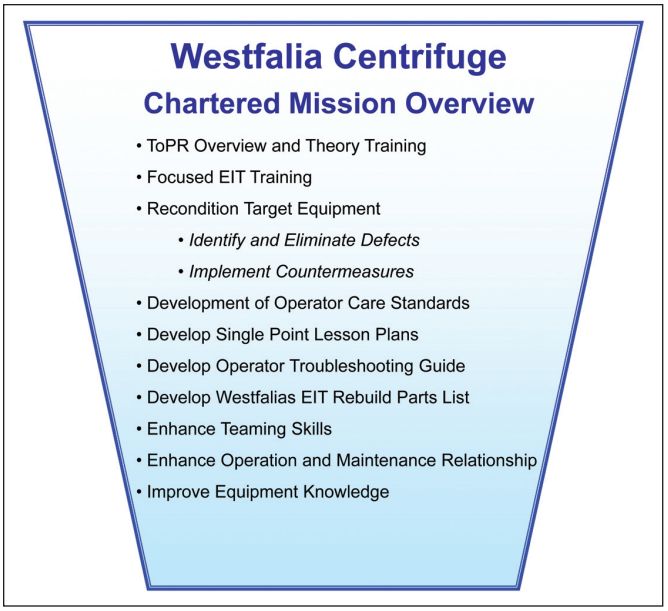


Figure 2. Westfalia centrifuge chartered mission overview.

Inspect What You Expect

Monthly inspections in the form of audits are performed to ensure that the desired level of equipment stewardship is sustained. Equipment audits are used to ensure that whatever the team evaluates – in this case Westfalias – is maintained at the highest level of Tighten, Lubricate, Clean (TLC). Fasteners, such as gaskets, nuts, and bolts, must be in place, including the right quantity and type to ensure the equipment is tight. Lubricants, such as oil, must be at the right level and quality. In addition, the equipment and its parts must be clean. Deficiencies discovered during the audit require immediate follow-up and corrective action.

Results

At the completion of the EIT, the Westfalia was tested in the maintenance shop. Each component was inspected by the team members. In addition, vibration readings were recorded by predictive maintenance technicians for baseline data and trending. The team goals (to restore the Westfalia to like new condition, develop best practices and operator care standards and to measure MTBF to show results) had been achieved. Each team member participated in a debriefing with senior management to share their experiences from the event.

As a result of the EIT, the Westfalia centrifuge's MTBF increased from an average 34 days between failures to 165 days and counting. Following another EIT, a second Westfalia centrifuge's uptime is 479 days where, at one time, it was functioning at 204 days. In total, the performance of four Westfalia centrifuges has improved through EIT activities.

Summary and Conclusion

Total Process Reliability facilitates a cultural change at every level. It emphasizes leadership and the communal ownership and stewardship of equipment. ToPR also assists employees in providing therapies that improve people's lives, a vision that they believe in.

With a two-fold improvement in the performance of one centrifuge and an almost five-fold improvement of another, it becomes clear that the Total Process Reliability program yields exceptional results. The production of life-enhancing therapies at Talecris is more efficient, orderly, and productive, directly reflecting two of the company's seven core values: Operational Excellence and Teamwork.

About the Authors

Kevin Pait has more than 30 years of experience in plant maintenance and engineering, production management, process development, and strategic planning in the pharmaceutical, specialty chemical, utility, and biotechnology industries. He has extensive experience in plant and fleet maintenance. He is the Director of Plant Engineering and Maintenance for Talecris Biotherapeutics, located in Clayton, North Carolina. His educational background includes a BS in chemical engineering and an MS in financial management, both from North Carolina State University. He is a registered Professional Engineer in the State of North Carolina. Pait can be contacted by telephone: +1-919-359-5028 or by email: kevin.pait@talecris.com.

Preston Ingalls is the President and CEO of TBR Strategies LLC, a maintenance and reliability consulting firm located in Raleigh North Carolina. He has more than 37 years in the field of maintenance, engineering, and reliability. As a consultant for the last 20 years, he has implemented maintenance improvement efforts with numerous manufacturers, construction companies, oil and gas producers, and public utilities across 27 countries. Ingalls holds undergraduate degrees in manufacturing engineering and engineering operations, as well as a master's in organizational development. He can be reached by telephone: +1-919-341-1387 or by email: pingalls@tbr-strategies.com.

TBR Strategies LLC, 7000 Harps Mill Rd., Suites 102 and 202, Raleigh, NC 27615.