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# Case Study: Genentech's ECP-1 Bacterial Manufacturing Facility, Overall Winner, 2010 Facility of the Year Awards

## *Innovative Project Execution Outpaces Ambitious Schedule*

by Rochelle Runas, ISPE Technical Writer

### Introduction

Standing on a greenfield site once part of a shipping channel in Tuas, Singapore is an unassuming structure with a remarkable story. The structure was designed in four different locations spanning 12 time zones. It was built and shipped in pieces across thousands of miles of rough seas. It was reassembled at a site where six languages were spoken. All of this was accomplished ahead of a very ambitious schedule so that patients could have access to an important medicine.

This article presents the story of how innovative project execution and strong teamwork overcame numerous challenges in the making of Genentech's ECP-1 Bacterial Manufacturing Facility, Overall Winner of the 2010 Facility of the Year Awards. Genentech's win of this coveted award was announced at ISPE's 2010 Annual Meeting in November 2010 in Orlando, Florida, USA. Initially developed by Genentech, a wholly owned member of the Roche Group, the facility is now operating as Roche Singapore Technical Operations.

### A Motivating Vision

The E. Coli Plant 1 (ECP-1) Bacterial Manufacturing Facility was built to increase production capacity of Lucentis® (ranibizumab injection), a novel therapy used to treat neovascular (wet) Age-Related Macular Degeneration (AMD). Wet AMD is a retinal disease that causes irreversible vision loss and is one of the leading causes of blindness in people over 55 years of age. Produced using *E. coli*, Lucentis inhibits the formation of new blood vessels which can grow under the retina and cause damage to the macula.

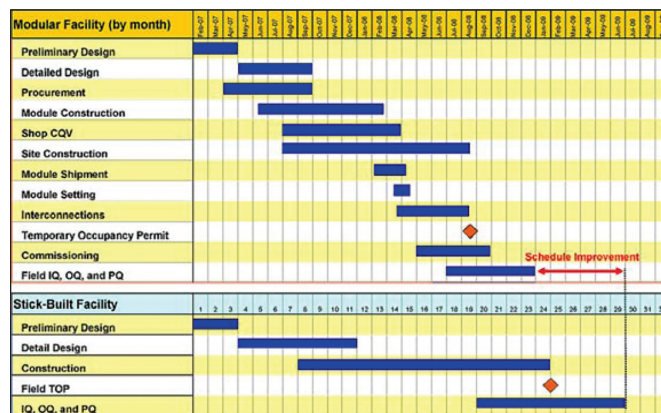
The 2006 FDA approval of Lucentis for the treatment of wet AMD was followed by rapidly escalating patient demand. Needing additional capacity to manufacture Lucentis drug substance, Genentech established a highly ambitious project schedule to construct a new production facility halfway around the world from its headquarters in South San Francisco, California, USA.

### Project Overview

The project goals were to deliver a licensable manufacturing site that: provided for safe, reliable, and cost effective production; met construction safety targets; remained within the approved budget of \$217 million; and completed OQ within 24 months from engineering kickoff.

A worldwide selection effort yielded a 30-acre greenfield site bordering a shipping channel in Tuas, Singapore. Singapore was chosen for its knowledgeable, highly supportive business environment, a modern infrastructure, and improved cost structure. Additionally, Singapore houses a thriving pharmaceutical

Project completed in 23 months.





Buffer prep area in shop fabrication.

community, which enabled Genentech to benefit from a deep regional talent pool.

Meeting an ultra-fast-track schedule on an international project required a collaborative team to develop and execute an innovative strategy. A design build team – comprising contractor Jacobs Engineering Group located in Cincinnati, Ohio, USA, Charleston, South Carolina, USA, and Tuas, Singapore and contractor Bovis Lend Lease Pharmaceutical located in Tuas, Singapore, and owner Genentech located in South San Francisco, California, USA – developed a strategy utilizing large-bay modules integrated with traditional stick-build construction.

The project comprises a total building area approximately 102,000 square feet, more than 30,000 square feet of which is manufacturing space (modular construction) on two levels. Jacobs headed the module building work, which included process areas (including Grade C rooms), process equipment, and process utilities. Bovis headed the site/stick built work, which included production support areas, including administrative offices, a GMP warehouse, and a central utility building stick-built on the site. Additional site scope included infrastructure, such as roads, main utility services, landscaping, and an electrical substation.

## Why Modular Construction?

“The decision to use modular construction was in large part to meet an aggressive schedule and we were able to take advan-

### Advantages and Disadvantages of Modular Construction for ECP-1

#### Advantages

- Potential for faster schedule due to parallel construction
- Better QC and safety, as work occurs in a controlled environment
- Access to additional skilled craftsmen, who may be in short supply at the jobsite

#### Disadvantages

- Can be more expensive
- Requires considerably more coordination between the site and modular construction firms



Route from South Carolina to Singapore.

tage of the overlap in construction provided by this delivery methodology,” said Jon Reed, Vice President, Engineering, Genentech. “We were able to perform considerable activities on the site while at the same time the modular manufacturing building was being constructed in South Carolina.”

ECP-1 utilized 24 large bay structural modules measuring 25' W × 21' H × 45' L as opposed to the standard module size of 14' W × 12'6" H × 45' L. One large bay module is equivalent to roughly four standard modules. The use of large bay modules resulted in a 75% reduction in the number of modules, further accelerating schedule completion.

Nearly all acceptance testing and qualification work was executed before module shipment to Singapore, thus reducing the time to start up once the modules were installed at the ECP-1 site.

Two ocean shipments of the oversized modules were each transported almost 14,000 miles, enduring weather, the rough Atlantic Ocean in late winter, and traffic logistics. The total ocean transport time from Charleston, South Carolina to the site in Singapore was 45 days per shipment, which represented a significant block of time on the schedule's critical path. “We couldn't ship too early or too late,” said George Mackey, Project Director, Genentech. “We had to be exact.” Planning for dedicated “last on, first off” ocean shipping and pre-approval of all permits and customs documents was key to maintaining the planned project schedule. All modules arrived fully intact and on schedule.



Ocean transport of finished modules.

The site being located directly on a shipping channel indeed helped module transportation logistics. But regardless of the location in Singapore, Genentech would have used modular construction, “provided that a reasonably direct path from the channel to the jobsite was available,” said Reed. “With large modular construction there may be restrictions on transportation that would prohibit their use. However, modules can be adjusted in physical size to meet most transportation requirements.”

Modules were moved after midnight with police escort on roads that were closed to other vehicles. In advance of the move, trees were trimmed, lights removed, and utility lines relocated.

The construction site was prepared for the modules by setting drain piping, base plates, rigging and soil compaction (for the crane), scaffolding and safety barriers. Upon arrival at the site, each module was carefully lifted and set in place with a 500 ton crane/220 foot boom, and a dedicated team of tradesmen under Bovis’ direction.

Taking into account the process piping, ductwork, structural slab, flooring, wall partitions and ceilings, thousands of module/field connections had to be made. “A large team of craftsmen planned every detail of the field assembly work,” said Reed. “Upon module arrival, the teams executed like clockwork and completed their work flawlessly. No connections were out of tolerance by greater than 0.375 inches!”

Key project participants were pleased and impressed with the modular approach. “Large modules utilized for the process and clean utilities areas provided a ‘spaciousness’ that belied the

fact that the entire area was built as a series of module ‘boxes’ half way around the world, shipped, and then set in place and bolted together,” said Pat Sanders, Project Manager, Jacobs.

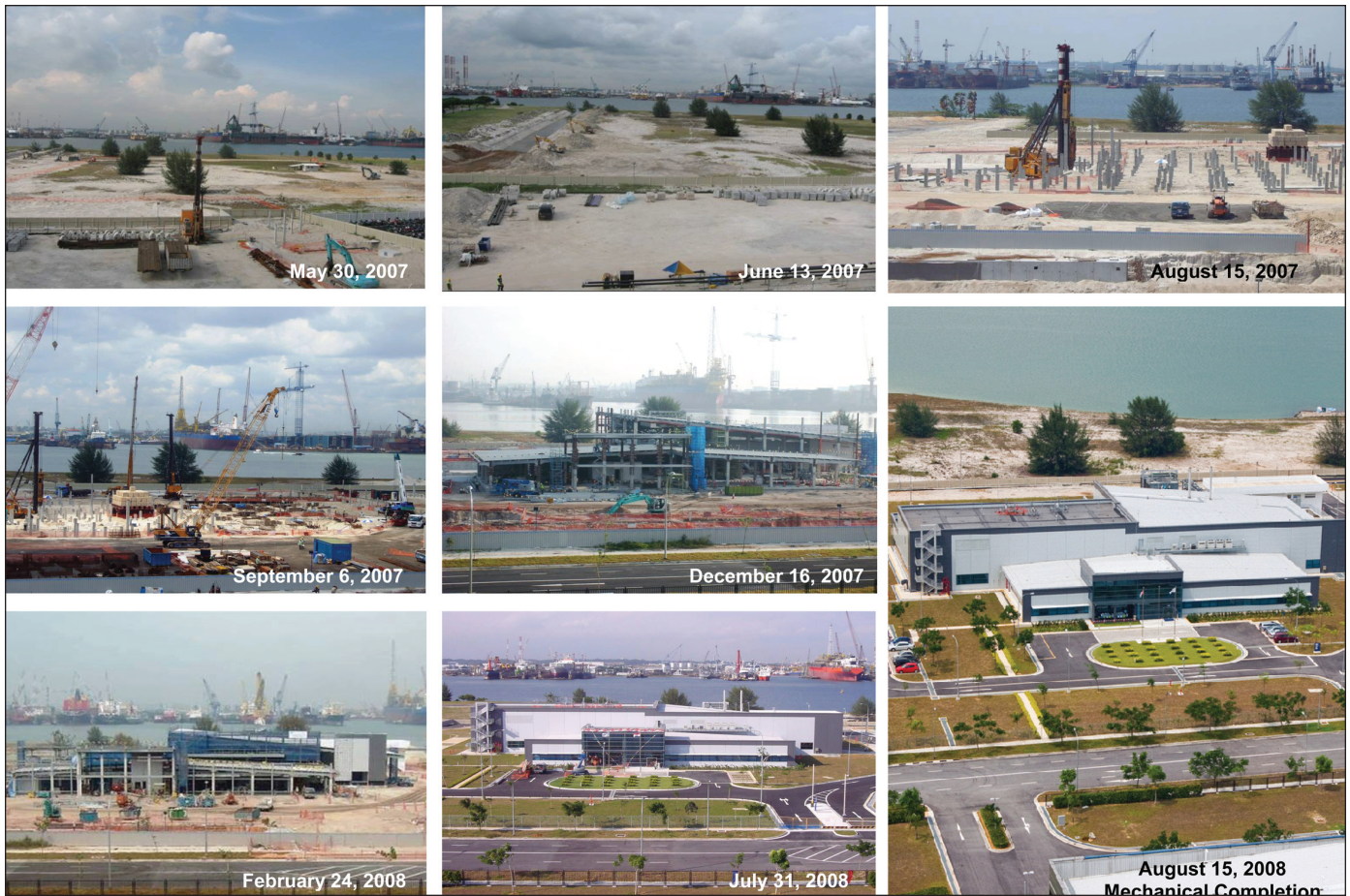
“Dealing with modules was easier than I expected simply because we had great quality in our information transfer from the Jacobs team in Charleston: ship books, schedules, interconnection scopes of work, etc.” said William McNamara, Project Manager, Bovis. “The accuracy of the build contributed to the ease of setting and interconnecting the modules.”

Mackey said several project company executives walked through the plant upon mechanical completion and the question often asked was: Where are the modules? “You cannot find the difference between the modules and site construction,” said Mackey.

## Overcoming Unique Project Challenges

There were some challenges unique to the ECP-1 project that tested the team’s project management skills as well as its commitment to the project and all parties involved.

For example, the modules arrived in Singapore with more incomplete work than planned. “This was primarily due to the need to stay aligned with the ocean shipping timeline,” said Reed. “Coordination between the on-site construction work and the arrival of the modules was aggressively planned and missing the ship date would have delayed the overall project severely. Teams avoided finger pointing and blame and worked out a resourcing plan to deal with the problem and maintained schedule.”



Campus construction progress.

Another challenge was communications. "Working across 12 different time zones assured work was occurring 24/7, but effective communication was essential," said Reed. "While technology (videoconference, WebEx, email) was employed, the most effective tool was co-locating project staff together."

Also, six languages were spoken at the site. Daily team "toolbox" talks held in each language were communicated through multi-language signage throughout. "Multi-lingual superintendents were a must!" said Reed. "Even the cafeteria had separate menus and facilities to address the needs of our staff's appetites."

Mother Nature also proved challenging. Daily rains, frequent thunder/lightening storms, and constant high humidity made construction work difficult. Lightening detectors were required

safety equipment. "During module setting, we constructed a football-sized 'umbrella' that was held by a second crane over the open modules while they were being set on their respective foundations to prevent rain from getting into the open sides of the modules," said Reed.

## Success Factors for the ECP-1 Project

Overall, the project was successful because of strong teamwork, effective decision making, and constant communication, according to Reed. Contracting partners that are aligned and staying focused on the mission are major factors, as well as having the site's General Manager, Jim Miller, as an integrated partner that supported the construction team and helped remove barriers along the way to keep project teams moving.

## Facility of the Year Awards

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

More information on the Facility of the Year Awards program can be found at [www.FacilityoftheYear.org](http://www.FacilityoftheYear.org).

### 2010 Facility of the Year

**Genentech's ECP-1 Bacterial Manufacturing Facility**, category winner for Project Execution, was selected as the Overall Winner of the 2010 Facility of the Year Awards among four other Category Winners in 2010:

- **Biogen Idec**, winner of the Facility of the Year Award for *Operational Excellence* for its Large-scale Manufacturing (LSM) Technology Map Project in Research Triangle Park, North Carolina, USA
- **MannKind Corporation**, winner of the Facility of the Year Award for both *Equipment Innovation* and *Process Innovation* for its Technosphere® Insulin Manufacturing Facility in Connecticut, USA
- **Pfizer Biotechnology Ireland**, winner of the Facility of the Year Award for *Sustainability* for its Monoclonal Antibodies (MAbs) Small-scale Facility in County Cork, Ireland
- **Pfizer Ireland Pharmaceuticals**, winner of the Facility of the Year Award for *Facility Integration* for its Aseptic Facility Expansion Project in Dublin, Ireland

"FOYA is a good venue to showcase excellence in engineering and allows companies an opportunity to discuss new and innovative ways to provide these services to our industry, which ultimately benefit our patients and communities. Our organizations all benefit from learn-

ing about best in class methods or innovations around process design, sustainability, efficiency, and delivery innovations which drive better quality into our products, higher efficiencies in our production operations and more cost effective ways to deliver our services." – Jon Reed, Vice President, Engineering, Genentech, for Genentech's ECP-1 Bacterial Manufacturing Facility, Overall Winner of the 2010 Facility of the Year Awards.

### 2011 Facility of the Year

The 2011 Facility of the Year Category Winners are:

- **F. Hoffmann – La Roche Ltd**, winner of the Facility of the Year Award for *Process Innovation* for its "MyDose" Clinical Supply facility in Kaiseraugst, Switzerland
- **MedImmune, LLC**, winner of the Facility of the Year Award for *Project Execution* for its Frederick Manufacturing Center (FMC) Expansion facility in Frederick, Maryland, USA
- **Merck & Co., Inc.**, winner of the Facility of the Year Award for *Facility Integration* for its Global Clinical Supplies Manufacturing, Packaging and Warehouse expansion project in Summit, New Jersey, USA
- **Novartis Vaccines and Diagnostics GmbH**, winner of the Facility of the Year Award for *Equipment Innovation* for its "MARS Project" (Marburg Site) facility in Marburg, Germany
- **Pfizer Health AB**, winner of the Facility of the Year Award for *Operational Excellence* for its Project Pegasus – Bio 7 Manufacturing facility in Strängnäs, Sweden
- **Pfizer Manufacturing Deutschland GmbH**, winner of the Facility of the Year Award for *Sustainability* for its SPRING and E-MAP (Strategic Plant Restructuring and Energy Master Plan) project in Freiburg, Germany
- **Shire HGT**, Facility of the Year Award *Honorable Mention* for its Project Atlas, Building 400 facility in Lexington, Massachusetts, USA.

The Category Winners of the 2011 Facility of the Year Awards will be featured in a Supplement to the May/June 2011 issue of *Pharmaceutical Engineering*.



Multiple languages were spoken on site.

“The teamwork exhibited by our employees, partners, and leadership team was exceptional,” said Reed and Miller. “With an aggressive schedule such as this, we didn’t have time to spend talking about any one subject. It was imperative that we made good, timely decisions and that the teams quickly aligned and executed those decisions.”


As for success factors for projects employing modular construction, according to Mackey they are the same as those for projects using standard construction. “However, they demand flawless execution and attention to detail. Everything is on the critical path.”

### A Worthwhile Premium

This decision to use modular construction came at a small premium, however to Genentech it was worth it to get the product to market. “Every day this facility was not in operation, we risked patients not having access to this important medicine,” said Reed.

“The operation of this facility improves the efficiency of our ability to produce Lucentis. Coupled with the close proximity to our much larger facility across the street, we are able to leverage a common workforce and didn’t have to duplicate many support facilities in this facility, such as a full service cafeteria, large meeting rooms, warehousing, etc.”

### Conclusion

The guiding principle throughout the project was the need to provide patients with products that addressed an unmet medical need, and the end users with facilities that were fit to operate. The business requirements presented the team with significant schedule, cost, and execution challenges. However, by committing to a modular approach from the beginning, along with an early focus on site issues, outstanding project planning, execution techniques, and team development, the project beat the aggressive schedule target of 24 months by two weeks and 10.5% under budget. As a result, facility production capacity goals were met, delivering a high quality, licensable manufacturing site that continues to meet future Lucentis market demand. 

Tim Tyson discusses how his career has evolved since his first interview with Pharmaceutical Engineering 18 years ago; his current role as Chairman and CEO of a Contract Research, Development, and Manufacturing Organization; and his work with the ILF's Factory of the Future initiative.

## PHARMACEUTICAL ENGINEERING Interviews

# Timothy C. Tyson, Chairman and CEO, Aptuit, Inc.



**Timothy (Tim) C. Tyson** has been the Chairman and CEO of Aptuit since 2008. Aptuit is a global pharmaceutical services company focused on providing integrated contract research development and manufacturing for biotechnology and pharmaceutical innovators. Aptuit provides a comprehensive suite of product development services and competencies to more than 800 biotechnology and pharmaceutical companies worldwide. A 33-year pharmaceutical industry veteran, Tyson is the former President and CEO of Valeant Pharmaceuticals International, where he served from 2002 to 2008. Prior to Valeant, Tyson's pharmaceutical industry experience includes a 14-year tenure at GlaxoSmithKline (GSK), where he was President of Global Manufacturing and Supply and ran Glaxo Dermatology and Cerenex Pharmaceuticals. There, he managed all sales and marketing for GlaxoWellcome's U.S. operations. Tyson also has held executive positions at Bristol-Myers in technical operations and R&D. Previously, he was a manufacturing manager for Procter & Gamble. A longtime active member of ISPE, in 1994, Tyson led a team of pharmaceutical executives to approach the US FDA with a proposal to create a partnership that paved the way to the creation of ISPE's world renowned Baseline® Guides. He is currently leading ISPE's Factory of the Future initiative on behalf of the International Leadership Forum (ILF). The ILF is an industry group founded by Tim Tyson that has been hosted by ISPE since its inception in 1998. Although not officially an ISPE group, the ILF has provided guidance and support for Society programs and activities over the years.

**Q** You were the first industry executive to be profiled in Pharmaceutical Engineering's Industry Interview Series in 1993. At that time, you were with GSK. Much has transpired in your career since then. Can you take us through a brief tour of the evolution of your career, from GSK to Valeant to Aptuit?

**A** In 1993, I was VP, Engineering for Glaxo. I moved into General Management and ran the Dermatology and Cerenex division, progressed to leading marketing and sales for about six years before becoming President of Global Manufacturing and Supply. I was there about five years before I left and had an opportunity to go to Valeant Pharmaceuticals. I was a global CEO at Valeant, was there for about six years, and then joined Aptuit, which is a Contract Research, Development, and Manufacturing Organization. I have significant experience in all phases of the industry and marketplace and throughout all that time had continued experience and a relationship with ISPE.

**Q** Has your management and leadership style changed since working with a Contract Research, Development, and Manufacturing Organization?

**A** Although I maintained a style that continues to focus people on teamwork and results, I needed to be a lot more flexible and customer focused in this role as head of a Contract Research, Development, and Manufacturing Organization to assure satisfaction of customer expectations and to focus the people in my organization to deliver on the results expected.

**Q** "The pharmaceutical industry is in a phase where past and present success models are obsolete or at least in question. The foundation of the industry will be redefined due to new

business opportunities, eroding success models and mandatory challenges.” (“The Future of Contract Manufacturing,” Engels and Brookman, Contract Pharma, September 2010) In the context of the above statement, what are your views on the direction of the CMO industry?

**A** The pharmaceutical and biotech industries are under revolutionary change that is creating a new model for the industry and the way it brings life saving and life improving medicines to the marketplace and to people who need them. A new virtual model where pharmaceutical and biotech companies get the support and resources necessary to develop and commercialize products is evolving. That is going to require some significant strategic partnerships in this new virtual organization and structure. And in that structure, contract organizations or services organizations will become extremely important and elevate from tactical delivery of certain aspects and capabilities to integrated capabilities that will be required over multiple years. And so the evolution of the industry is expecting that there will be competent, capable, and customer focused organizations in the marketplace that will be able to deliver on those increasing needs from an outsourced and pharmaceutical services standpoint.

**Q** You recently co-lead the Seminar on FDA Inspection Enforcement Trends in Pharmaceutical Inspections and Compliance at the 2011 ISPE Tampa Conference. What are your thoughts on the FDA’s current approach to enforcement and why it was so important to have offered such a seminar to the industry?

**A** The enforcement attitude of the FDA and other regulatory authorities indicates one of some increasing concern about the commitment to quality and regulatory compliance. It is essential for us to continue to partner with the regulatory authorities, including the FDA, to show them that the

industry cares and has the intent to do what’s right and necessary to deliver quality products to patients in need and ensure that we comply with regulatory expectations. Through these types of relationships, we can show that we all have the same objective; that we’re working on the same team; and that together, we can improve the companies’ and the industries’ compliance posture and reduce the concern that regulatory authorities have.

**Q** If you were to devise a “mantra” industry could use in regard to its approach to enforcement, what would that be?

**A** I think that mantra would be “Prevention – Do It Right the First Time,” representing our requirement to ensure that there is an understanding of our compliance posture. The approach to enforcement would be to convince the regulatory authorities that we are doing whatever it takes to prevent problems and that inspection and enforcement is less necessary because there is a commitment and focus on doing things that are necessary to deliver quality and regulatory compliance each time and every time.

**Q** Can you explain what the Factory of the Future initiative means?

**A** The Factory of the Future initiative is a vision for the industry of what is necessary for manufacturing capabilities and factories to be able to deliver in the future to satisfy and service the pharmaceutical industry’s needs.

**Q** What is your direct involvement in the Factory of the Future initiative?

**A** I am leading this on behalf of the International Leadership Forum (ILF) with a team of people committed to developing and communicating a clear vision for ILF, ISPE, and the pharmaceutical industry.

**Q** Why did the ILF feel there was a need for such an initiative? What does the ILF hope to accomplish with this initiative?

**A** The ILF felt that there was a need to identify the key issues facing the industry today and develop some specific action steps that could help progress these issues over a multi-year program. The ILF wants to demonstrate to the industry and regulators that there is a focused leadership intent and commitment to allocating the appropriate resources to help take the steps necessary to move things forward into the future over the next few years.

**Q** How is the Factory of the Future initiative different from the Facility of the Year Award?

**A** The current Facility of the Year Award program is a review of current, actual facilities that exemplify the current state of the art finish, functionality and quality standards. The Factory of the Future is an initiative to create a vision for which future facilities should be designed and operated to help move the industry from where we are today to establish facilities and capability to meet future needs.

**Q** How is the Factory of the Future initiative going to impact ISPE Members in their current roles on a day to day basis? Now and in the future?

**A** The initiative will impact ISPE Members by establishing a vision of where industry’s manufacturing capability will need to go to be able to serve and support the industry’s needs in the future. This vision will help provide some understanding of things that companies can do. Each company will be able to analyze their current position and the intended future state and determine what they have to do to progress from current to future. This will help ISPE Members and their companies understand the things they need to do to change or improve on a day to day basis.

**Q** When will the Factory of the Future initiative launch?

**A** It has launched. It's under development. It's part of an overall plan that the ILF will complete in the next few months and this is one component of that plan which lists the major issues that the industry faces, providing some direction of where the ILF thinks that technical resources should be deployed to help to satisfy or solve those issues and support creating the capability the industry will need. The Factory of the Future initiative is one of the components of that overall plan and the deliverable of that initiative is a vision with some action steps to help drive the industry forward.

**Q** What are the planned deliverables for the Factory of the Future initiative and what is the time frame for deliverables?

**A** Those deliverables could include awareness and training initiatives, some publications, including ISPE Guidance Documents, and conferences and meetings to allow the open discussion of where things are and where they need to go. Those deliverables are intended to lay out a road map for the next three years. The first deliverable will be a white paper, which is expected to be published within the next few months. That white paper will have some action steps. The objective is taking it from talk to action.

**Q** What role has ISPE played in your career growth?

**A** ISPE has been very important for me in providing a venue and an independent society of technical professionals as a source of collaboration, networking, training, and awareness; an opportunity for non-confrontational regulatory interaction; a place for the discussion and challenge of evolving

industry needs and requirements; a source of technical expertise and guidance documents, information sharing, and conferences, as well as through the magazine and interaction with colleagues. ISPE has been very important in helping to progress my understanding and knowledge of the technical needs, requirements, capabilities, and future needs of the industry.

**Q** As an active long time member and advocate of ISPE, you've encouraged others to get involved in ISPE who have in turn become loyal, active members. What sets ISPE apart from other organizations?

**A** ISPE is the only technical organization that has an independent focus on engineering and manufacturing excellence that provides the forum that allows the creation of guidances and standards for the pharmaceutical industry.


**Q** How do you see ISPE assisting the industry and regulators in the years ahead?

**A** ISPE is an essential organization because it is 1) independent and 2) has membership from all the major pharmaceutical and biotech companies and service providers and regulators coming together as professionals looking to provide knowledge, awareness, and technical understanding of issues facing the industry. I see ISPE as being an essential component for establishing strategic focus on technical issues, as well as guidance documents, and a location where different members of the industry, from the regulatory, industry, and services sectors, can come together to collaborate, challenge, and develop a clear understanding of what's necessary to operate, maintain, and to design and construct the capabilities of the future.

**Q** To our growing young professional audience who will be implementing some of the major concepts of the Factory of the Future initiative, including developing more agile and responsive drug manufacturing, what message do you have for them?

**A** Now is the time for us to move from the old ways of working that were developed in the late 40s early 50s into the new millennium. We need the young professionals with the understanding and savvy of the internet's responsiveness to help accelerate the industry into the future. There are so many issues we face today that require a new mentality. We need real time information to do real time release. We need to ensure that we are using information on a minute to minute basis to operate and maintain our capabilities. We need to be able to communicate on an international basis instantaneously to run and maintain and improve our capabilities. Only by connecting all the pieces of data that are available in a real time fashion, using the capability that the electronic media provides, will we be able to accelerate the industry into the future to gain efficiencies and effectiveness necessary to continue to develop medicines that are life saving and life altering in efficiencies and methodologies that are affordable and accessible to all who need them.

**Q** Is there anything else you would like to say to ISPE Members?

**A** The revolutionary change occurring in the industry requires visionary direction from the technical experts in this Society and I challenge them all to get on the field and work together toward helping to create a better future for our industry. 



This article discusses HEPA filter leak detection methods that provide robust alternatives to current filter testing practices.

# Alternative Methods for HEPA Filter Leak Detection

by Jim Meek, Dan Milholland, and Laszlo Litauszki, PhD

## Introduction

**S**ilicone gel seals (Polydimethylsiloxanes) used in HEPA filter applications may have a shortened life span when exposed to Poly-Alpha-Olefin (PAO) as identified by Dean Hale in his report presented at the 2006 Annual Meeting for the Controlled Environment Testing Association (CETA).<sup>1</sup> The following engineering study examines alternative methods for glass media HEPA filter leak detection, which involve the use of Discrete Particle Counters (DPC) with reduced PAO concentrations or microspheres as aerosol challenge materials.

## Background

Polydimethylsiloxane gels are used as a seal to prevent air bypass around HEPA filters in ceiling grids and filter housings. During HEPA filter testing, the challenge aerosol material (PAO) has been found over time to accelerate the expression of unbounded small molecular weight components in some gel seals. Variations in the preparation of each gel batch, (the potential issue being the completeness of the mix and the impact of this on the resulting reaction) can impact the final properties of the cured gel. Although inadequate gel preparation provides one potential mode of gel seal failure, evidence in the field and supporting research suggests that PAO is a significant contributor to accelerated gel breakdown. At this time it is unknown if the breakdown is continuous once it has initiated or if additional PAO is required for continuation of the breakdown process.

In 2007, Hale's presentation to the International Society for Pharmaceutical Engineering (ISPE)<sup>2</sup> identified a potential link between the breakdown of the filter gel with exposure to PAO. Analysis of gel material migration across a media substrate revealed elevated levels of gel molecule dissociation after exposure to PAO.

The findings presented in the report identified a need to define and validate alternative test methods that will eliminate or limit the exposure of gel seals to PAO, while maintaining or improving on the overall quality of the current test methods.

Challenge aerosol requirements have developed over many years. From the 1960s to mid 1980s, dioctyl phthalate (DOP) was used in concentrations of 80 mg/m<sup>3</sup> of air (µg/L) to 100 mg/m<sup>3</sup> (µg/L) as an aerosol challenge for leak testing High Efficiency Particulate Air (HEPA) filters.<sup>3</sup>

In the 1980s aerosol photometers progressed to using solid state electronics, thus resulting in a more sensitive instrument to identify filter leaks. With the implementation of these more sensitive and stable units, the recommendation for DOP aerosol challenge concentrations of 80 mg/m<sup>3</sup> (µg/L) to 100 mg/m<sup>3</sup> (µg/L) was reduced to ≥ 10 mg/m<sup>3</sup> (µg/L).<sup>4</sup> The early 1990s brought a change to the challenge material with Emery 3004 Poly-Alpha-Olefin (PAO) replacing DOP for safety reasons.<sup>5</sup> Dioctyl Phthalate (DOP) is considered as a potentially hazardous material. Emery 3004 Poly-Alpha-Olefin (PAO), a non-hazardous material, is now the industry standard for filter testing. Today, even though PAO or DEHS may be the challenge material used, the term "DOP testing" is sometimes used as the acronym for HEPA filter integrity testing. The use of Discrete Particle Counters (DPC) and Di-Ethyl-Hexyl-Sebacate (DEHS) has been an acceptable test method for several years and is used in Europe for testing of filters installed in ISO Class 4 and better grade areas.

With the implementation of highly sensitive Discrete Particle Counters (DPCs), the opportunity for a reduction of the current PAO aerosol challenge concentration was identified. Particle counters are capable of sizing and counting the number of particles in a given air sample

volume. These instruments can be used for scanning filters when using ultra low PAO or microspheres as an aerosol challenge for filter integrity testing.

## Executive Summary

This engineering study conclusively identified two methods of filter leak detection as robust alternatives to the current practices used in the United States. These alternative methods should reduce or completely eliminate the issues of accelerated gel seal degeneration related to the use of Poly-Alpha-Olefin (PAO) during glass media filter leak testing. Testing using an ultra low PAO aerosol challenge method ( $< 0.1 \text{ mg/m}^3$  ( $\mu\text{g/L}$ ), achieved a 99% reduction in silicone gel seal exposure to PAO. This reduction is also advantageous where reduced filter loading with PAO is desirable as in depyrogenation tunnels where PAO burn off in filters occurs due to the high operating temperatures. The use of microspheres as an aerosol challenge method for glass media filter testing has no negative effects on the silicone gel seals. Both detection methods were proven to be equal to or potentially more sensitive than the standard PAO filter testing method.

To reduce the negative effects of PAO on gel seals and provide the next step in glass media HEPA filter leak testing, discrete particle counters used in conjunction with ultra low PAO or microspheres are evolving as the next phase in glass media HEPA filter leak testing.

## Test Overview

This engineering study of alternative methods for detecting leaks in glass media HEPA filters was performed at the Baxter BioScience Thousand Oaks, California location by the authors of this report.

The study was performed using a 610 mm  $\times$  1220 mm (2 ft  $\times$  4 ft) horizontal Unidirectional Flow Hood (UFH). The HEPA filter used for the study was an H13 (EN1822) filter rated for a nominal flow of 630 cfm with an efficiency rating of 99.95% at the MPPS. H-14 filters are commonly used in European pharmaceutical applications. They are 99.995%

at the MPPS and are comparable to a Type C filter 99.99% efficient for 0.3  $\mu\text{m}$  particles used in the US.

The UFH was tested for airflow velocity, leaks, and unidirectional flow prior to beginning the study. Twelve defects were created on two horizontal rows of the HEPA filter face with six defects per row. The upper and lower rows were 10 cm (4 in) vertically off the center horizontal plane with 12.5 cm (5 in) horizontally between each defect. Defects were created by inserting a 30 gauge hypodermic needle with an outside diameter of 0.030 cm (.012 in) into the filter face.

## Equipment and Materials

- Lighthouse World Wide Solutions Discrete Particle Counter Solair 3100
- Airgo Portable Aerosol Generator XMG
- TEC Portable Self Contained Aerosol Generator AG-E1
- Poly-Alpha-Olefin (PAO) CAS# 68649-12-7
- ATI Photometer TDA-2G
- Streamline Horizontal Unidirectional Flow Hood SHC-4AX with H13 HEPA filter

- Milholland Aerosol Dilutor 450AD
- Milholland Microsphere 0.32 Microspheres Concentrate
- Sunbeam Ultrasonic Humidifier/Aerosol Generator 696

PAO challenge generation was accomplished by using a self contained Laskin nozzle aerosol generator. Aerosol challenge concentrations upstream of the HEPA filter were determined using an aerosol photometer. The photometer also was used to verify the upstream PAO aerosol challenge concentrations for the ultra low PAO testing in conjunction with the DPC.

Determination of the uniformity of the upstream aerosol challenge was an important variable. Sampling the upstream concentration was accomplished by fabricating and installing a stainless steel guide upstream of the filter housing. Positioning of the guide with the aerosol challenge sample tube inserted, allowed aerosol challenge sampling at any point along the center horizontal plane of the filter within 10 cm (4 in) of all defect locations. During sampling of the upstream PAO challenge, sample concentration variance was  $< 1\%$  which is well below the variance limit of  $\pm 15\%$

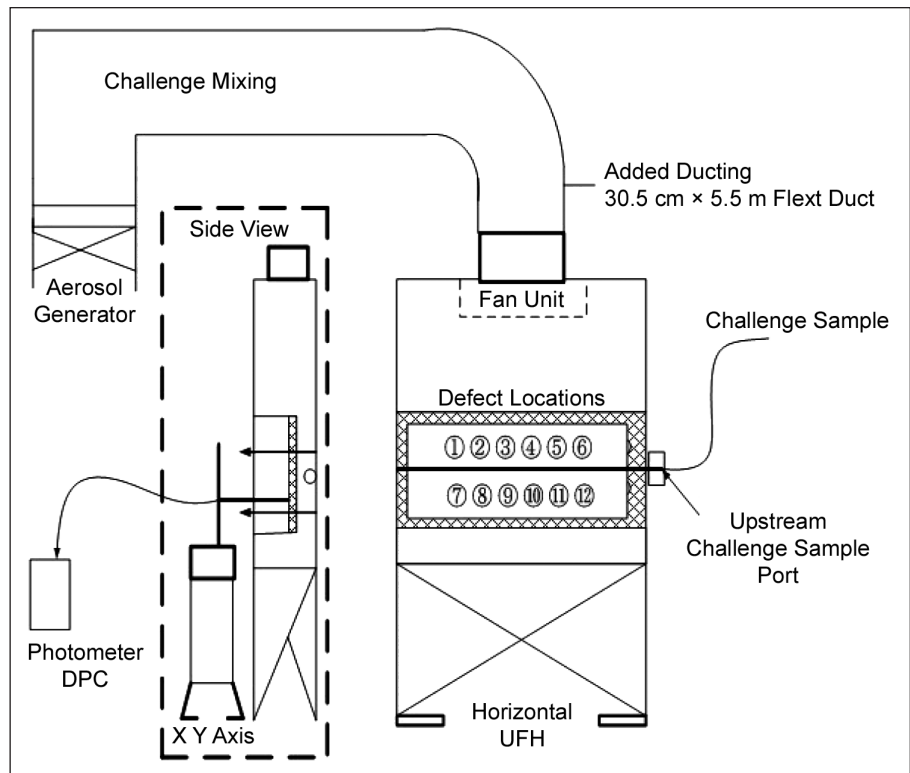


Figure 1. Test equipment.

across the challenge area as stated in ISO 14644-3.

Test methods included using the photometer with a PAO concentration of 22.2 mg/m<sup>3</sup> (μg/L) of air. Tests also were performed with a reduction in the concentration of PAO from standard ≥ 10 mg/m<sup>3</sup> (μg/L), to 6 mg/m<sup>3</sup> (μg/L) to identify a practical lower operational range of the photometer. Alternative test methods included using a DPC with an ultra low concentration of PAO at ≤ 0.1 mg/m<sup>3</sup> (μg/L) of air, and testing using the DPC and microspheres with ≥ 2.1 × 10<sup>8</sup> particles ≥ 0.3 μm/m<sup>3</sup> of air (6.0 × 10<sup>6</sup>/ft<sup>3</sup>). Initial testing was carried out with the generated defects on the downstream face of the filter media. Because defects are not always located on the downstream side of the filter media, the filter was reversed in the housing and testing was repeated with the generated defects on the upstream side of the filter. Reversing the filter changed the relationship of the air flow to the defect, effectively doubling the number of defects from 12 to 24 without physically creating more defects in the filter.

### Study Conditions

Six evaluated test conditions were derived from a combination of the particle sizes (≥ 0.3 and ≥ 0.5 μm particle counter channel), photometer, DPC test equipment, and the selected aerosol challenge media types/concentrations (PAO and microspheres). Table A defines the test instruments, challenge media, concentrations, and particle sizes tested.

The minimum challenge for scanning with a DPC per NEBB is 2.1 × 10<sup>8</sup> particles ≥ 0.3 μm/m<sup>3</sup> of air (6 × 10<sup>6</sup>/ft<sup>3</sup>). The minimum challenge concentration for an aerosol photometer is ≥ 10 mg of PAO/m<sup>3</sup> (10 μg/L).<sup>6</sup>

For comparative information, PAO aerosol challenge concentrations were measured with both the aerosol photometer and the particle counter. Twelve photometer measurements averaged 0.10 mg/m<sup>3</sup> (0.10 μg/L). The corresponding 12 particle counter measurements averaged 6.7 × 10<sup>8</sup> particles ≥ 0.3 μm/m<sup>3</sup> of air (19 × 10<sup>6</sup>/ft<sup>3</sup>), of which 3.7 × 10<sup>8</sup>/m<sup>3</sup> (11 × 10<sup>6</sup>/ft<sup>3</sup>) particles were ≥ 0.5 μm.

### Test Details

Discrete particle counts for the microsphere aerosol challenge concentrations for study conditions 1 and 2, and the ultra low PAO study conditions 3 and 4, were determined using a laser particle counter<sup>7</sup> in combination with an aerosol dilutor. The aerosol dilutor accurately provides a reduced PAO concentration to prevent coincidence counting error by the particle counter. A sample volume of 70 cc per minute of the undiluted upstream challenge aerosol was introduced into the particle counter after being diluted with sufficient volume of filtered/particle free air to satisfy the full air sample volume requirement of the counter (28.3 L/min). The particle counts were normalized to 1.0 ft<sup>3</sup>.

PAO challenge concentrations (mg/m<sup>3</sup> of air (μg/L) were determined using a photometer. For study conditions 3 and 4, ultra low PAO readings were taken with the photometer for comparative values only. Study condition 5, reduced PAO (6 mg/m<sup>3</sup> (μg/L), and study condition 6, the standard PAO (22.2 mg/m<sup>3</sup> (μg/L), also were taken with the photometer. To measure each of the PAO challenge concentrations, the photometer gain was set to read PAO directly in mg/m<sup>3</sup> of air (μg/L) using its internal reference. The photometer gain was set to 100%, while measuring the upstream challenge aerosol to determine the defect sizes for Conditions 5 and 6. The resulting leak penetration was displayed as a percent of the upstream challenge concentration. All DPC challenge readings for study conditions 3 and 4 ultra low PAO, were calculated by using the actual number of particles measured multiplied by the dilution factor of 400.

The testing sequence for all study conditions started with the defect labeled #1 and continued through defect 12 in sequential order (refer to Figure 1). Each defect location for Conditions 1, 2, 3, and 4 were sampled for 30 seconds using the DPC with a round, 3.5 cm (1.375 in) diameter probe prior to moving to the next location. The sample probe was positioned 12.5 mm (0.5 in) from the filter face. Conditions 5 and 6 were sampled until a stable reading was observed on the photometer. The

process was repeated 10 times for a total of 120 measurements for each of the six study conditions.

After completion of the forward air flow filter testing (defect on the downstream face of the filter), testing was performed to simulate the condition of a defect on the upstream side of the filter media. The filter was removed, rotated from end to end, and then reinstalled. Reverse air flow testing (defect on the upstream side of the filter) was then completed.

### Aerosol Challenge Setup PAO

For the initial uniformity challenge validation, a self contained PAO aerosol generator using one Laskin-nozzle was used with a UFH air flow of 630 cfm. The air pressure supply for the generator was adjusted to achieve an approximate aerosol challenge of 11 mg/m<sup>3</sup> (μg/L). Eighteen aerosol challenge readings were taken on the upstream side of the filter using the photometer to ensure a homogeneous mixture of the PAO. PAO challenge uniformity was measured at 11.5 mg/m<sup>3</sup> (μg/L) of air ± 0.5 mg/m<sup>3</sup> (μg/L) for the 12 locations. This testing provided assurance of the homogeneous challenge distribution that was required.

### Microspheres

Microsphere testing required a challenge generation of ≥ 2.1 × 10<sup>8</sup> particles ≥ 0.3 μm/m<sup>3</sup> of air (6 × 10<sup>6</sup>/ft<sup>3</sup>). The challenge was generated using an ultrasonic aerosol generator. Preparation of the microsphere challenge aerosol consisted of mixing 25 mL of the 0.32 μm microsphere concentrate in 1900 mL of tap water. Only 700 mL of the final working solution was added to the ultrasonic aerosol generator. The water droplets generated by the ultrasonic aerosol generator transducer contain the 0.32 μm microspheres. As the water evaporated, the microspheres were left in the air stream.

The discrete particle counter and the aerosol dilutor were used to determine the challenge concentrations. Microsphere challenge concentrations averaged 1.6 × 10<sup>9</sup> particles ≥ 0.3 μm/m<sup>3</sup> of air (44 × 10<sup>6</sup>/ft<sup>3</sup>) and 3.5 × 10<sup>8</sup> par-

ticles  $\geq 0.5 \mu\text{m}/\text{m}^3$  ( $10 \times 10^6/\text{ft}^3$ ). Downstream sampling was performed using the discrete particle counter. Samples downstream of the defect are reported as the number of particles per  $\text{m}^3$  ( $\text{ft}^3$ ) of air. This downstream count is divided by the upstream challenge concentration and reported as a percent of the challenge. All DPC challenge readings were calculated by using the actual number of particles measured multiplied by the dilution factor of 400.

### Ultra Low PAO 0.1 mg/m<sup>3</sup> (μg/L)

To achieve an ultra low PAO concentration, the aerosol generator (1/4 Laskin nozzle) was operated at 5 psi while connected to a 25 cm (10 in) HEPA vent filter. The filter was placed at the inlet of the 30.5 cm (12 in) round flex duct. The leakage around the filter connection provided the required final reduction of the challenge for the test. The PAO challenge concentration was then measured using a photometer and results were 0.1 mg/m<sup>3</sup> (μg/L) of air, with an air flow rate of 630 cfm. PAO challenge concentrations measured using the discrete particle counter and the dilutor averaged  $9.0 \times 10^8$  particles  $\geq 0.3 \mu\text{m}/\text{m}^3$  of air ( $25.6 \times 10^6/\text{ft}^3$ ) and  $3.0 \times 10^8$  particles  $\geq 0.5 \mu\text{m}/\text{m}^3$  ( $8.6 \times 10^6/\text{ft}^3$ ). This ultra low PAO challenge concentration is only capable of being measured accurately with a DPC when using an aerosol dilutor. Each particle in a 70 cc volume of raw, undiluted air is counted and the concentration is extrapolated to particles per 28.3 L (1.0 cu ft). Downstream sampling was performed using the DPC to capture all the unfiltered air passing through the defects. Samples downstream of the defect are reported as the number of particles per  $\text{m}^3$  ( $\text{ft}^3$ ) of air. This downstream count is divided by the upstream challenge concentration and reported as a percent of the challenge.

### Reduced PAO 6.0 mg/m<sup>3</sup> (μg/L)

To achieve a reduced PAO concentration, a self contained PAO aerosol generator (1.5 Laskin nozzle) was operated at 10 psi. The measured average concentration of the PAO challenge uniformity at six locations was 6.0 mg/m<sup>3</sup> of air (μg/L)  $\pm 0.3 \text{ mg}/\text{m}^3$  (μg/L) using

the photometer with an UFH air flow rate of 630 cfm.

The FDA no longer expects a set minimum aerosol concentration. As stated in the FDA's Guidance for Industry Sterile Drug Products Produced by Aseptic Processing Current Good Manufacturing Practice, September 2004, "It's important to introduce an aerosol upstream of the filter in a concentration that is appropriate for the accuracy of the photometer."<sup>8</sup> Downstream sampling was performed using the aerosol photometer.

### Standard PAO 22.2 mg/m<sup>3</sup> (μg/L)

Standard testing required a PAO concentration of  $\geq 10.0 \text{ mg}/\text{m}^3$  of air (μg/L). A self contained PAO aerosol generator (1.5 Laskin nozzle) was operated at 20 psi. The measured average concentration of the PAO challenge at six locations was 22.2 mg/m<sup>3</sup> of air (μg/L)  $\pm 0.3 \text{ mg}/\text{m}^3$  (μg/L) using the photometer with an UFH air flow rate of 630 cfm. Downstream sampling was performed using the photometer.

## Statistical Analysis of Leak Test Results

Data were analyzed using JMP version 5.1 by SAS Institute. The leak rate was set to be the dependent variable or output (Y) expressed in %. The following independent variables (X) were used in the analysis:

- Measurement conditions, six levels: See Table A.

Air flow direction relative to generating the holes, two levels:

- Initial, i.e., holes generated opposite to the air flow.
- Reversed, i.e., the filter was turned such that hole generation direction was aligned with the airflow.

An Analysis of Variance (ANOVA) was performed to investigate potential statistical differences for the different measurement conditions. All six measurement conditions produced tightly distributed leak rate data for each defect. The data distribution per defect is significantly narrower than the difference mean between the defects. The analysis shows that the most significant impact on the leak rate originates from the defect itself. Comparing the six different measurement conditions, there is no statistically significant difference between the investigated conditions at the 95% confidence level. The p value of 0.0998 is greater than the cut off value of 0.05 below which a statistical difference would be concluded.

Visual evaluation of the comparison suggests a potential advantage of the proposed measurement conditions as compared to the current standard. Each of the proposed measurement conditions appears to report a slightly higher numerical value than the current 22.2 mg/m<sup>3</sup> of air (μg/L) PAO challenge. If this assumption is proven true, the proposed methods would be more sensitive to leak detection as the cut off for

Method		Instrument	Challenge Concentration Measured
<b>Alternative Microspheres No PAO</b>	1	Discrete Particle Counter $\geq 0.3 \mu\text{m}$	$1.6 \times 10^9 \geq 0.3 \mu\text{m}$ Microsphere particles/ $\text{m}^3$ of air ( $44.0 \times 10^6/\text{ft}^3$ )
	2	Discrete Particle Counter $\geq 0.5 \mu\text{m}$	$3.5 \times 10^8 \geq 0.5 \mu\text{m}$ Microsphere particles/ $\text{m}^3$ of air ( $10.0 \times 10^6/\text{ft}^3$ )
<b>Alternative Ultra Low PAO</b>	3	Discrete Particle Counter $\geq 0.3 \mu\text{m}$	$9.0 \times 10^8 \geq 0.3 \mu\text{m}$ PAO particles/ $\text{m}^3$ of air ( $25.6 \times 10^6/\text{ft}^3$ )
	4	Discrete Particle Counter $\geq 0.5 \mu\text{m}$	$3.0 \times 10^8 \geq 0.5 \mu\text{m}$ PAO particles/ $\text{m}^3$ of air ( $8.6 \times 10^6/\text{ft}^3$ )
<b>Lower Limit Test Reduced PAO</b>	5	Aerosol Photometer	6.0 mg/ $\text{m}^3$ (μg/L) of air
<b>Standard PAO Method</b>	6	Aerosol Photometer	22.2 mg/ $\text{m}^3$ (μg/L) of air

Table A. Study conditions.

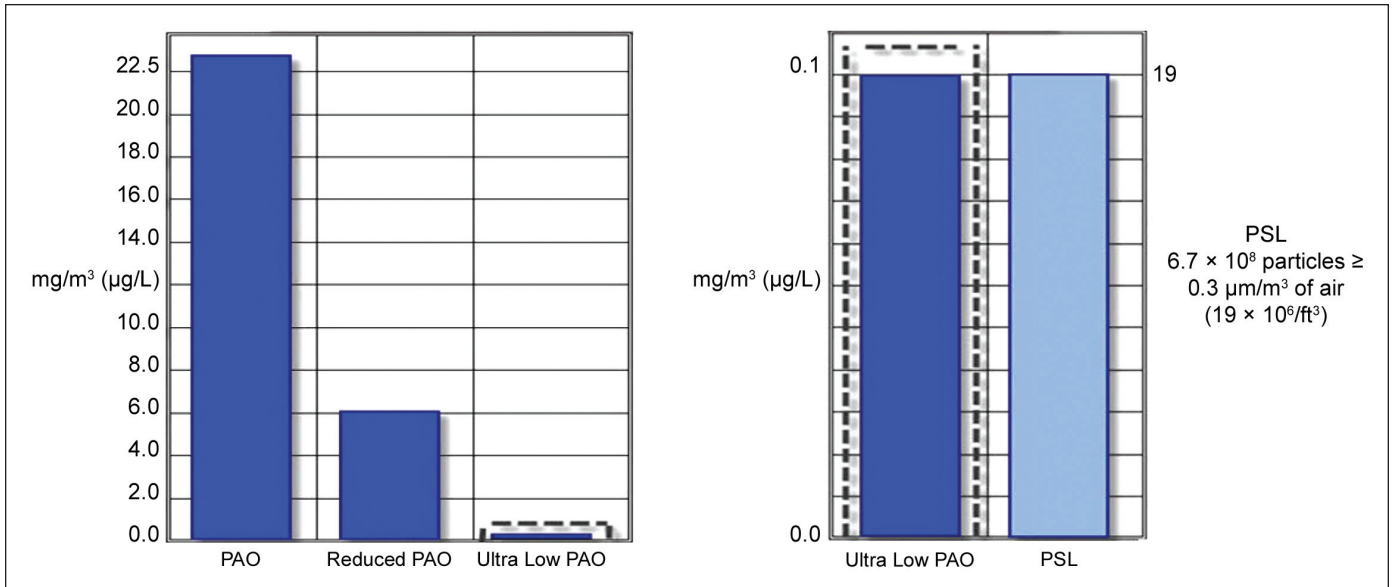


Figure 2. Challenge concentrations.

accepting or rejecting a HEPA filter is expressed as a maximum leak rate. A method that inherently reports a higher value than the current standard would err on the safe side of the 0.010% leak criteria.

For this discussion, three defects are identified by the overall leak rate of the

defect to represent the full range of the observed leaks:

- **Defect #2 Minimum Leak**, where the leak rate was observed to be  $\leq 0.004\%$  of the challenge.
- **Defect #12, Medium Leak**, where the leak rate was found to be  $0.05 -$

$0.08\%$  of the challenge.

- **Defect #10, Maximum Leak**, where the leak rate was found to be  $0.16 - 0.22\%$  of the challenge.

At leak rates above the medium leak size, the obtained leak rate data no longer overlap and the proposed methods produce a visibly higher numerical value. The current dataset is insufficient to arrive at a definitive conclusion supporting this visual interpretation. However, if this finding is substantiated by additional data, the proposed methods provide an advantage as compared to the current standard, by being more sensitive. Measurements recorded with the DPC averaged slightly larger leak values.

Analysis of the data indicated that there was a statistical difference for the forward and reverse filter flow measurements. The geometry change associated with reversing the filter and the potential for the filter fibers to shift (flap in or out) at the defect location during the reverse filter measurements could provide the explanation of the difference noted in the forward and reverse filter data. Although statistically different, the forward and reverse flow conditions are not considered to be practically different due to the minimal  $0.004\%$  difference noted in the collected data.

All test data were included in the evaluation to provide the best overall

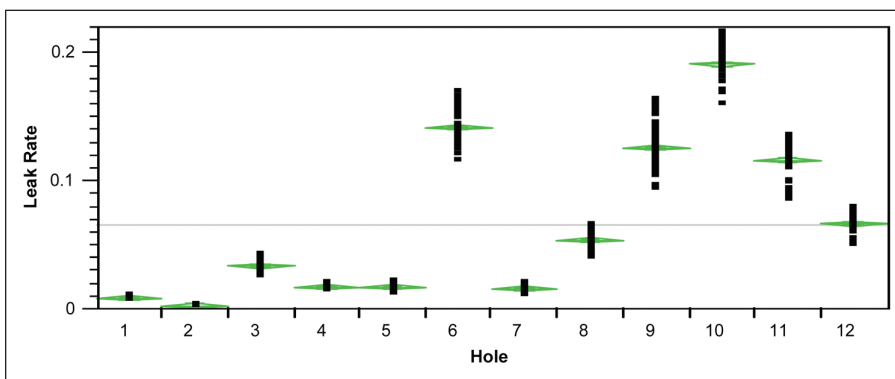


Figure 3. Fit Y by X group oneway analysis of leak rate by hole.

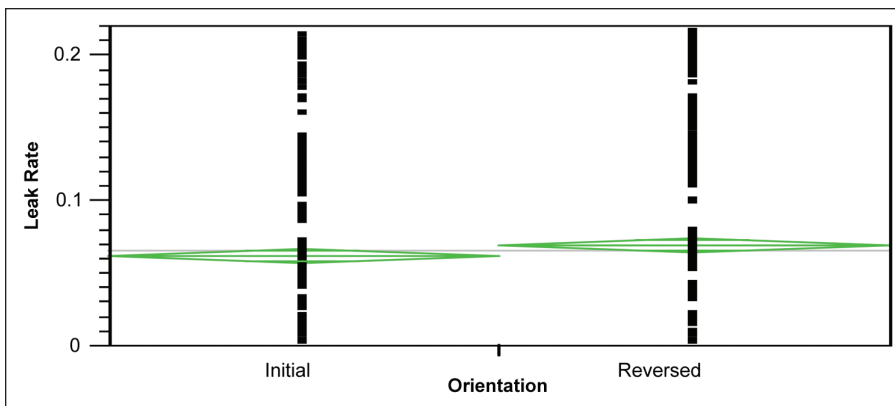


Figure 4. Oneway analysis of leak rate by orientation.

analysis of the method comparisons. It is concluded by analysis, that defect leak rates in HEPA filters can be accurately determined using an aerosol photometer with a PAO aerosol challenge concentration of  $6 \text{ mg/m}^3$  of air ( $\mu\text{g/L}$ ). Furthermore, defects can be accurately determined with a discrete particle counter while using a PAO challenge concentration of  $\leq 0.1 \text{ mg/m}^3$  of air ( $\mu\text{g/L}$ ) or microspheres at a challenge concentration of  $\geq 1.4 \times 10^9$  particles  $\geq 0.3 \mu\text{m/m}^3$  of air ( $44 \times 10^6/\text{ft}^3$ ). There is no difference if the  $\geq 0.3 \mu\text{m}$  or the  $\geq 0.5 \mu\text{m}$  size channels of the particles counter are used.

It is also noteworthy that the visual evaluation suggests a slightly higher, though statistically not different leak rate, when  $\geq 0.3 \mu\text{m}$  particles were measured versus the  $\geq 0.5 \mu\text{m}$  particles. This observation is scientifically supported by the measurement principle, as testing at the  $\geq 0.3 \mu\text{m}$  particle size also captured all particles  $> 0.3 \mu\text{m}$ . Testing at the  $\geq 0.5 \mu\text{m}$  particle captured only the particles  $\geq 0.5 \mu\text{m}$ . Additionally, there is no difference between the data sets when the different types of micro particles, PAO or microspheres, are used regardless of the measurement's cut off level.

Figure 2 demonstrates the significant reduction in PAO usage when using DPCs with an ultra low PAO aerosol challenge.

## Conclusion

The statistical analysis of the test data indicated that all six study conditions produced tightly distributed leak rate data for each defect for all conditions. Comparing the six different measurement conditions, there is no statistically significant difference between all investigated conditions.

While the overall analysis fails to detect a statistically significant difference between the proposed and the standard methods, analysis of the leak rate on a defect by defect basis suggests that higher leak rates will be reported by the proposed methodologies.

As shown with defect leak rates greater than the medium leak, the data no longer overlap and the proposed methods produce a visibly higher numerical value. The proposed methods could provide an advantage as compared to the current standard by being more sensitive.

Glass media HEPA filter leak rates can be accurately determined using a particle counter with a PAO concentrations  $\leq 0.1 \text{ mg/m}^3$  of air ( $\mu\text{g/L}$ ) or microspheres with concentrations  $\geq 1.4 \times 10^9$  particles  $\geq 0.3 \mu\text{m/m}^3$  of air ( $40 \times 10^6/\text{ft}^3$ ).

**Note:** The complete statistical analysis was not included in order to meet the document length requirements. Complete statistical analysis is available upon request.

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5. Moore, Jr., Donald R., P.E., Marshall,

### Three Selected Data Points – Minimum, Medium, and Maximum

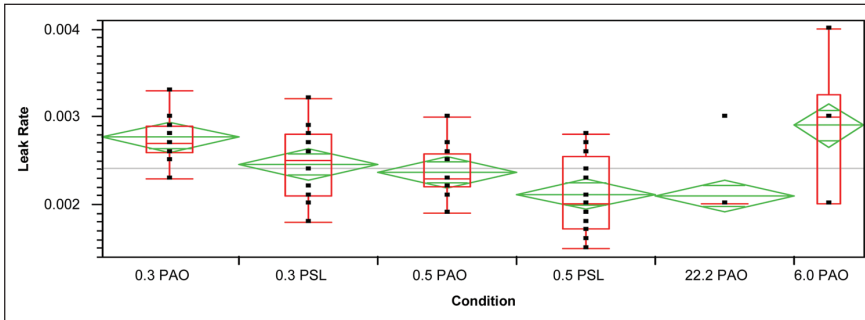


Figure 5. Defect #2 minimum leak volume in % of upstream concentration oneway analysis of leak rate by condition.

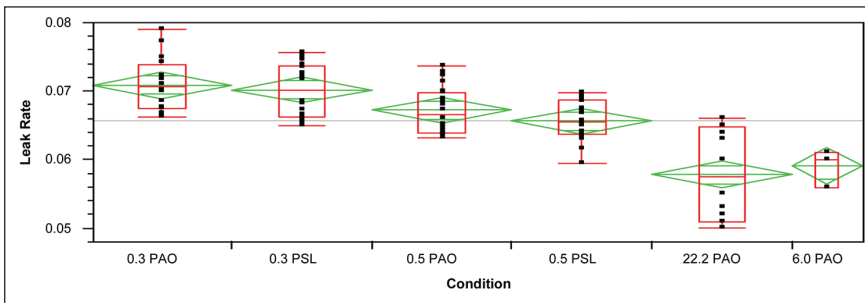


Figure 6. Defect #12 medium leak volume in % of upstream concentration oneway analysis of leak rate by condition.

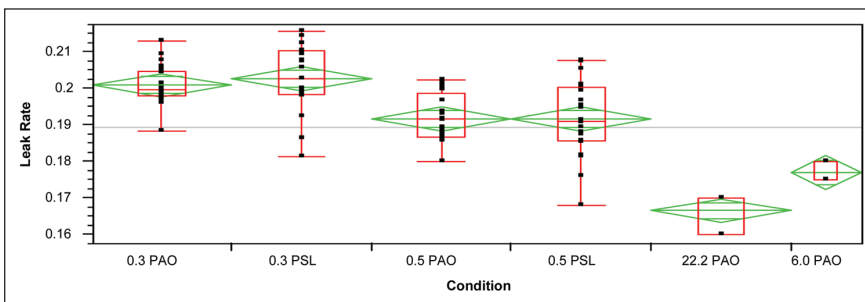


Figure 7. Defect #10 maximum leak volume in % of upstream concentration oneway analysis of Leak rate by condition.

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This article presents the latest status of single-use technologies in biomanufacturing processes.

# Single-Use Components for Flexible Biomanufacturing Processes

by Thorsten Peuker and Jean-Marc Cappia

## Introduction

**M**odern biopharmaceutical production has changed in the last couple of years due to overall process improvements and the availability of new materials and components. Single-use components, modules, or even complete systems are getting more important for the biopharmaceutical industry. The reasons for this attractiveness are obvious: faster set-up of the process equipment, less cleaning efforts and hence less validation work for cleaning, higher flexibility, lower capital expenditures, and overall, less risk for the investment.

In process development and production of clinical material, the biopharmaceutical industry requires high flexibility. Several products are manufactured in parallel or shortly one after another which is challenging with respect to cleaning and set-up times. Product titres are increasing due to improved cell-line performances. Personalized medicine will lead to tailor-made drugs for a smaller group of patients. Reduced up-stream volumes are the result, which enhance the opportunities for complete single-use manufacturing trains.

In the future, there will be two main classes of biopharmaceutical manufacturers. The first group represents big pharma, which has existing production networks with corresponding capacities. These companies with their large amount of blockbusters will produce bulk drug substance still in conventional ways since this is validated and has a proven track record. Since their blockbusters are patent protected and can be sold in developed countries, cost of production is only a minor aspect. The second group are the small emerging companies with innovative products, but less capital. This group of biopharm companies has to go different ways. For toxicity-studies and first clinical phases, they are looking for fast implementation of

manufacturing capacities without high investments.

## Benefits of Current Single-Use Technologies for Upstream and Downstream Processes

Single-use equipment is established in several unit operations already and will be accepted in others in the near future. However, it is obvious that flexible multi-product processes have different requirements than large-scale processes for bulk drug substance which is produced in stationary and hard piped stainless steel equipment. Time-to-market and cost pressure on the biopharmaceutical industry will become more and more important in the near future. Development of new drug substances has to follow a strict and regulated clinical test procedure. If a candidate was successful in toxicological studies, pre-clinical, and clinical Phase I and II, the material for Phase III has to be produced using the same equipment which is designated for market supply.<sup>1</sup> Since the time for engineering, construction, and qualification phases of customized production plants is tough to predict, those activities should start almost at the same time than the drug development entering Phase II. As a consequence, companies have to decide on major investments at very early stages (pre-clinical), where there is no guarantee to be successful. Suppliers should support the manufacturing industry by pre-defined configurable unit operations or even generic platform processes, which are well defined sequences of unit procedures. This will reduce time and engineering efforts during design and construction of such development and manufacturing plants and hence could make postponing the investment decision to a later phase possible without losing time.

A process platform is a well defined sequence of unit operations. It will support present and



# Single-Use Components

future progress in biopharmaceutical development and production in order to speed-up time to market.

Major benefits of process platforms are:

- efficient engineering workflow
- precise cost determination and allocation in early design phases
- no mobilization of engineering groups for conceptual design
- late decision for investment
- fast project execution
- possibilities for process optimization
- accelerated and reliable start of production
- security of supply

All process platforms consist of several unit operations as basic steps in a process. In general, processes may have many unit operations to obtain the desired product. Unit operations are:

- media/buffer preparation
- fermentation
- cell removal/harvest
- pooling/storage
- sterile filtration
- capturing/polishing
- virus inactivation/virus clearance
- ultra filtration/diafiltration
- freeze and thaw

Each unit operation is made of standardized technological modules (e.g. sensors, storage bags, mixing devices, filter, transfer sets, connectors, sampling devices, etc.). In order to be fast and efficient in design and execution of projects, those technological modules should be well defined and not be changed or even newly developed.

- mixing systems (various designs and volumes)
- sensors, for example, dissolved oxygen, pH, flow rate, and conductivity
- sterile fluid transfer connectors and tubing
- fluid sampling devices
- bioreactors (different designs, volumes, and agitation technologies)
- fluid and solids aseptic transfer systems
- freeze/thaw bags
- ultra- and diafiltration
- membrane chromatography (ion exchange)
- viral clearance (filters and UV inactivation)

Currently, there are efforts to harmonize single-use process equipment in the same way like stainless steel bioprocess equipment in the past (e.g., ISPE Guidance Documents and ASME BPE).<sup>2-3</sup>

In general, there are a number of issues that have to be determined before implementing single-use equipment. There is common understanding that the following points are of utmost importance:<sup>4</sup>

1. process compatibility
2. process efficacy
3. volume
4. fill and discharge
5. degree of agitation
6. operating pressure and temperature
7. measurement of process values
8. material handling/space requirements
9. environmental, health, and safety

The first indication for the decision on technologies will be developed when looking at the scale of the process to be designed. Figure 1 visualizes a possible decision tree based on volume. It confirms that purely single-use products are widely specified up to the pilot plant level. Hybrid scenarios based on re-usable and disposable unit operations start at USP volumes  $\geq 1,000$  L.

As the question whether a manufacturing plant will follow a hybrid or a fully single-use strategy is mainly raised during the first planning phase of completely new plants engineering gains utmost importance. Due to capacity constraints and connectivity limitations of existing single-use systems, engineering is the key aspect that determines the success of a newly designed biomanufacturing facility.

Process engineering for plants that rely on re-usable unit operations is highly sophisticated and looks back on more than 30 years of experience. Process engineering for plants that rely on hybrid approaches instead is in its infant stage.

In order to evaluate the impact of single-use equipment on the design of biopharmaceutical manufacturing facilities, one needs to distinguish between clinical development and commercial production.<sup>5</sup> In media preparation, disposables have been applied over the years within nearly all volumes up to even 3,000 L. Cell cultivation steps in clinical development and small to mid scale production benefit from the use of disposable systems in recent years. Single-use seed cultivation systems based on rocking motion agitation have been implemented successfully in many processes but also production size stirred tank bioreactors are today very often single-use. In this area a lot of new developments have been

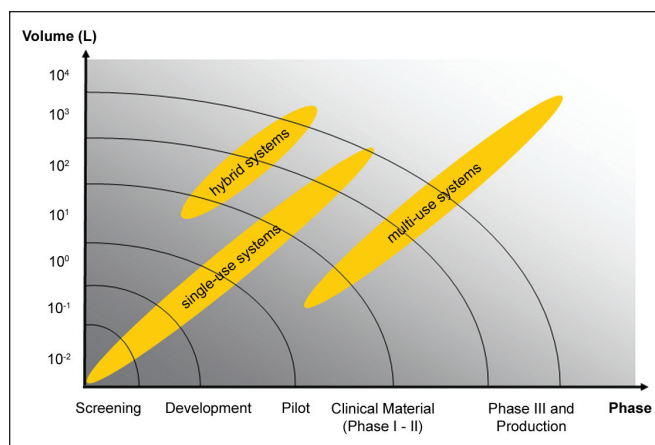


Figure 1. Implementing single-use technologies into process equipment during different phases and in varying volumes.

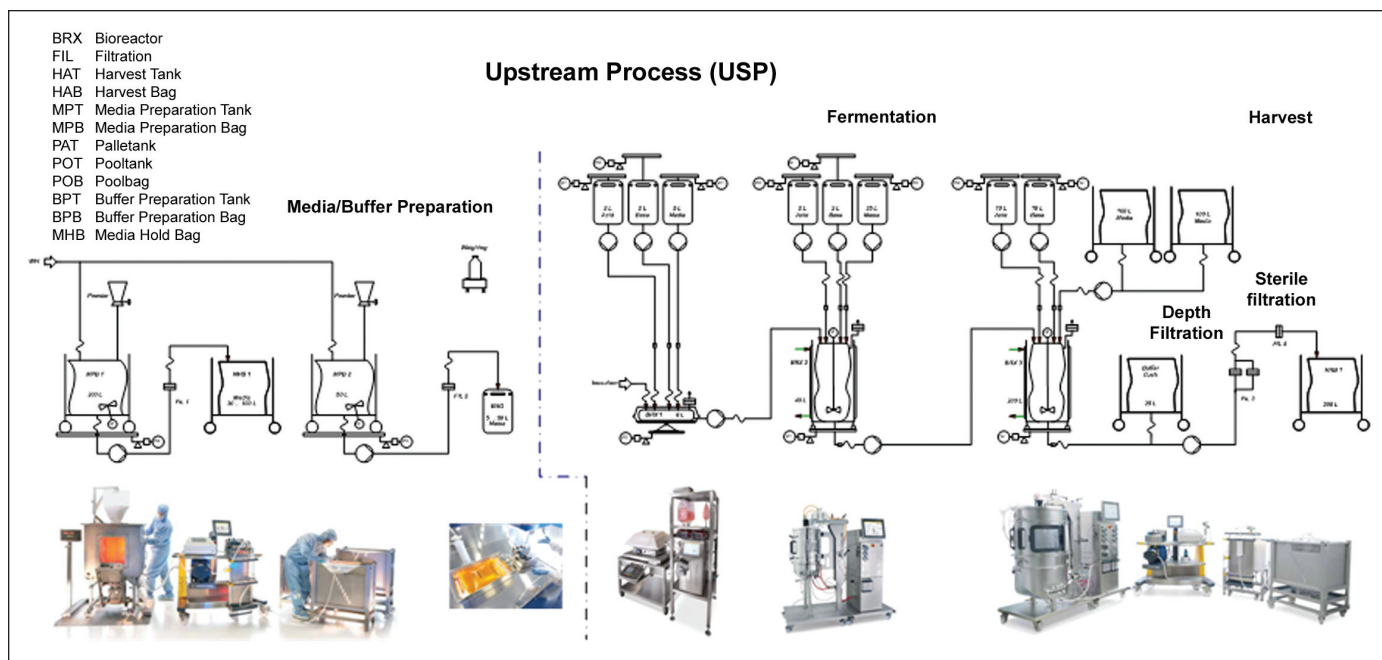


Figure 2. Single-use mAb upstream process.

presented by multiple vendors. Figure 2 shows an upstream process (USP) for 1,000 L batch volume. Most of those systems are now derived from the main features of re-usable systems like height to diameter ratio, agitation method, and gassing strategies.<sup>6</sup>

Harvesting and cell retention in cell cultivation processes at a scale-up to 2,000 L is commonly done by applying disposable depth filter systems. However, centrifuges are now becoming single-use.

If one looks at the downstream processing unit operations, it is even more important to distinguish between clinical development and commercial production. Some technologies can be applied up to commercial scale and some technologies are not capable of handling volumes larger than 500 L. Ultra filtration and concentration steps began to become fully disposable in scales up to 100 L. Protein A chromatography steps are re-usable which will not change in the near future. Polishing steps, filtration, and mixing steps are more or less occupied by the use of disposables up to mid scale commercial production since the volume of the purified product at this stage is already less by a factor of at least 10. Product hold, transfer, and storage are classical areas where single-use systems are already fully established throughout the clinical development phases up to mid-scale commercial production.

The already mentioned connectivity constraints lead to multiple options for connection of unit operations. Sterile thermal tube connections of thermoplastics, sterile connectors, steam-to-connectors, steam-through connectors as well as non sterile quick connections need to be equally considered for a proper process design depending on the interfaces.<sup>7</sup>

Accepting this level of limited penetration, how can one simplify the complexity of such processes in regard to the proper implementation of single-use technologies? In fact, looking at all these process steps and talking about single-use technologies as being partly implemented already, one

needs to consider that some of the single-use technologies have historically been implemented because of the advantages they provide and not because users are fully confident to “own” this technology. There are just a few areas where users in large scale commercial production, for example, are fully satisfied with the historical performance and process integration compared to the re-usable world. This is one of the reasons why large biopharmaceutical companies preferably use single-use technologies in clinical development phases. Contract manufacturers instead benefit from the single-use technologies more drastically as the advantage of being highly flexible by not having invested in a fully piped plant might overrule existing deficiencies.

One can conclude from this distinction that there is huge area where processes will need to rely on hybrid approaches depending on the specific process needs, of course. Translated back to our question, yes there will be a further penetration of single-use technologies, but increasingly embedded into hybrid approaches.

From the pure technology evaluation angle, there is one approach that might help to reduce the complexity. Looking at some limiting factors for the penetration like connectivity, capacity, regulatory compliance, and facility layout, a further separation of the process into its unit operations looks like a method that can help evaluate which technology is best for an individual task. For example, a unit operation like mixing will appear multiple times within the manufacturing process. Media preparation, harvest suspension before purification, intermediate hold steps during purification that require gentle agitation, virus inactivation, and final formulation require mixing. This requires the definition of a mixing technology module that allows a proper and uniform design for each of the mentioned applications. Once defined, this mixing module needs to be able to serve the needs throughout the volume range from 10 L to 2,000 L.



or final processing), dedicated cleanroom environments have to be considered. ISO 8 (Class C) air classification must be provided if open top mixing is used. If closed bag systems are applied for raw material addition and liquid mixing, air classification can be reduced to controlled, but non classified area (CNC). Reduced HVAC demands lead to cost savings for on going operational costs.

By applying single-use unit operations, tracing of material becomes more and more a challenge. Looking at the life cycle of a complex disposable bag assembly, for example, that is equipped with multiple tubing lines, a filter, and a sample bag, it becomes increasingly difficult to apply proper SOPs that allow full traceability. In instances, 2-D bar codes are utilized either to track equipment or process units or to connect the appropriate process units together. These tags also will be able to create appropriate and necessary shelf life information since gamma irradiated polymers have limited shelf lives as well as product life cycle information since they can be re-written by end users.

### Challenges to Future Expansion of Single-Use Technology

For re-usable equipment, well established design criteria and experienced engineers are available to erect production facilities almost everywhere around the world. But due to long lead items and extensive construction and qualification efforts, it takes more than five years to bring such a new facility into operation.

During the last decade, single-use equipment has become more important due to the fact that new materials are available, which have been considered safe and reliable by US and European Pharmacopeia. In order to make maximum use of the benefits that disposables can bring to production of biopharmaceuticals, the challenge is to design and implement application specific integrated process solutions that follow in respect to process engineering, automation, and control, the same principles as conventional process designs. Single-use technologies are not the universal solution, but have to be intelligently integrated in new and existing process designs. How much disposable and where to use disposables has to be evaluated from various aspects and needs to be carefully analyzed in respect to application and customer specific situation. In addition, the possibility of a combination of re-usable and single-use technologies must be considered as a “hybrid technology.”

Currently, disposables are mainly used during scale-up and clinical production. In commercial manufacturing, the use of disposables is most of the time still limited to tubings and filter cartridges; however, with the development of the single-use technologies into the area of commercial production the need of integrated single-use process designs becomes absolutely obvious.

By recognizing this, well established industry value proposition like engineering, process integration, as well as automation and control receive increased attention. Due to the nature of the disposable supply chain and implementation scenarios assurance of supply and thorough vendor support

during the entire drug product life cycle become essential for establishing confidence of ownership in this technology.

Traditional stainless steel product plants are highly automated. There are only few procedures with human interaction, e.g., inoculation or sampling. This leads to high process safety and less loss of batches. Industrial standards are available for the overall automation system but also for almost every package unit. The majority of automations tasks for those kind of plants are required for Cleaning In Place (CIP) and Sterilization In Place (SIP) of the re-usable equipment.

Automation solutions ranking from dedicated local controllers to high-level system integration using PLC/SCADA or DCS control systems cannot be fully applied to the single-use parts yet. Common standards need to be adjusted considering the different nature of both technologies. By applying more and more single-use products and equipment, CIP and SIP can be significantly reduced or made completely redundant. On the other hand, the unit operation approach discussed earlier will help combine unit operations by using platform technology connection methods and with well established SCADA platforms. It serves mixing systems, cell cultivation systems, as well as filtration systems at all stages. All these unit operations can now be equipped with either re-usable or single-use components relying on a well established automation platform.

Disposable sensors that are fully integrated into the respective single-use containment need to assure the control of the important process values for each unit operation (e.g., DO, pH, Conductivity etc.). However, if users want to integrate classical sensors, this is also possible applying autoclavable connection systems.

Considering that single-use equipment leads to more interference with the personnel, integration into plant-wide Manufacturing Execution Systems (MES) is a pre-requisite for a safe and documented production process.

The validation requirements for single-use aseptic processing are not different than that of a traditional stainless steel process. Because single-use systems are pre-assembled and sterilized by vendors, there is a higher level of involvement of the supplier in the validation work. End users and suppliers work together at specifying the expected product performance for a given application and agree on the level of validation and certification required for the specific assembly.

To be a qualified vendor of single-use aseptic processing requires an in depth understanding of the application of current regulatory and GMP requirements.

Since most disposable devices are gamma irradiated, between 25 and 50 kGy, short and long-term stability studies with the irradiated devices have to be performed. The irradiation commonly reduces the shelf life of such devices and the limits have to be determined. Furthermore, the irradiation step could accelerate the degradation of the polymeric substances used, which can impact leachable/extractable levels. To determine the effects of irradiation and the stability of the polymer used, the manufacturer subjects the devices to a considerable regime of qualification tests, before the device is launched. The qualification tests can be utilized as guid-

ance by the end-user and commonly encompass, but are not limited to, the following tests:

- biocompatibility testing
  - USP<87>: biological reactivity tests, in vitro
  - USP<88>: biological reactivity tests, in vivo.
- mechanical properties
  - tensile strength
  - elongation at break
  - seal strength
  - air leak test
- gas transmission properties
  - ASTM D3985: oxygen
  - ASTM F1249: water vapor
- USP<661> test for plastics
- E.P. 3.1.7.: EVA for containers and tubing
- E.P. 5.2.8. on TSE-BSE
- TOC analysis
- pH/conductivity
- extractable/leachable tests with standard solutions
- chemical compatibility testing
- protein adsorption studies.
- Endotoxin testing
- gamma irradiation sterilization validation
- bacterial ingress test

These tests are performed under standard settings with standard solutions. The data of these tests are available from the manufacturer.

Since qualification tests run under standard conditions, possible process specific validation requirements need to be met. Such validation studies can be supported by the services of the vendor. Process validation studies would, for example, utilize a model solvent and simulate the process parameters within the end-users specifications. Leachable testing with product cannot always be achieved since the product would cover any potential peaks. For this reason, model solvents are often used which are similar to the solvent used within the product stream. However, possible influences by the environmental conditions used within the end-users processes require to be tested to assure that the disposable device performs to specifications.

The process validation steps vary as the disposable devices have different purposes. Sterilizing grade filters have to undergo a product bacteria challenge test under end-users process conditions. If the actual fluid is bactericidal or bacteriostatic, a placebo solution could be used. In any case, the influence of the process conditions and fluid toward the challenge organisms or separation mechanisms need to be determined. Product hold bags or mixing bags do not have to undergo bacteria challenge tests, but possibly bacteria ingress tests. Both filter and bags systems require to be tested for leachable or extractable. As mentioned, the end-user should take advantage of the vendor's services, which are supported by the qualification documentation and process validation.

## Conclusion

A multitude of single-use systems are already available, most commonly as a single entity, but in instances already connected as in the case of filter/bag or bioreactor/filter systems. Rapidly developing connectivity will enhance the development of connected, integral systems, and potentially total single-use processes. Some developments, especially in the filling area are still necessary. The last step in aseptic processing has not reached the level one finds in the intermediate steps.

The benefits of disposability within aseptic processes are obvious. Cleaning deficiencies are a main regulatory observation, which would be eliminated by single-use equipment. The risk of cross contamination is greatly reduced. Moreover, disposable, aseptic connectivity will reduce the level of end-user manipulation within the process and create higher safety. Disposability is also valuable from an economic and environmental stand-point, as cleaning causes costs due to cleaning solutions and copious amounts of water, as well as high energy levels required to heat the cleaning solutions or steam sterilized the re-usable equipment.

Since single-use technologies are getting more and more mature, they will be implemented into various applications in the future. However, there is a need for harmonization between different technologies of different suppliers. Users are expecting open interfaces between different systems and components. Several organizations, such as ISPE, are working currently on guidance to address these issues.

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This article presents examples and methodologies for optimizing the design and operation of fill-finish facilities using process simulation and scheduling tools.

# Optimizing the Design and Operation of Fill-Finish Facilities using Process Simulation and Scheduling Tools

by Demetri Petrides, Charles Siletti, José Jiménez, Petros Psathas, and Yvonne Mannion

## Introduction

The manufacture of most parenteral drug products involves the formulation, filling, and finishing of Active Pharmaceutical Ingredients (APIs). In general, these processes include a formulation step, a sterilization step, filling into a primary container (e.g., vials, ampoules, syringes), and for some products, a lyophilization (freeze drying) step. The properties of the active compound, the dosage, and the method of drug administration are the key determinants of the type and amount of excipients, the method of sterilization, the type of container, and necessity for lyophilization.

The fill-finish industry employs different methods for sterilization of the final product. The regulatory agencies specify that parenterals should be terminally sterilized. However, temperature-sensitive products are traditionally passed through a sterilizing filter prior to filling. This is where the sterile boundary in production starts and must be maintained until the final sealing of the container. Some products are subsequently freeze dried in a lyophilizer which increases their shelf life by diminishing the rate of formation of degradation products.

A typical fill-finish facility includes multiple compounding suites and filling lines. Only rarely is a production facility dedicated to a single drug product. Instead, such facilities tend to campaign manufacturing of different products in order to reduce cost by achieving economies of scale. Facilities that have multiple production lines usually employ shared utilities (e.g., supply of steam, purified water), and shared resources such as labor, and auxiliary equipment, such as Cleaning-In-Place (CIP) skids. Ideally, a facility should be designed so that the filling lines and

lyophilizers have minimal downtime between batches or campaigns.

The design and operation of multi-product and multi-line fill-finish facilities requires decisions about campaign size and line assignment. Process simulation and scheduling tools can play an important role in this endeavor. The role of such tools in the development and manufacturing of APIs has been reviewed in the past.<sup>1-7</sup> This article focuses on the role of such tools in the development and manufacture of pharmaceutical products that require fill-finish. During process development and facility design, simulation tools facilitate analysis tasks that include the following:

- Represent the entire process on the computer.
- Perform material and energy balances.
- Estimate the size of equipment.
- Calculate demand for utilities as a function of time.
- Estimate the cycle time of the process.
- Perform cost analysis.
- Assess the environmental impact.

The availability of a good computer model assists in improving the understanding of the entire process by the development and technology transfer team members and facilitates communication. Engineers may use process modeling tools to conduct sensitivity analyses to evaluate the impact of critical parameters on various Key Performance Indicators (KPIs), such as production cost, cycle times, and plant throughput. Cost analysis, especially capital cost estimation, facilitates decisions related to in-house manufacturing versus outsourcing. Estimation of the cost-of-goods identifies the

expensive processing steps and such information is used to guide development work. When a process is ready to move from development to manufacturing, process simulation facilitates technology transfer and process fitting. A detailed computer model provides a thorough description of a process in a way that can be readily understood and adjusted by the recipients. Process adjustments are commonly required when a new process is moved into an existing facility whose equipment is not ideally sized for the new process. The simulation model is used to adjust batch sizes, fix the cycling of certain steps (for equipment that cannot handle a batch in one cycle), estimate recipe cycle times, and determine the overall capacity.

Production scheduling tools play an important role in manufacturing, both at a large scale, typical for commercial manufacturing, as well as at a small scale for clinical manufacturing. These tools are used to generate production schedules on an on-going basis in a way that does not violate constraints related to the limited availability of resources, including equipment, labor, utilities, and inventories of materials. Production scheduling tools close the gap between Enterprise Resource Planning (ERP)/Manufacturing Resource Planning (MRP II) tools and the plant floor.<sup>8</sup> Production schedules generated by ERP and MRP II tools are typically based on coarse process representations and approximate plant capacities, and as a result, solutions generated by these tools are not sufficiently detailed for actual manufacturing. Sometimes ERP-generated schedules may not even be feasible. This is especially true for multiproduct facilities that operate at high capacity utilization. An infeasible schedule can lead to late orders that require expediting and/or large inventories in order to maintain customer responsiveness. “Lean manufacturing” principles, such as “just-in time production,” “low Work-In-Progress (WIP),” and “low product inventories” cannot be implemented without good production scheduling tools that can accurately estimate capacity.

The section that follows provides information on commercially available process simulation and scheduling tools. The benefits of process simulation are illustrated using a vial manufacturing process. The process is described in considerable detail, including thorough material balances. The batch execution of the process is visualized through Gantt charts and concepts of cycle time analysis and reduction are presented. Information on the capital and operating cost of such processes is provided with detailed breakdowns. The role of scheduling tools for modeling, scheduling, and managing of multi-product facilities is presented with an illustrative example. Finally, a methodology for sizing of purified water supply systems and other utilities of fill-finish facilities is described.

## Simulation and Scheduling Tools

Computer-aided process design and simulation tools have been used in the chemical and petrochemical industries since the early 1960s. Simulators for these industries have been designed to model continuous processes and their transient behavior for process design and control purposes. However, most pharmaceutical products are manufactured in batch and

semi-continuous mode. Such processes are best modeled with batch process simulators that account for time-dependency and sequencing of events.

Simulators specific to batch processes were first commercialized in the mid-1980s. In these, operation models were dynamic and simulation always involved integration of differential equations over a period of time. Recipe-driven batch process simulators appeared in the mid 1990s. These simulators initially targeted batch pharmaceutical and biopharmaceutical processes. They subsequently included models for fine chemicals and consumer products.

Discrete-event simulators also have found applications in the pharmaceutical industries, especially in modeling and debottlenecking of packaging operations. The focus of models developed with such tools is usually on the minute-by-minute time-dependency of events and the animation of the process. Material balances, equipment sizing, and cost analysis tasks are usually out of the scope of such models. Some of these tools are quite customizable and third party companies occasionally use them as platforms to create industry-specific modules.

Spreadsheets are another common platform for creating models for pharmaceutical processes that focus on material balances, equipment sizing, and cost analysis. Some companies have even developed models in spreadsheets that capture the time-dependency of batch processes. This is typically done by writing extensive code in the form of macros and subroutines using tools that come with the spreadsheet application.

Production scheduling tools have historically focused on discrete manufacturing and their success in the pharmaceutical industry has been rather limited in the past. Finite capacity scheduling tools that focus on scheduling of batch and semi-continuous chemical and pharmaceutical processes are now available, as recipe driven tools with emphasis on generation of feasible solutions that can be readily improved by the user in an interactive manner. Examples that illustrate the benefits from the use of simulation and scheduling tools in the production of pharmaceutical parenteral products follow.

## Modeling a Fill-Finish Process

The first step in building any simulation model is always the collection of information about the process. Documents that describe the various processing steps and provide information on material requirements, duration, and sequencing of operations are a good starting point. Reasonable assumptions are made for missing data based on experience from similar processes and using engineering judgment. SuperPro Designer will be used to illustrate the role of batch process simulators in the design and development of fill-finish processes.<sup>12</sup>

It is highly advisable to build the model step-by-step, gradually checking the functionality of its parts. The registration of materials (pure components and mixtures) is usually the first step. Next, the flow diagram is developed by putting together the required processing steps and joining them with material flow streams - *Figure 1*. The individual tasks or operations that make up each processing step are added



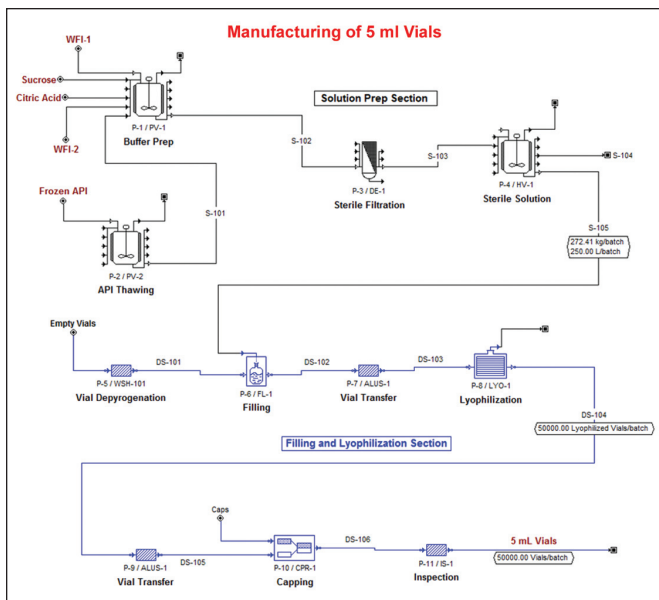


Figure 1. The flowsheet of the fill-finish process.

and their operating conditions and performance parameters are specified.

Most pharmaceutical processes operate in batch or semi-continuous mode. This is in contrast to the heavy chemical industries that handle large throughputs and operate continuously. In continuous processes, a piece of equipment performs the same action all the time, which is consistent with the notion of unit operations. In batch processing, on the other hand, a single basic processing step is called a “unit procedure” and it usually includes multiple tasks called “operations.” For instance, a typical formulation unit procedure includes the following operations: SIP, Charge WFI, Charge Sucrose, Receive API Sltn, etc. A unit procedure is displayed on the flowsheet with an icon that represents the main equipment used. The above terminology, and approach to batch process modeling, is based on the ISA S-88 standards for batch recipe representation.<sup>9</sup> A batch process model is in essence a batch

recipe that describes how to make a certain quantity of a specific product. Unit procedures are the processing steps of a recipe. Operations are the tasks of a unit procedure. The combination of unit procedures and operations enables users to describe and model batch processes in detail. Figure 2 displays the dialog window through which operations are added to a vessel unit procedure.

For every operation within a unit procedure, the simulator solves a mathematical model representing the material and energy balance equations. Equipment-sizing calculations are performed based on the results of the material and energy balances. If multiple operations within a unit procedure dictate different sizes for a certain piece of equipment, the software reconciles the different demands and selects an equipment size that is appropriate for all operations. The equipment is sized so that it is large enough (e.g., vessels are not overfilled during any operation), but no larger than necessary (in order to minimize capital costs). Equipment sizes also can be specified by the user, in which case, the simulator checks to make sure that the provided size is adequate.

Operation durations are either calculated or set by the user. The user also must set the relative sequencing of operations, i.e., the scheduling information. The simulator calculates the overall schedule and displays the results graphically. Additional information on batch process modeling and the design, analysis, and optimization capabilities and limitations of specific tools is available in the literature.<sup>3,10-12</sup>

## Process Description

For a typical biopharmaceutical, the fill-finish step involves thawing of the frozen product solution, preparation of the pH buffering agent, sterile filtration of the solution, and filling the solution into vials or syringes. For sensitive products, such as proteins, the vials are often lyophilized (freeze dried) in order to increase shelf-life. The fill-finish process modeled here represents the manufacture of 5 mL lyophilized vials containing a therapeutic protein.

The entire flow diagram is shown in Figure 1. A batch begins with compounding of the solution to be filled. First, water for injection (WFI) is charged, followed by the addition of sucrose and citric acid to a previously sterilized compounding vessel (PV-1). The solution is then agitated for 15 minutes and sampled. If the buffer meets specifications, the frozen API solution is thawed and sampled in another previously sterilized vessel (PV-2). The API solution is then added to the compounding vessel and its final concentration is adjusted to 5 g/L by diluting the solution with WFI.

The protein solution is then filtered using a 0.22 μm pore-size membrane depth filter (DE-1) that has undergone a pre-integrity test. The filtered sterile solution is collected in a storage tank (HV-1) that is subsequently used to feed the filler. A 2% solution loss within the pipes is assumed. Aseptic filling is then done using a filling machine (FL-1) which has been previously sterilized and tested for integrity. HV-1 feeds the solution to the filler while a depyrogenation tunnel (WSH-101) supplies the vials to be filled. The filler processes 250 L of sterile solution per batch at a rate of 7,200 vials per

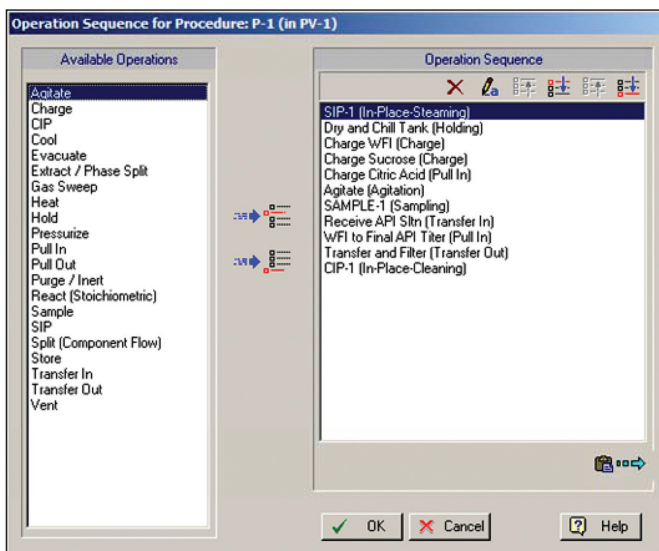


Figure 2. Specifying the operations of a unit procedure.

Material	kg/batch
WFI	12,662.39
Sucrose	22.86
Citric Acid (5%)	1.67
H3PO4 (5% w/w)	1,603.12
NaOH (0.5 M)	1,558.84
Frozen API Sln	128.15
Plastic	50.00
Glass	250.00
<b>TOTAL</b>	<b>16,277.03</b>

Table A. Bulk material requirements.

hour, resulting in 50,000 filled vials per batch.

During filling, the vials are loaded into a lyophilizer (LYO-1) using an automatic loader/unloader system (ALUS-1). The 50,000 vials are freeze-dried (lyophilized) for a period of 72 hours. The lyophilizer is sterilized and a leak test is carried out prior to operation. Once the lyophilization cycle is completed, the vials are fed into a capper machine (CPR-1) using the same automatic loader/unloader system (ALUS-1). The capped vials then go through an inspection station (IS-1). Both the capper and the inspection station operate at a rate of 7,200 vials per hour.

To maintain the quality and purity of the product, aseptic filling is carried out in a Class 100 room (Grade A). Operators must adhere to strict gowning and other procedures when entering the filling room. For instance, any movement by operators must be gentle so as not to affect the laminar flow within the room. Advanced isolator technologies have been developed in the last 20 to 30 years that greatly minimize the risk of contamination. The filling machine is enclosed in a glass box and access is provided through glove ports only.

Table A provides information on raw material requirements for the entire process (excluding the API). The quantities are displayed in kg/batch. A batch consists of 50,000 filled 5 mL vials. Plastic and glass consumption account for the materials of the caps and vials, respectively. The large amounts of WFI, H3PO4 (5% w/w), and NaOH (0.5 M) result from the cleaning operations of the various equipment items.

Figure 3 displays the Equipment Occupancy Chart (EOC) for two consecutive batches (each color represents a different batch). Equipment is displayed on the y-axis and time on the x-axis. The total time between the start of the first step of a

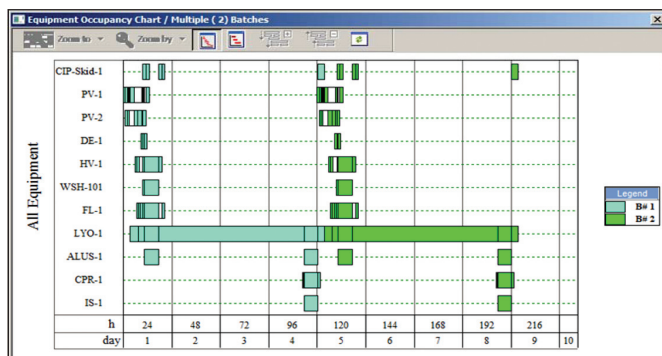


Figure 3. Equipment occupancy chart for two consecutive batches.

batch and the end of the last step of the same batch, known as recipe *batch time*, is 4.14 days. However, a new batch is initiated every four days since equipment items are utilized for shorter periods within a batch. This is known as the recipe *cycle time*. Multiple bars of the same color on the same line represent reuse (sharing) of equipment by multiple procedures or operations. CIP-Skid-1 and ALUS-1 are the only shared equipment in this process - Figure 3.

White space between procedure bars represents *idle time*, while white spaces within a procedure bar represents *waiting time*. For instance, the white space in PV-1 represents a waiting time until the API has been thawed and sampled. This type of chart is a valuable tool for visualizing cycle times and scheduling bottlenecks.

Figure 4 displays the operations Gantt chart which provides more detailed scheduling information. The Gantt chart displays the activities of a batch at various levels of detail. The light orange bar at the top represents the time required for one full batch. The procedures within the batch (Buffer Prep, API Thawing, Sterile Filtration, Storage, Depyrogenation, Filling, Vial Transfer, Lyophilization, Capping, and Inspection) are displayed with solid blue rectangles. The operations within each procedure are represented by the turquoise (cyan) bars. The duration, start time, and end time of the various activities are displayed in the corresponding columns of the grid on the left. Scheduling dependencies can be easily visualized through the operations Gantt chart. Notice, for instance, how the “API Charge and Thaw” operation in P-2 is aligned with the end of “SAMPLE-1” in P-1. Such links are specified through the scheduling tab of an operation’s dialog window.

Scheduling in the context of a simulator is fully process-driven and the impact of process changes can be analyzed instantly. For instance, the impact of an increase in batch size (that affects the duration of charge, filtration, filling, capping, inspection, and other scale-dependent operations) on the recipe cycle time and the maximum number of batches can be seen instantly. Due to the many interacting factors involved with even a relatively simple process, simulation tools that allow users to describe their processes in detail,

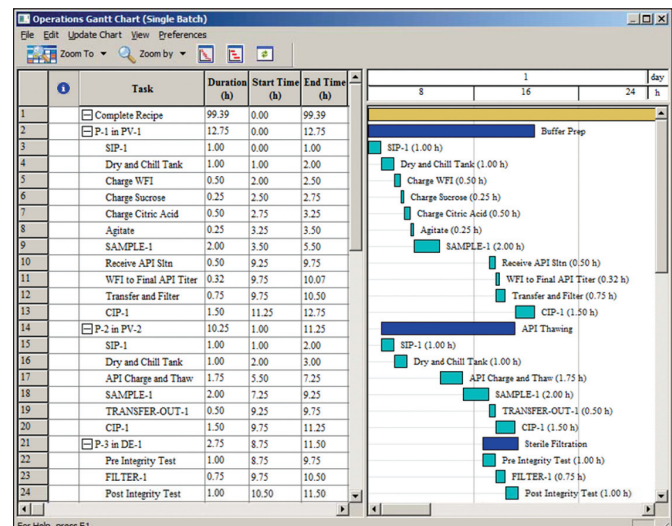


Figure 4. The operations Gantt chart.

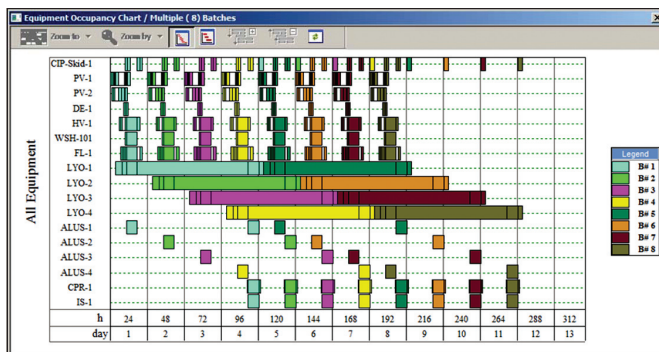


Figure 5. Eight consecutive batches with four staggered lyophilizers.

and to quickly perform what-if analyses, can be extremely useful.

### Cycle Time Analysis and Reduction

The annual throughput of a batch process is equal to its batch size times the number of batches that can be processed per year. Consequently, increasing either the batch size or the number of batches per year can increase the annual throughput.

In this example, the process operates at its maximum batch size determined by the capacity of the lyophilizer (50,000 vials). The number of batches can only be increased by reducing the recipe cycle time, which is determined by the cycle time of the lyophilizer (four days). Any process changes that can reduce the cycle time of the lyophilizer (e.g. shorter setup or faster lyophilization cycle) will have a direct impact on productivity. However, major process changes in GMP manufacturing require regulatory approval and can be expensive. Addition of extra equipment is a practical way to reduce cycle time.

Figure 5 represents a situation where four lyophilizers (LYO-1, LYO-2, LYO-3, and LYO-4) serve the same filling line. The four lyophilizers operate in staggered mode, i.e., each subsequent batch uses a different lyophilizer. The fifth batch recommences with the first lyophilizer. The cycle time of the process is reduced to one day (a new batch can be initiated every day) and the annual throughput is increased by a factor of four.

It is actually possible to add two more lyophilizers (for a total of six) before the filler becomes the bottleneck. Expected market demand for the products manufactured by this facility should determine the actual number. Typically, such facilities manufacture a variety of products by campaigning production (see Production Scheduling section). The rates and durations of the various processing steps depend on the type of product. Consequently, the bottleneck of a production line may be product specific.

For situations where the filler is the bottleneck, its cycle time can be reduced and the process throughput can be increased through the use of disposable technology (single-use systems). The market currently offers disposable tubing, filling needles, and pumps.<sup>13</sup> In general, disposables reduce the time required for equipment setup and cleaning.<sup>14</sup> Cycle time reduction and batch size increase are the common ways for optimizing batch processes.

Total Capital Investment	157,860,000	\$
Operating Cost	50,496,000	\$/yr
Revenues	81,750,000	\$/yr
Production Rate	16,350,000	Vials/yr
Unit Production Cost	3.09	\$/Vial
Selling Price	5.00	\$/Vial
Gross Margin	38.23	%
Return On Investment	18.12	%
Payback Time	5.52	years
IRR (After Taxes)	14.30	%
NPV (at 7.0% Interest)	68,623,770	\$

Table B. Key economic evaluation results.

### Cost Analysis

Cost analysis and project economic evaluation are important for a number of reasons. For a new product, if the company lacks a suitable manufacturing facility with available capacity, it must decide whether to build a new plant or outsource the production. Building a new plant is a major capital expenditure and a lengthy process. To make the decision, management must have information on capital investment required and time to complete the facility. When production is outsourced, a cost-of-goods analysis serves as a basis for negotiation with contract manufacturers. A sufficiently detailed cost model can be used as the basis for the discussion and negotiation. Contract manufacturers usually base their estimates on requirements for equipment utilization and labor per batch. A good model can provide this information by performing thorough cost analysis and project economic evaluation calculations and by estimating capital and operating costs. The cost of equipment can be estimated using built-in cost correlations that are based on data derived from a number of vendors and literature sources. The fixed capital investment can be estimated based on equipment cost and using various multipliers, some of which are equipment specific (e.g., installation cost) while others are process specific (e.g., cost of piping, buildings etc.). The approach is described in detail in the literature.<sup>3,15,16</sup>

Table B shows the key economic evaluation results for the case of four lyophilizers operating 24/7 for 330 days/year and processing 327 batches per year (50,000 vials per batch). This analysis assumes that a new facility will be built for this process and the project lifetime is 15 years. The capital investment for a plant of this capacity is around \$160 million. The annual operating cost is around \$50 million and the unit manufacturing cost is around \$3.1 per vial. Table C provides a breakdown of the manufacturing costs. The cost of

Cost Item	\$	%
Raw Materials	9,784,000	19.38
Labor-Dependent	15,336,000	30.37
Facility-Dependent	20,765,000	41.12
Laboratory/QC/QA	4,164,000	8.25
Consumables	327,000	0.65
Waste Treatment/Disposal	29,000	0.06
Utilities	90,000	0.18
<b>TOTAL</b>	<b>50,496,000</b>	<b>100.00</b>

Table C. Breakdown of the annual operating cost.

raw materials accounts for the cost of excipients and cleaning solutions, but not the cost of the API. The facility-dependent cost, which primarily accounts for the depreciation and maintenance of the facility and equipment, is the dominant cost (41% of total). Labor is the second most important cost item accounting for 30.4% of the total manufacturing cost. The profitability figures were generated assuming a selling price of \$5/vial resulting in annual revenues of \$82 million.

## Production Scheduling

After the process is developed and transferred to a manufacturing facility for clinical or commercial production, it becomes the job of the scheduler to ensure that all the activities are correctly sequenced and the necessary labor, materials, and equipment are available when needed. The short-term schedule includes the upcoming production campaigns and may span from a week to a month. The general workflow begins with the long-term plan which describes how much of each product should be made over the planning period. The long-term plan is usually based on approximate batch or campaign starts and does not include details about process activities. The scheduler uses the plan and knowledge about the process and available equipment and resources to generate a detailed production plan, i.e., the short-term schedule, and communicates it to the appropriate staff. As the schedule is executed, there may be deviations between the schedule and the actual process execution. Tests, for example, may need to be redone, operations may take longer than assumed, or equipment may fail. The scheduler must recalculate the production schedule to reflect changes in resource availability and notify the staff.

Pharmaceutical companies use a variety of plant systems. Enterprise or Manufacturing Resource Planning (ERP/MRP II) systems keep track of the quantities of resources, such as materials or labor. Manufacturing Execution Systems (MES) ensure that the process proceeds according to precise specifications. Process control systems interface with the equipment and sensors to carry out steps and to maintain the process parameters according to specification.<sup>17</sup> Short term scheduling is often managed manually or with stand-alone systems, but it could potentially interface with ERP/MRP II and even MES programs.

SchedulePro will be used to illustrate the role of scheduling tools in the design and operation of fill-finish manufacturing facilities.<sup>18</sup> The tool does not close material and energy balances; it is mainly concerned with the time and resources that tasks consume. Users interested in both process modeling and scheduling, may generate the process model in a batch process simulator, perform the material and energy balances there, and then export it as a recipe to the scheduling tool for a thorough capacity planning or scheduling analysis in the context of a multi-product facility. Scheduling tools explicitly model the activities of each batch and differ from batch process simulators in the following ways.

- Alternative resources (e.g. equipment) may be assigned for a procedure or operation allowing different batches to have different resources.

- Material inputs and outputs may be tracked, but strict material balances are not enforced.
- Recipes may have the flexibility to delay for resource availability for a given batch.
- The user may modify the scheduling of an individual batch.
- Scheduling tools can model competition for resources among multiple processes.

Many of the tool's capabilities are primarily motivated by the needs of the pharmaceutical industry where bottlenecks often exist in the use of auxiliary equipment (e.g., CIP skids, transfer panels) or are related to support activities (e.g., cleaning, buffer preparation) which tend to have flexible execution.

With the resources and facilities in place, simulation of the production activity in the tool can proceed through the definition and scheduling of campaigns. A *campaign* is defined as a series of batches of a given recipe leading to the production of a given quantity of product. A series of campaigns organized in a priority list constitute the production plan that needs to be realized. As a finite capacity tool, SchedulePro attempts to schedule production of campaigns, while respecting capacity constraints stemming from resource unavailability (e.g., facility or equipment outages) or availability limitations (e.g., equipment can only be used by only one procedure at a time). Resource constraint violations or *conflicts* can be resolved by exploiting alternative resources declared as candidates in pools, introducing delays or breaks, or moving the start of the batch. Users can interactively modify the schedule through local or global interventions in every scheduling decision. Through a mix of automated and manual scheduling, users can formulate a production plan that is feasible and satisfies their production objectives.

## Illustrative Example

As mentioned in the introduction, fill-finish facilities are rarely dedicated to the manufacture of a single product. Instead, they tend to campaign production of different products in order to increase asset utilization and reduce manufacturing cost. In addition, it is common to have two or more lyophilizers associated with a filling line. The long cycle time of lyophilization leaves the formulation equipment and filling machine idle

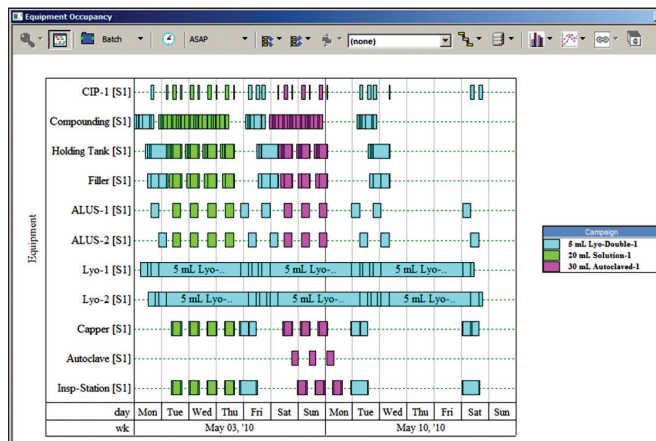


Figure 6. Campaigns of three different products.

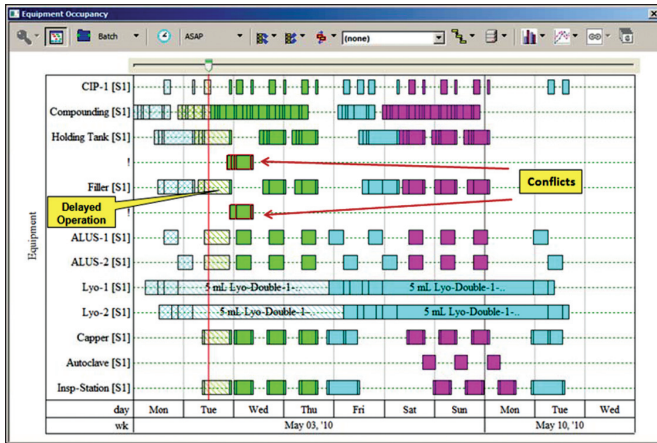


Figure 7. Conflicts created by a delay in the first batch of the green campaign.

most of the time. Products that do not require lyophilization are usually manufactured during those time intervals in order to increase the utilization and the profitability of the facility without the procurement of additional equipment. The chart in Figure 6 represents a multi-product fill-finish scenario modeled in SchedulePro. The cyan (light blue) bars correspond to a campaign of three batches of 5 mL vials that require lyophilization. In this case, large formulation batches are prepared that utilize both lyophilizers. The green bars correspond to a campaign of four batches of 20 mL vials that do not require lyophilization. Finally, the magenta color bars correspond to a campaign of three batches of 30 mL vials that do not require lyophilization, but are terminally sterilized using an autoclave. This type of operation increases the utilization of the facility and reduces the manufacturing cost.

### Production Tracking and Rescheduling

Tracking the status of production during manufacturing is facilitated by the concept of **current time** which separates past from future activities. The current time represents the time as of which the status of the various activities is determined. It does not necessarily correspond to the actual com-

puter clock-time. The red vertical line on the chart of Figure 7 represents the current time. The current time line results in the division of activities in three categories: completed (displayed by a crossed hatch pattern), in-progress (diagonal hatch), and not-started (filled pattern). The classification of activities is automatically updated when the current time is changed. The use of the current time facilitates the monitoring of the production progress.

In manufacturing environments, the execution of certain operations may be delayed due to equipment failures and other unexpected events. The chart in Figure 7 represents a situation where due to equipment failure, the filling time of the first “20 mL solution” batch is increased from seven to 12 hours. Such a delay leads to scheduling conflicts with future activities. Conflicts are displayed with multiple lines for the conflicting equipment and an exclamation mark on the y-axis. Also, the outline of the conflicting activity is displayed in red.

The user may resolve conflicts manually by using the drag and drop capabilities of the tool or automatically by using its conflict resolution algorithms. The scope of automatic conflict resolution is controlled by the user. Conflicts can be resolved for a batch, campaign, or the entire schedule.

The tool employs a graduated approach to resolving resource conflicts with a general goal of minimizing delays. The tool first attempts to find alternative resources. If none are available, the tool will attempt to use local flexible shifts to resolve the conflicts. If that fails, the tool will delay the entire batch. In the case of Figure 7, the conflict resolution only affects the subsequent two batches of the “20 mL solution” campaign. A delay in a bottleneck equipment item (e.g., one of the lyophilizers) would affect many subsequent batches. In general, a certain amount of idle time is desirable in manufacturing because it provides flexibility for absorbing delays.

Completed batches and campaigns can be deleted from the schedule. This enables the human scheduler to focus on the current and future campaigns.

Contemporary scheduling tools use a relational database for tracking the status of production as a function of time and for communicating the data to the various stakeholders. Any

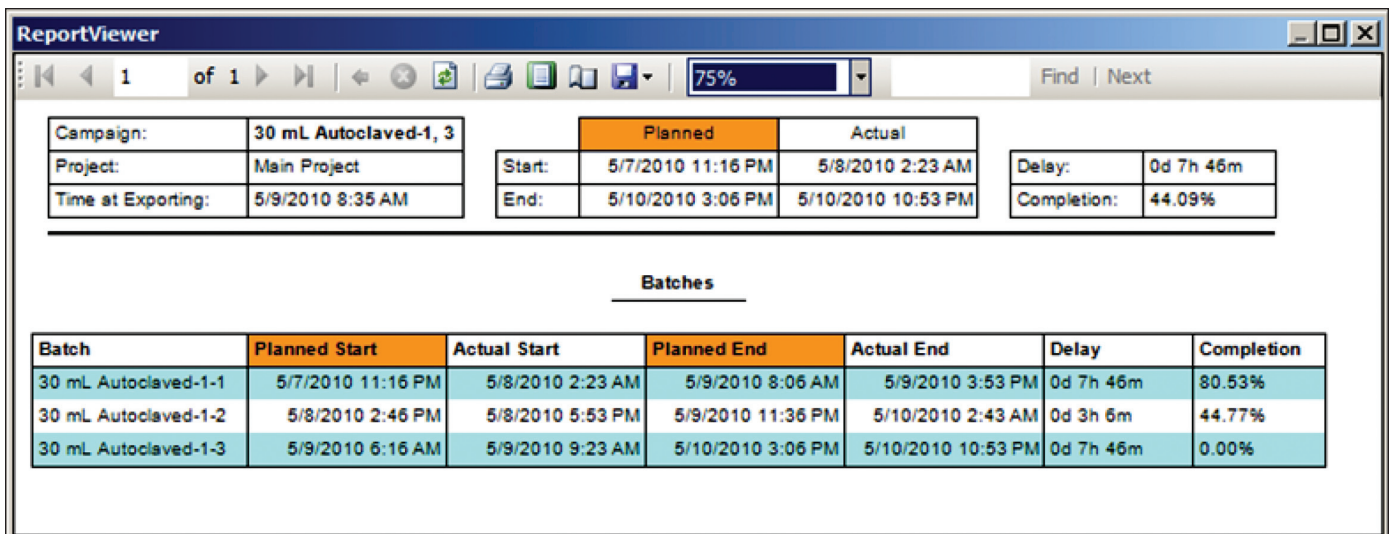


Figure 8. Database information on the batches of the “30 mL Autoclaved” campaign.

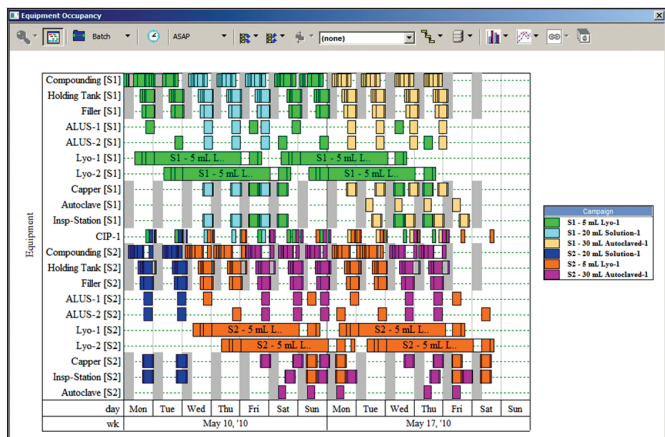


Figure 9. Two-line facility with downtimes.

number of snapshots of an evolving production schedule can be deposited into the database. The results are viewed using the database report viewers or through appropriate Internet applications that utilize browsers. Figure 8 provides a sample data report for the “30 mL Autoclaved” campaign. The campaign includes three batches. The right-most column displays the completion (%) of a batch which is calculated based on the start and end times of each batch relative to the current time. The delay of a batch is calculated by comparing its expected completion relative to its originally planned completion. Additional detail can be displayed by generating the report at the procedure or operation level.

Such reports, in combination with the graphical displays, can be used to publish production scheduling information to the manufacturing floor. Any deviations occurring during execution can be recorded by operators into the database and the data can be transferred into the scheduling tool in order to check for conflicts and for rescheduling.

In addition to storing historical data and tracking the status of production, a central database facilitates communication with Enterprise Resource Planning (ERP), Manufacturing Execution Systems (MES), and related tools. For instance, an ERP tool may deposit an unscheduled campaign in the database (representing a new work order). Such a campaign can be imported into the scheduling tool, scheduled and executed with the help of an MES tool. Multiple snapshots

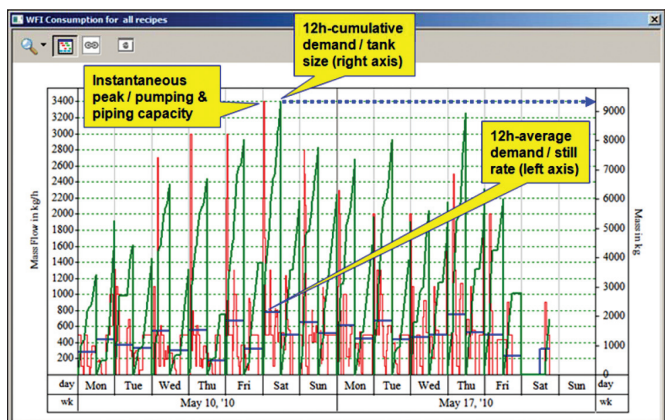


Figure 10. WFI consumption chart.

of the campaign can be deposited into the database during execution. The status of the campaign can be communicated back to the ERP tool from time to time.

A variety of third-party reporting tools are available for viewing data stored in third party databases. Users can create their own reports which can be viewed through Internet browsers and smart phones. Thus, project managers can remotely monitor the status of campaigns and projects of their organization on an on-going basis. Simplified reports and metrics that provide high level information are recommended for the members of the executive suite of a corporation. Detailed reports that focus on the activities of a specific production line for a specific date or shift are useful for providing execution instructions to operators and line supervisors.

## Multi-Line Facilities

Large scale fill-finish facilities are often equipped with multiple manufacturing lines in order to handle high production demands and a wide variety of products. The schedule in Figure 9 represents a two-line facility that includes three campaigns in each production line. The equipment items that display **S1** in brackets correspond to Line-1 and those displaying **S2** correspond to Line-2. The gray columns represent downtime for the night shift.

The facility of Figure 9 employs full crews during the day shifts (that can perform any activity) and a limited crew during the night shift for cleaning and setting up equipment for the following day shifts. In general, cleaning and setup activities can be executed around the clock. Formulation is restricted to day shifts. However, the highly automated filling machines are allowed to run during the night shift assuming their operation is initiated during the day shifts. The lyophilizers operate 24/7. Both lines share a single CIP skid (CIP-1).

Modeling of multi-product and multi-line facilities is greatly facilitated by the copying/pasting capabilities of scheduling tools. To represent a new product, the user simply copies and modifies an existing recipe. Similarly, to represent a new manufacturing line, the user simply copies and adjusts an existing line. Shift and operating patterns are specified with appropriate constraints at the facility, equipment, and operation levels. However, it should be noted that each additional constraint slows down the solution generation algorithm. Furthermore, the algorithm may fail to generate a conflict-free solution for over-constrained problems.

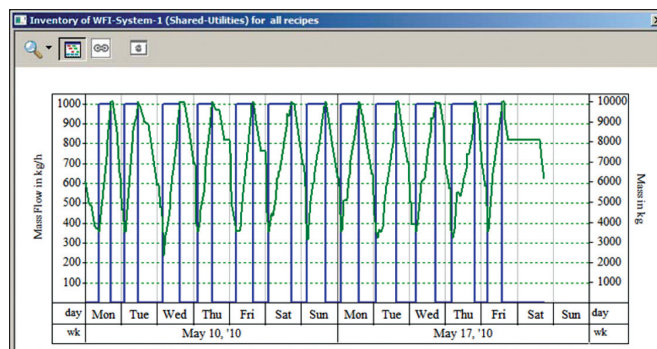


Figure 11. WFI inventory (green lines) and still operating profile (blue lines).

## Constraints Imposed by Non-Equipment Resources

Production schedules are often constrained by the limited availability of materials, utilities, and labor. Water for injection (WFI) is a common material utilized by fill-finish facilities for preparation of process and cleaning solutions. In a typical multi-line facility, a single WFI system supplies water to the various operations that utilize it. A WFI system consists of a still that generates the distilled water, a surge tank, and a circulation loop for delivering the material around the plant. Process simulation and scheduling tools can provide reasonable estimates for the sizes of the still, the surge tank, and the pumping capacity of the circulation loop. This is valuable information during the design of a new facility or the retrofit of an existing facility. The sanitization of the WFI loop also can be added as a constraint in the schedule and activities requiring WFI can be rescheduled around it.

Figure 10 displays the demand of WFI for the multi-line and multi-product scenario of Figure 9. The chart shows the instantaneous (red lines) and the 12-hour average (blue lines) demands. The chart also shows the 12-hour cumulative demand (green lines) that corresponds to the y-axis on the right. The peak instantaneous demand indicates the minimum pumping capacity for the system (3,400 kg/hour). The peak 12-hour average rate provides an estimate for the still capacity (800 kg/hour) and the corresponding 12-hour cumulative peak is an estimate of the surge tank capacity of 9,500 kg. The trade-off between still rate and surge capacity can be examined by changing the averaging time. Selecting a longer period predicts a larger surge tank and a lower still rate.

Figure 11 displays the inventory profile of WFI in the surge tank (green lines) for a tank size of 10,000 L and a still rate of 1,000 L/hour. The still starts when the level in the tank falls below 35% and remains on until the tank is full. The operation rate and frequency of the still is depicted by the blue step-function lines. During the design of a new facility, charts similar to those of Figures 10 and 11 are generated for a variety of expected production scenarios. The results assist engineers to judiciously size such utility systems. For existing facilities, the same charts can be used to schedule production so that WFI does not become a limiting resource.

Constraints imposed by the limited availability of labor, electrical power, heating and cooling utilities are handled in a similar manner. Scheduling and simulation tools track and display the demand of these resources as a function of time. The user also can specify the availability of each resource as a function of time. If the demand for a resource exceeds its available capacity during a time interval, the system flags it as a conflict that can be readily visualized by the user. The resolution of such conflicts is accomplished either by the scheduling algorithm or the user. It typically involves the delay of some operations that contribute to the peaks.

Constraints imposed by inventories of input, intermediate, and output materials are also handled in a similar manner. The scheduling tool calculates the level of materials and either warns the user of conflicts or automatically schedules to avoid them. In summary, scheduling tools enable manufacturing personnel to maintain a time-dependent model of the entire plant and

facilitate generation of production schedules that are feasible and easily modifiable. The end result is increased productivity, improved customer service, and reduced manufacturing cost.

## Conclusion

Process simulation and production scheduling tools can play an important role throughout the life-cycle of pharmaceutical product development and commercialization. In process development, process simulation tools are becoming increasingly useful as a means to analyze, communicate, and document process changes. During the transition from development to manufacturing, they facilitate technology transfer and process fitting. Production scheduling tools play a valuable role in manufacturing. They are used to generate production schedules based on the accurate estimation of plant capacity, thus minimizing late orders and reducing inventories. Such tools also facilitate production planning, capacity analysis and debottlenecking tasks. Production planning is a more long-term look for each product to be made over a period of months to more than a year. It requires input data from sales and marketing in addition to manufacturing capacity. Debottlenecking refers to the identification of resources (e.g., equipment, utilities, labor, and materials) that limit the level of production. The pharmaceutical industry has only recently begun making significant use of process simulation and scheduling tools. Increasingly, universities are incorporating the use of such tools in their curricula. In the future, we can expect to see increased use of these technologies and tighter integration with other enabling IT technologies, such as supply chain tools, ERP/MRP II tools, Manufacturing Execution Systems (MES), batch process control systems, and process analytics tools. The result will be more robust processes and efficient manufacturing leading to more affordable medicines.

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This article discusses the increasing use of isolator technology in modern aseptic processes and presents the latest developments and possibilities for this key equipment.

# Trends and Advances in Isolator Technology

by Volker Sigwarth and Thomas Huber

## Introduction

Some clear trends can be observed in the pharmaceutical industry. First: more and more drug substances are biotech based and therefore highly sensitive to environmental influences. They also require aseptic production processes. Second: drug substances in development and in production are becoming increasingly more potent so that operator and environmental safety issues have gained higher priority. Additionally, there is increasing pressure on the cost effectiveness and flexibility of pharmaceutical production processes. Due to these facts, current production processes and production equipment are deeply challenged to improve operational availability.

## Isolator Technology Overview

Isolator technology has gained a strong position in the pharmaceutical industry within the last 15 years with the most significant developments in production technique. Its use starts in R&D, continues with the manufacturing of pharmaceuticals – filling lines, freezer/vial lines, transport systems, and production equipment – and is found for many routine testing in final quality control, for example, sterility testing, etc. In the first phase of development, mainly technical solutions were implemented to get appropriate hardware. Later, the focus was directed toward process engineering, especially the decontamination with  $H_2O_2$  and the validation of the decontamination success. Important fundamental work on the decontamination effect of  $H_2O_2$  upon biological indicators has unraveled their behavior and made a considerable contribution to the acceptance of the method.<sup>1,2</sup> Thanks to this basic work, both manufacturers, as well as users, have gained insight into isolator processes and their contribution to safety and quality of pharmaceutical products. Fortunately,

this knowledge has found quick acceptance through authorities worldwide, which helped to establish well accepted standards. Isolator technology is described today in all major directives (FDA, USP, PIC/S, Ph. Eur., ISO, VDI, etc.) and supported by the large pharmaceutical communities (ISPE, PDA, APV).<sup>3-12</sup> The FDA's statement in 2006:

*“Isolator technology is an advanced technology to meet 21st century objectives for process consistency, well established, providing significantly increased sterility assurance.”<sup>13</sup>*

In short, isolator technology is widely known and successfully implemented, well understood and accepted from both users and authorities.

## Focus and Requirements

Biotech based products are increasing in importance as pharmaceutical products, because as designed, they are highly potent as well as potentially toxic.<sup>14</sup> Because of their nature, they cannot be terminally sterilized by autoclave and therefore need to be processed aseptically. All of this results in more stringent requirements for containment to protect personnel as well as the environment. The manufacturing of these drugs is complex, sophisticated, and typically very expensive. Manufacturers achieve a better chance to improve the cost-benefit ratio by handling large batches of mono products applying high speed filling, for example, vaccines in prefilled syringes. Biosimilars and generic products are highly cost sensitive, but requirements for safety aspects remain at the same level as for original products. The development and manufacturing of new and specialty products in “fast track” programs require very flexible equipment, handling small batches efficiently, and avoiding cross contamination. The change-over from one

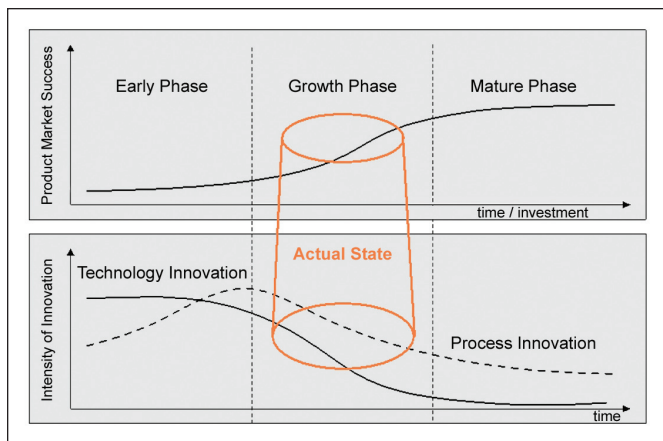


Figure 1. Actual state of isolator technology, life cycles, and intensity of innovation.

product to another implies reducing down time due to cleaning, modifications, and commissioning. Here, pharmaceutical manufacturers ask for flexibility of the equipment and request minimum down time to comply with new requirements and to raise production efficiency.<sup>15</sup>

From a technical viewpoint, the isolator is in a state of maturity today. Technological innovations are becoming more complex and expensive and result in only limited benefits. For this reason, process innovations get more focus: to use the isolator equipment more efficiently and to master process and technology to improve output volume and lower costs. The cost-benefit ratio actually drives the trend - *Figure 1*.

Therefore, the trend moves toward more operational availability of the equipment and to improve reliability and production capacity of the existing technology in order to raise quality and safety, reducing cost at the same time. Downtime either for setting-up, maintenance, or for transfer steps is to be reduced further. The use of Process Analytical Technology (PAT) helps to improve the pharmaceutical process, making it more robust and safe and hence improving product quality.<sup>16,17</sup> Technological process changes allow for shorter cycle time for specific steps, transfer, or decontamination, e.g.

Comprehension of safety aspects gained in production asks for analogue safety concepts to upstream processes with bulk material as well as for downstream quality control steps. The same is observed in the application of pharmaceuticals in hospitals for the preparation of cytostatics, e.g., here safety standards equal more and more the standards of the manufacturing industry. Summarizing these aspects, one recognizes that future isolator technology can achieve:

- higher and faster throughput,
- shorter transfer and process times, reduced shutdown, and decontamination time
- increased safety as to service and maintenance aspects
- more flexibility of the equipment
- quicker and easier qualification of the production line

Briefly: more quality and speed.

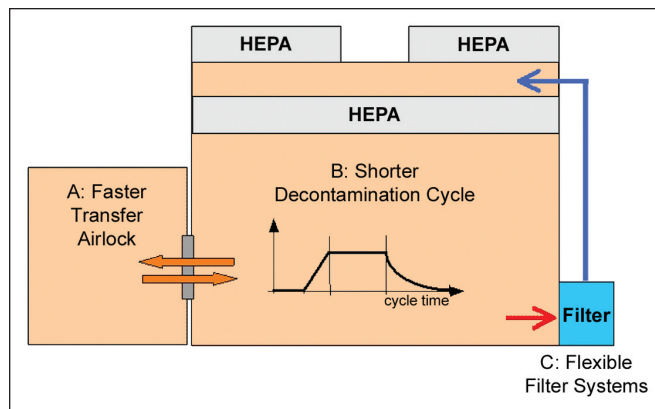


Figure 2. Technological process developments for isolators. Focus is set to: rapid transfers (A), short decontamination cycles (B), and flexible filter systems (C).

## Trends in Isolator Technology

Trends in isolator technology are demonstrated with two aspects: treating the requirements for more throughput and solutions to improve product quality and operator safety - *Figure 2*.

### Faster Transfers and Short Downtime

Typical hospital pharmacies prepare up to 40,000 individual “cocktails” a year, many of them containing toxic active ingredients requiring increased protection for operators and the environment. Due to the low stability and the highly individual preparation, these cocktails have to be concocted fully aseptically and just shortly before administration. This requires very flexible and short transfer steps for inlet, decontamination, subsequent preparation, and outlet.

Isolators for sterility testing are today’s standard in the pharmaceutical industry. Short transfer and decontamination cycles are requested to increase capacity and throughput and to enable prompt analysis of the production samples.

In order to realize large production lots, it is necessary to transfer the considerable sample volume for the environmental monitoring rapidly without interruption of the process. Personnel and environmental safety must be maintained at all times.

All three applications have demand for more throughput and shorter cycle time without degrading safety to personnel and environment. Analyzing productive and non-productive phases of the processes, the time for the decontamination and for transfers contributes considerably to the total cycle time. For sterility test isolators, these were the limiting factors enabling only one sterility test session per work shift (12 tests per session).

A further development of the process allowed the optimization of the evaporation of  $H_2O_2$  directly within the work chamber with the items to be decontaminated. Therefore, pre-conditioning is avoided and higher instantaneous concentrations of  $H_2O_2$  are obtained. Together with an improved purging, much shorter decontamination cycles are achieved. D-values obtained reach 0.3 minutes for the reference microorganism *Geobacillus stearothermophilus* spore compared to 1.5

minutes in the hitherto process. The new improved procedure is very effective and safe. The inactivation using  $H_2O_2$  corresponds to a simple dose-time relationship. Interfering factors, such as humidity and temperature are virtually eliminated, which improves the process even more and renders it more robust.<sup>18</sup>

For two of the above applications, this fast  $H_2O_2$  decontamination process has already been integrated successfully - *Figure 3*. For sterility test isolators, the parallel fast decontamination of the material in the transfer airlock allows for continuous sterility testing improving throughput to approximately 40 tests per shift and isolator. Processes with many transfers through airlocks profit mostly from the new development: cycle times of only 10 to 15 minutes are achieved with an unchanged 6-log total kill and purging down to 1 ppm residual concentration  $H_2O_2$ .

The new process results in distinctly improved productivity and capacity through shorter transfer cycles and will quickly become widely accepted for these applications. Other applications, such as filling lines, will follow in a medium term because actual (non-productive) decontamination cycle times limit productivity directly.

The E-beam tunnel, integrated in the isolator and directly coupled to the filling line is another successful example of a high capacity transfer system new in the market. The exterior of tubs packed with syringes to be filled are decontaminated by means of electron beam.<sup>19</sup> A major advantage of this process is the continuous flow of material making it even more beneficial for the integration with filling lines.

## Isolating Isolators

Isolators for handling active ingredients aseptically constitute a barrier to the surrounding area and protect effectively product and operator. Many steps, especially cleaning, require additional barriers for the specific work. Cleaning of air return ducts, e.g., is laborious and complex in particular for potentially contaminated areas. This holds true



Figure 3. Isolator system for pilot plant and sterility testing applications with double integrated rapid transfer airlocks and new filter box.

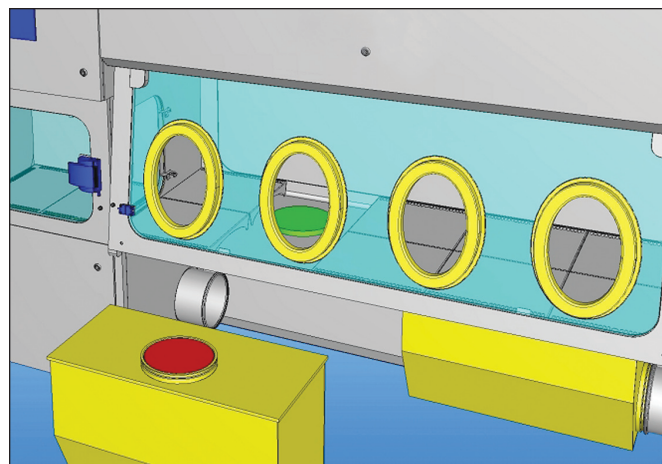


Figure 4. New self-contained filter box and its position for handling.

for the filter change on the downstream side. If an isolator is to be adopted for different products in a simple way – an important flexibility feature – there is a high risk for cross contaminations. A way to eliminate this problem is to reduce the potentially contaminated volume to its minimum and to optimize cleanability.

Over the years, special filter systems have been developed to address the requirements for safe and simple filter change. Bag-in bag-out filters have been known in the nuclear industry for years and constitute the first generation of this type. A major drawback of this system is the complex filter change procedure with the bag over bag concept. Later on, especially in the handling of active ingredients, push-push filter cartridges have been introduced to separate the work space of powder isolators from the exterior environment. However, these isolators are typically flushed with fairly low air volumes and their pressure drop is significantly high. With regard to aseptic processing and controlled clean zones – usually ISO 5 or Class A respectively – high air volume flows associated therewith, can not be achieved reasonably. For these reasons and practical needs, a new filter box unit has been developed to respond to the market requirements of safety, simple handling, high air flow volume rates characteristics, and absolute filter retention. The filter box is a self-contained unit which includes H14 filter media, housing, and closure. The filter box is shipped scanned and integrity tested and allows for quick fitting and qualification of the unit. The box is placed directly below the working space and reduces the potentially contaminated volume to a minimum - *Figure 4*. The filter change procedure is greatly simplified, as it can be easily performed from the front. The filter box is closed and safely disposed of after filter change. This way, the isolator remains closed and isolated at all time. The new filter box is already in use in isolators for hospital pharmacies, where cytostatic cocktails are prepared - *Figure 5*.

In the future, sterility testing isolators also will profit from this technology: for samples to be sterility tested that contain highly active ingredients, the same safety measures for containment must be respected. Also, more attention will be paid for the removal of samples (from the environmental



Figure 5. Isolator system for pilot plant and cytostatic applications with integrated rapid transfer airlock and new filter box.

monitoring, e.g.) and of waste. For all of these steps, the total process gains safety, reliability, and time due to well adopted solutions for the safe and contamination free filter change.

A remarkable interest for the new system has been found in applications, where the filter change occurs after every single product lot to avoid cross contamination. It simplifies production and cleaning, especially in product development and contract manufacturing. The filter box contributes to quick product changes, providing higher productivity. The development of even more compact filter systems will significantly increase efficiency and safety.

## H<sub>2</sub>O<sub>2</sub> – a Contribution to Process Safety

More and more substances and active ingredients processed in isolators are highly sensitive to chemical modification, oxidation, etc. Thus, the question is presented: how do residual concentrations of H<sub>2</sub>O<sub>2</sub> influence product quality and stability? Usually the isolator chamber is purged extensively with air after decontamination to reduce the residual concentration of H<sub>2</sub>O<sub>2</sub> typically to less than 1 ppm. Until the start of the next production run, this value may be lowered even more. What will be the influence of the remaining residual concentrations of 10 to 300 ppb H<sub>2</sub>O<sub>2</sub> on the product? How much H<sub>2</sub>O<sub>2</sub> is adsorbed to the vial? How much H<sub>2</sub>O<sub>2</sub> can be tolerated during filling?<sup>20,21</sup> Instruments and samples are packed in bags during the quick decontamination cycle in transfer airlocks of sterility and hospital pharmacy isolators. Will the H<sub>2</sub>O<sub>2</sub> penetrate the bags or into the products or solutions during the transfer steps, and if yes, how much? This requires a different point of view of the suppliers of equipment, away from strict hardware to more comprehensive process technology.

To reply to these questions, specific test methods for residual concentrations of H<sub>2</sub>O<sub>2</sub> in the ppb range are to be developed. First, the tiny gas concentrations must be made available for standard curves and tests, easily reproducible and stable over several hours. If this succeeds, then penetration studies with product containers, stoppers, and packaging materials will give insight to diffused and adsorbed quantities of hydrogen

peroxide. Such investigations also reveal the desorption behavior of product containers and packaging material allowing a more appropriate selection. In the same way, small quantities of active ingredient are exposed directly to small concentrations of H<sub>2</sub>O<sub>2</sub> to determine the stability of the product under standardized conditions.

When compared to other decontamination reagents, H<sub>2</sub>O<sub>2</sub> offers distinct advantages: hydrogen peroxide is a simple compound and decomposes into two known components with which pharmaceutical products typically come into contact – water and oxygen. The kill characteristic of H<sub>2</sub>O<sub>2</sub> for many different microorganisms on a wide range of materials has been extensively investigated and is well documented.<sup>1,2</sup> Such catalogs already give important information and indications as to the suitability of various materials, to the conditions of decontamination, to potential success or failure. Actual development work in progress, in view of product stability, shall help to identify strengths and weaknesses of packaging materials under exposure to minor concentrations of H<sub>2</sub>O<sub>2</sub>, for both actual and future products. This work asks for complex trace analysis tests requiring special instrumentation and environmental conditions to deliver consistent results. These questions do not only arise for H<sub>2</sub>O<sub>2</sub>, but basically with every decontamination reagent, as those used for conventional cleanrooms or RABS.

Entering the field of trace analysis testing, one has to consider the quality of the air at the point of use, but specifically the supply air. The influence of (unknown) components on the decontamination process, not considered so far, needs to be evaluated (NO<sub>x</sub> from combustion processes) and separated from the effects of the decontamination reagent itself. It may well raise more questions yet disregarded. It looks like the pharmaceutical industry approaches chip manufacturing in the electronic industry: the problems of molecular contamination (impurities) of process gases and air<sup>22</sup> - Figure 6.

## Isolator Technology of the Future

The before-described technological development of isolator technique shall ensure robust, flexible, and well adopted production processes:

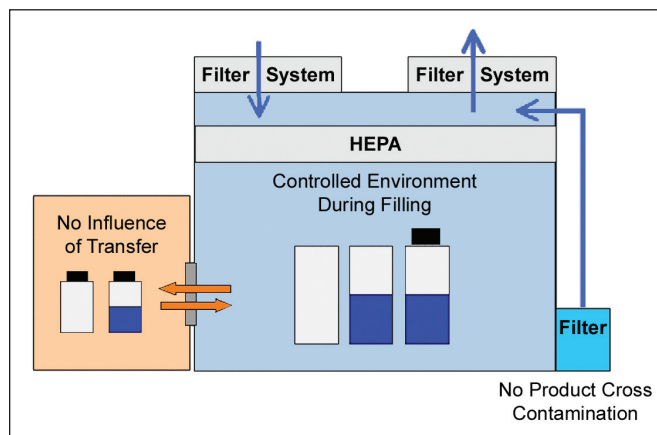


Figure 6. Specific questions to pharmaceutical process technique. Focus here: impact of the process on the product quality during transfer steps and of environmental conditions during filling as well as prevention of cross contaminations.

- The fast decontamination process increases the flexibility and availability of the production line.
- The rapid transfer of materials leaves more time for production and thus permits running larger batches.
- Filter systems that are easily replaceable also increase the flexibility of the production line.

All the scientific research efforts in the field of pharmaceutical process technology contribute significantly to the process quality of isolated production systems:

- The effects of the environment ( $H_2O_2$ ) and of transfer steps ( $H_2O_2$ ) to the product are known and minimized to assure stability and potency of the product.
- The characteristics and behaviour of materials are recognized and considered in the process design.
- The risk of cross contamination is eliminated.

Once the suitability of the process equipment is given for the production process and the factors influencing the process quality are known, specific production systems can be designed that comply with the requirements of high operational availability: to achieve robust process and production quality at an optimum cost-benefit ratio. Nevertheless a third factor is needed to bring the projects to success: corporate responsibility for all the project objectives is the “active pharmaceutical ingredient” to that goal - *Figure 7*.

## Project Responsibility – Key Factor to the Proper Production System

Improvements either through sophisticated hardware and/or perfected processes do not guarantee you will reach the overall objective of a project. A major “inhibitor” is distributed respon-

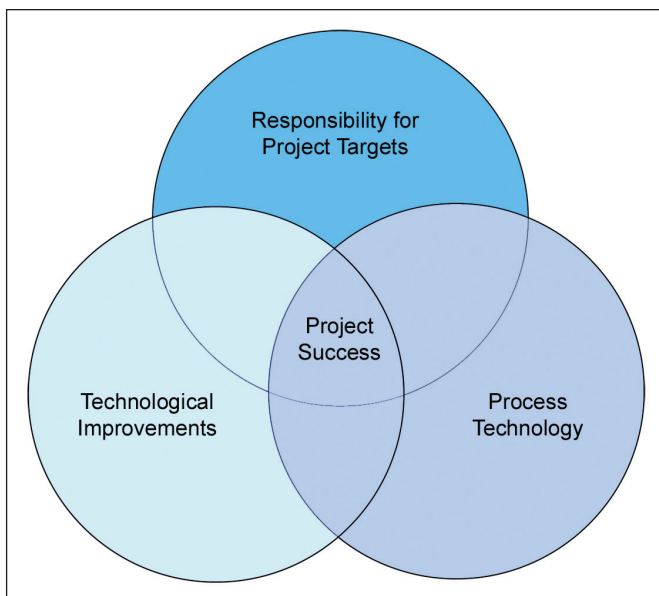


Figure 7. Factors to successfully reach corporate production objectives.

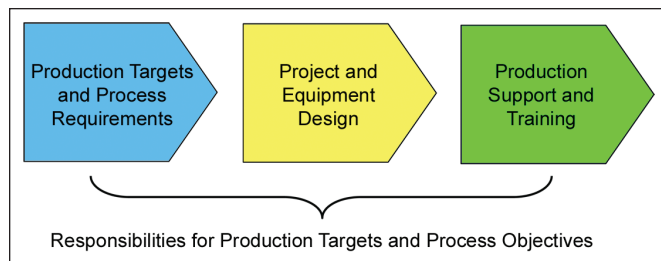


Figure 8. Extended responsibility for project objectives.

sibility: responsibility is assigned for single process steps (to individual specialists), for specific equipment pieces (isolator to supplier) or for process environment (building, HVAC). This often leads to a misunderstanding of the complete process, painful lengthy commissioning, and unsatisfactory output.

It is imperative for every isolator system – either for production, for preparations in hospitals or for sterility testing – that it can be implemented with commercial success. The system fits the objectives only if the projected value is reached in respect to production output at intended cost benefit and with suitable quality. To reach and assure this projected value in the future, a firm and perfect cooperation of all involved groups is needed, as well as an extended acceptance of responsibility for the project. This includes the responsibility for the project objectives, such as production output, production costs, flexibility of production line, and process quality. The responsible individuals:

- take the lead for the project from A to Z, from the idea to the day to day routine production
- need experience for the requirements of the production
- know the individual requirements of production, such as batch size, flexibility, and costs
- are conscious of the complexity of the product and its characteristics to the process
- understand the design of the production line and the opportunities and limits of the specific equipment
- conduct the qualification work and production start with support and trainings
- optimize the production in a concerted way
- and for these reasons, assume full responsibility for the implementation of the production objectives - *Figure 8*

The team play of all three factors – technological development, pharmaceutical process technique, and corporate responsibility for the production objectives – allow for a successful design of isolated production lines that fulfill the future requirements and trends in the pharmaceutical industry: highly economical and with excellent quality, flexible in operation, and the perfect safety when handling valuable active pharmaceutical ingredients.

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## About the Authors



**Volker Sigwarth** studied medical engineering at the Technical University of Ulm and was awarded his degree as Dipl. Ing. (FH) for his investigation of factors influencing hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) decontamination. As a member of the R&D group at Skan AG, he has been responsible for the development, integration, and qualification strategy of the H<sub>2</sub>O<sub>2</sub> decontamination method SIS 700. Sigwarth is author of international, scientific publications in the field of H<sub>2</sub>O<sub>2</sub> decontamination, biological indicators, and isolator technology. As head of the R&D department at Skan AG, he has issued several patent files concerning isolator technology. As Director of Business Development, Sigwarth was leading the Technology Department at Skan AG and was responsible for research and development, microbiological qualification, H<sub>2</sub>O<sub>2</sub> Decontamination, automation, GAMP- and CE- Conformity. Currently, he holds the position of CEO, Skan AG. He can be contacted by email: [volker.sigwarth@skan.ch](mailto:volker.sigwarth@skan.ch).

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**Thomas Huber** received his diploma in engineering at the Federal Institute of Technology in Zürich. After working several years in engineering and project management, he joined Skan AG in 1996 with a full focus on isolator technology. Since then, he was not only involved in the development of isolator technology in general, but also won a broad

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**This article presents the challenges in patient safety risk management for the Patient, US Food and Drug Administration (FDA), Healthcare Provider, and Sponsor. The article reviews specific risk management tools to show how audits can be leveraged by the Sponsor to provide additional patient safety focus and consistency across the medical product supply chain.**

# Standardizing Patient Safety Risk Management

by Mark Cupryk

**W**hile Sponsors must navigate through multiple challenges in today's competitive environment, keeping their medical products safe always tops their extensive "to do" list. The use of medical products, which include drugs, biological products and medical devices, involves balancing the risks versus the benefits for the patient. From medical product development and testing, through manufacturing to patient delivery and care, the safety risks to the patient must be managed continually.

Patient safety accountability for the numerous medical products can be divided across four primary groups – the US Food and Drug Administration (FDA), the Sponsor, the Healthcare Provider, and the Patient as depicted in Figure 1. Each group's unique objectives and constraints have yielded a non-uniform approach to patient safety risk management. However, a convergence of patient safety is evolving at a rapid pace with each stakeholder increasing patient safety communication through new and established communication channels.

The regulatory audit, a significant process in the Sponsor's quality management strategy, helps extract valuable compliance data to mitigate patient safety risks from day one. The purpose of this article is to contrast the challenges in patient safety risk management for the Patient, Food and Drug Administration, Healthcare Provider, and Sponsor and to review specific risk management tools to show how audits can be leveraged by the Sponsor to provide additional patient safety focus and consistency across the medical product supply chain.

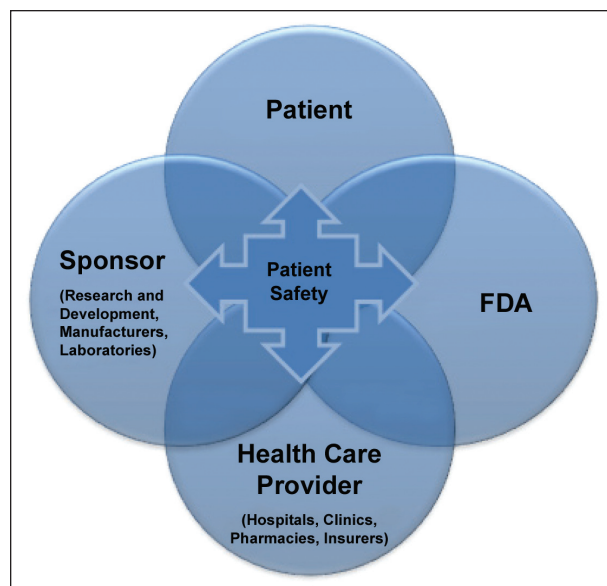
## What exactly is patient safety?

The patient safety domain assumes a sensible consensus about the efficacy of a treatment and focuses on whether these treatments have been delivered safely. For example, the definition can include harm to the patient, incidents that may give rise to harm, processes that increase the likelihood of incidents, and the attributes that help protect against harm and enable rapid recovery when risk escalates.<sup>1</sup>

Unfortunately, too many definitions of patient safety exist and these differences also diminish the focus on its principal elements. Even so, risk management has a governing role in providing strategies to protect the patient.

In 2009, a list of 50 research priority areas in developed, transition, and developing countries was compiled by the World Health Organization Patient Safety group.<sup>2</sup> Figure 2 identifies the top six priorities in developed countries, which can be equated to areas requiring significant improvement. For example, leading research priorities like communication, process improvement, clear safety measures, and adverse events are all representative of the current transformational targets in the US. What's

Figure 1. The four key stakeholders in increasing patient safety.



# Standardizing Patient Safety Risk Management

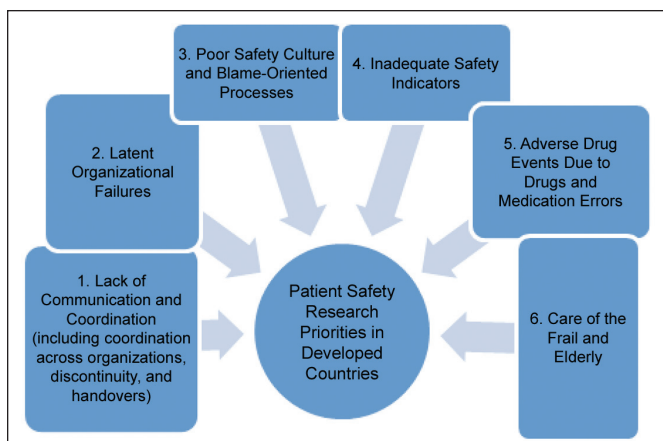


Figure 2. Top global patient safety research priorities in developed countries WHO.<sup>2</sup>

more is that latent organizational failures, such as lacking an adequate risk management strategy for a specific entity perhaps due to deficient procedures and/or training, are high on the research priority and therefore, a opportunity target for improvement.

The question evolves into how best can an organization structure itself to strategically manage the numerous patient safety risk events? A well aligned risk management program can provide the suitable infrastructure by applying continuous monitoring, internal and external audits of varying degrees, and reassessments of its tolerance limits for risk events. An example of such a frame work will be reviewed later.

Currently, each of the four stakeholders is using a number of paper and electronic patient risk communication tools to better manage patient safety as listed in Table A. Because of their unique processes and needs, each group focuses on different aspects of patient safety and they have taken different approaches to reducing and monitoring related risks within their sphere of influence. For example, the FDA and the sponsor evaluate patient safety at the pre-marketing phase through the data reports on the various clinical trial performed. Recently, during the post marketing phase, the communication has expanded into numerous forms of media as well as higher involvement from each of the stakeholders. Social networks, for instance, are driven by each of the four stakeholders and these complex associations are still forming to provide patients with substantial safety data. Higher performing networks will be the patient safety data mines of tomorrow.

## Challenges for the Patient

Each of us is personally involved in patient safety. Today, questions like “What is in this medical product? Are the effects really worth the benefits? Will it actually work? How do I know there is no mix up?” are still only partly answered in real time.

The patient plays an active role in monitoring their own safety. The internet is the preferred communication vehicle for current safety information from the FDA, Sponsor, and Healthcare Provider. Each group has broadened its reach

through diverse virtual hubs due to the realization that communication efforts, such as virtual patient forums for instance, apart from educating about treatment access, reimbursement options, disease complexities, may also provide a positive influence on dealing with the medical condition itself.

On the other hand, to gain more safety information from the patient is still the chief issue. If a patient experiences an effect while being treated, there is always the possibility of playing the symptoms down and relating other causes for the effect such as stress, fatigue, diet, etc. In fact, one in six Americans who have ever taken a prescription drug experienced a side effect serious enough to send them to a doctor or hospital, but only 35 percent were aware that they can report these side effects to the FDA and only seven percent indicated they

Marketing Phase	Medical Product Safety Data Communication	Patient Safety Data Description	FDA	Health Provider	Sponsor	Patient
Pre-Marketing	Pre-Clinical	Data demonstrating that the product is safe for clinical research on human subjects.	✓		✓	
	Clinical Trials Phase I, II, III	Data demonstrating that the product is safe and effective for market.	✓		✓	
Post-Marketing	Phase IV Studies	Data demonstrating that the product is still safe and effective while on market; may also include additional patient types.	✓	✓	✓	
	MedWatch	FDA volunteer safety information and adverse reporting program. Patients can use direct mail, fax, phone, or internet to report an adverse event. Uses form 3500 to capture data.	✓	✓	✓	✓
	AERS and VAERS	Systems containing all medical product adverse events. Vaccines Adverse Events are reported into their own database.	✓	✓	✓	✓
	MAUDE	Manufacturer and User Facility Device Experience Database for Adverse reports involving medical devices. Part of Medwatch, i.e., also uses form 3500 to capture events.	✓	✓	✓	✓
	Sentinel System	System designed to link additional data sources to enable queries on deidentified patient safety datasets of interest to the FDA.	✓			
	Periodic Safety Updates	Medwatch alerts, Drug Safety Podcasts, Quarterly Safety Newsletter, Recalls, Market Withdrawals, and Safety Alerts.	✓	✓	✓	✓
	Safety Announcements	Public Health Advisories, Letters to Health Care Professionals, Information Sheets.	✓	✓		✓
	CMS Data Bases	Centers for Medicare and Medicaid Databases have national coverage of patient safety information.	✓	✓		✓
	Commercial Data Bases	FDA works with commercial organizations to further understand patient safety trends and patterns.	✓			
	Patient Safety News	Televised Series for healthcare professionals regarding safety information on new drugs, biologics, and medical devices.	✓	✓		
	Drugs@FDA	Information on approved medical products.	✓	✓	✓	✓
	Social Networks	Facebook, Twitter, Flickr, etc. are being leveraged to share information to various groups.	✓	✓	✓	✓
DailyMed	Web site giving physicians and patients electronic access to FDA approved drug labels.	✓	✓		✓	
Collaborative Agreements	FDA collaborates with various institutions to further research patient safety trends and patterns.	✓	✓	✓		

Table A. Stakeholders and patient safety risk communication.



would inform the Agency.<sup>3</sup> With soundly designed technological improvements and effective educational campaigns, such reporting statistics will certainly get healthier. However, the main challenge within the Patient Group is securing their safety effect and event communication in a standard and thorough manner so that the other stakeholders as well as themselves reap more benefits. Barriers originating from confidentiality, motivation, and education of the patient will need to be removed.

## Challenges for the Healthcare Provider

In the last decade, healthcare activity focused on understanding the deeper patient safety pains by seeking the root causes and remedying with strategic and tactical countermeasures. In 1999, the “To Err is Human” publication served as the catalyst in highlighting the untold risks of the healthcare system.<sup>4</sup> The frightening numbers echoed – “Almost 100,000 people die in hospitals from preventable medical errors per year.” The visible analogy of a large aircraft crashing every other day loomed. One of the identified key root causes was poor information management practices, such as unconfirmed verbal orders, illegible prescriptions, unanswered telephone calls, and lost medical records.

In contrast, a March 2010 article indicated that the patient safety incidents had not yet declined from 1 million over 2006 to 2008 and that as a result, 10 percent of these incidents resulted in death.<sup>5</sup> Even with the many initiatives undertaken to reduce errors, clearly, opportunity for improvement still exists. To compound the burden, healthcare faces a lack of available nursing and medical expertise, and increasing regulations such as HIPAA.

These challenges have demanded continual improvement by standardizing healthcare data information systems across the nation. For the Healthcare Provider, patient safety information technology has evolved in three main areas.

First, in terms of vocabulary, although there is no single standard, the International Classification of Disease, 9th edition, Clinical Modification (ICD-9-CM), Current Procedural Terminology (CPT) and diagnosis groups are the most widely used for classifying diagnoses and procedures.<sup>6</sup> Second, data interchange standards – how and when healthcare applications exchange and integrate their data – has been led by the Health Level Seven (HL7) Standards. Finally, Health record content standards also progressed by HL7 Electronic Health Record (EHR) Functional Model and ASTM Healthcare Informatics subcommittee’s Continuity of Care Record (CCR) standard.

Also identified by the WHO in Figure 1, determining the right patient safety indicators for proper detection and observation is one of the developed countries’ top research priorities. By carefully transforming its past qualitative culture into quantitative system with measureable patient safety metrics, healthcare evolution albeit slower than desired, persists forward.<sup>7,8</sup> According to McGlynn, there are six challenges for measuring the quality of healthcare – balancing perspectives, defining accountability, establishing criteria, identifying reporting requirements, minimizing conflict between financial and quality goals, and developing information systems.<sup>9</sup>

An example of 21 indicators in Table B for patient safety was derived from a project, undertaken as part of the Organization for Economic Cooperation and Development (OECD).<sup>1</sup> The indicators are important patient safety events perceived as lapse of care in procedural complications, child birth trauma and medication error. At the healthcare level, patient safety indicators have been less about minimizing risk coming from the medical product itself like defects, but more attentive on reducing preventable errors. The Agency for Healthcare Research and Quality (AHRQ), also part of the OECD project, is performing significant patient safety indicator research including using composite measures.<sup>10</sup> However, the defect indicators are still low priority and a barrier to an overall view of the patient safety risk continuum. One additional data challenge is reconciling the hospital diagnosis data with the billing data to get patient safety indicators that reliably identify adverse hospital events.<sup>11</sup>

Many Lean Six Sigma initiatives are focused on the Healthcare Provider’s priority of reducing preventable errors and providing better communication. Using a data driven approach to better understand the issues has reduced blame-oriented processes. Cycling the event information back to the public is also not being taken lightly by the government. For example, California has already implemented penalty clauses for not making adverse event information available to the public in required time.<sup>12</sup>

## Challenges for the Sponsor

While delivering quality medical products meeting its established specifications, the Sponsor is facing its own obstacles in reducing patient safety risks.

First, the relentless increase in medical product counterfeiting is estimated globally at \$75 billion to \$200 billion.<sup>13</sup> The countermeasures include remarkable attention to the protection of each step in the medical product supply chain

Domain	Domain Name	Patient Safety Event
1	Hospital-acquired infections	1. Ventilator pneumonia 2. Wound infection 3. Infection due to medical care 4. Decubitus ulcer
2	Operative and post operative complications	5. Complications of anaesthesia 6. Post-operative hip fracture 7. Post operative pulmonary embolism or deep vein thrombosis 8. Post-operative sepsis 9. Technical difficulty with procedure
3	Sentinel Events	10. Transfusion reaction 11. Wrong blood type 12. Wrong-site surgery 13. Foreign body left in during procedure 14. Medical equipment-related adverse events 15. Medication errors
4	Obstetrics	16. Birth trauma - injury to neonate 17. Obstetric trauma - vaginal delivery 18. Obstetric trauma - Caesarean section 19. Problems with childbirth
5	Other care-related adverse events	20. Patient falls 21. In-hospital hip fracture or fall

Table B. Patient safety indicators from OECD project.<sup>10</sup>

# Standardizing Patient Safety Risk Management

from “factory to finger.” Database software cleverly coupled with radio frequency devices lead as the mainstream solution. Such innovative technology not only reduces the risk of counterfeiting, but it enables data transfer from each supply chain participant including the collection of patient’s safety information.

Manufacturing and design defects leading to lawsuits is another concern, especially in hard economic times. In 2009, the top five verdicts of the U.S. market rose 52 percent in total value to \$620 million, indicating a trend toward more favorable outcomes to the plaintiffs.<sup>14</sup>

From a survey of 538 life science companies, the major problem for pharmaceutical manufacturing is accessing and analyzing the process data. Forty-six percent of records are still in paper formats. Variability, also identified as a high risk ailment in manufacturing by 60 percent of participants, is now under aggressive treatment.<sup>15</sup>

In the past five years, one of the contributors for better risk management has been the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use with ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management and ICH Q10 Quality Systems. ICH Q9 provides the scientific tools and guidance for continual improvement to diminish potential patient risks coming from manufacturing, and development, both of which are also supported by ICH Q10 and ICH Q8, respectively, as shown in Figure 3.

In particular, the ICH Q9 provides a solid framework on the “what” of the quality risk management process.<sup>16</sup> It establishes a defined process through risk assessment in terms of identification, analysis, and evaluation; risk control in terms of reduction, acceptance; risk review, risk communication, and risk tools. Annex I provides the “how,” that is, Risk Management Methods and Tools, which in fact embrace the Lean Six Sigma toolset and methodologies including examples. Annex II, Potential Applications for Quality Risk Management, offers consideration on “where” to focus the risk management efforts. ICH Q10’s guidance, based on ISO norms quality system, runs across the entire medical product cycle. ICH Q8 supports the science behind pharmaceutical development.

Sponsor driven technology changes from paper to electronic

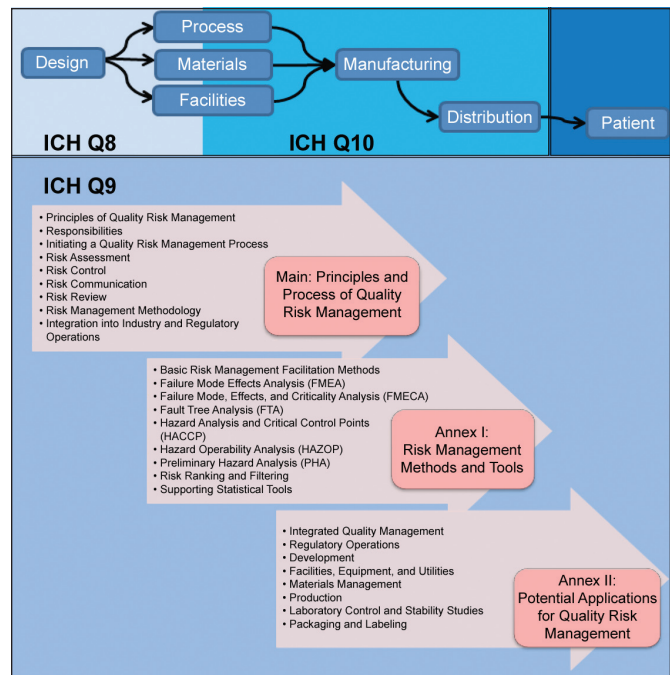


Figure 3. ICH Q9 guidance for risk management.

submissions have led to the Study Data Tabulation Model (SDTM) developed by the Clinical Interchange Standards Consortium (CDISC). The content of SDTM is typically exchanged by ASCII, HL7 v3 and SAS Transport files to the FDA.<sup>17</sup> Hence, the adverse events during pre-marketing also can be cataloged and analyzed electronically by the Sponsor and submitted to the FDA.

In manufacturing, process parameters are typically monitored using Programmable Logic Controllers (PLC) and Distributed Control Systems (DCS). ISPE’s GAMP 5 provides guiding principles and practices on ensuring product quality. These plant floor control systems are usually developed and configured with ANSI/ISA-88 (S88) standard and IEC 61131. S88 provides the models, terminology, data structures, and guidelines for language, recipes, production records and unit states. Also, ISA-95 and IEC 62264 are both international standards for enterprise control system integration, which provide consistent terminology for communications,

No.	Risk Identification	Risk Description	Potential Risk Impact
1	Product Defects	Product defects have been an important source of medical product-associated injuries. In pharmaceuticals, product defects are usually a lack of potency and lack of purity of drugs.	Preventable Adverse Events
2	Medication or Device Error	Medication or device errors involve the incorrect administration of the prescribed product or incorrect operation or placement of a medical device. Errors also can involve the unintended substitution of the wrong product for the prescribed product. These errors are often a result of a sequence of errors within the health care system.	Preventable Adverse Events
3	Known Side Effects: 1. Avoidable 2. Unavoidable	When using a drug or medical device, a patient has the risk of potential reactions from the medical product. These known side effects usually have been identified and are indicated as possible risks in a product’s labeling. Unavoidable known side effects are the source of the majority of injuries and deaths resulting from product use. Unavoidable known side effects are the price for the benefits of the medical product. Some known side effects are predictable and avoidable.	Preventable Adverse Events and/or death
4	Remaining Uncertainties	A degree of uncertainty always exists about both benefits and risks from medical products. Several types of uncertainties exist - unexpected side effects, long term effects, off label use effects, and unstudied populations.	Death and/or Unexpected Adverse Events

Table C. Categories of risk from medical products.<sup>20</sup>

information and operational models between enterprise and manufacturing systems. Manufacturers have been joining their internal disparate information systems, in order to provide real-time capabilities to effectively manage product defects through traceability of lots to raw materials, equipment utilized, personnel involved, and distribution points.<sup>18</sup>

## Challenges for the Food and Drug Administration

In the US, the FDA conducts monitoring of the patient safety risks associated with medical products through an extensive premarketing review and a series of post marketing programs.<sup>19</sup> Sources of risk related to medical product have been traditionally identified in four categories: product defects; known side effects, both avoidable and unavoidable; medication or device errors, and remaining uncertainties are shown in Table C.<sup>20</sup>

The FDA relies heavily on the Healthcare Provider, Sponsor, and Patient to communicate events associated with developed, manufactured, prescribed, dispensed, and/or used medical products. The patient safety risk monitoring challenge for the FDA has been the fragmented data systems providing partial visibility of the numerous medical products. The FDA is currently focusing on various medical product safety initiatives with adverse events leading the roll as shown in Table D.

In 2009, the FDA entered 490,835 AEs in their Adverse Event Reporting System (AERS). The AERS is designated to support all post marketing safety surveillance for approved drug and therapeutic biologic products. Various obstacles are preventing the capture related to adverse events.<sup>21</sup> Such “near miss” data is instrumental in detecting causes leading to more serious and/or even catastrophic conditions. The FDA driven MedWatch program has improved the capability of post-marketing reporting with the Adverse Event Reporting System (AERS) and the use of Form 3500 (FDA-regulated

No.	FDA 2010 Medical Product Safety Objectives
1	Increase the proportion of healthcare organizations that are linked in an integrated system that monitors and reports adverse events.
2	Increase the use of linked, automated systems to share information.
3	Increase the proportion of primary care providers, pharmacists, and other healthcare professionals who routinely review with their patients aged 65 years and older and patients with chronic illnesses or disabilities all new prescribed and over-the-counter medicines.
4	Increase the proportion of patients receiving information that meets guidelines for usefulness when their new prescriptions are dispensed.
5	Increase the proportion of patients who receive verbal counseling from prescribers and pharmacists on the appropriate use and potential risks of medications.
6	Increase the proportion of persons who donate blood, and in doing so ensure an adequate supply of safe blood.

Table D. Medical product safety objectives of FDA for 2010.

drugs, biologics, medical devices), while the Vaccine Adverse Event Report System (VAERS) maintains the vaccine adverse event information. These systems are leveraged by both Patient and Healthcare Providers so that both the FDA and the Sponsor can take the required action to protect other patient populations in a timely manner.

## Standardizing Patient Safety Risk Management

Quality by Design (QbD) is envisioned as the Sponsor’s next scientific game changer. Understanding how quantitatively the ranges of each process parameter correlates to the quality attributes of medical products will enhance the boundaries of development, i.e., the design space.

The Sponsors are refining their understanding of these relationships with a vision of greater manufacturing flexibility.<sup>22-25</sup> Case in point, multivariate predictive distribution using process parameters as inputs can help quantify the

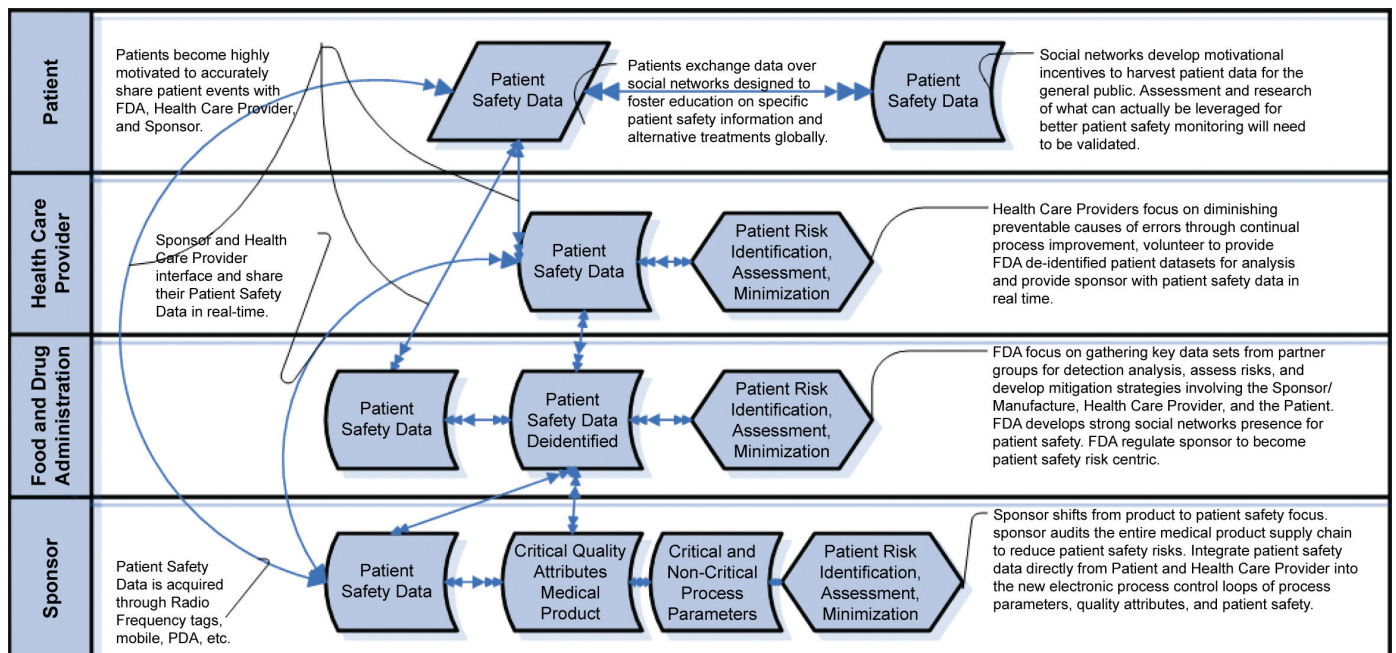


Figure 4. Patient safety risk management.

multiple quality responses so that the manufacturer has a broader band in which to manipulate their processes.<sup>26,27</sup>

In their next revolutionary leap, the Sponsor must expand the design space to incorporate the monitoring and correlating with actual patient effects and events in real time during both marketing phases. Such a tremendous enlargement of the design space will provide a safety process control model for patient safety awareness from product creation to treatment as depicted in Figure 4.

Much of the infrastructure is already work in progress at the stakeholder level, nevertheless, such a transformation will require the design build interface plan for secure real-time communication between Sponsor and their supply chain Healthcare Providers' information systems, including a consensus on vocabulary and data interchange standards on patient safety information.

## Patient Safety Risk Management Audits

Much like the results of FDA inspections, the data points detected and collected from regulatory audits performed by the Sponsor at specific phases of the medical product supply chain provide insight on the performance of their internal and partner clinical studies, laboratories, and manufacturing. Not only is the compliance level of each Sponsor partner vis-à-vis the pertinent regulatory requirements gauged; but the retrieved audit data helps forecast events for future medical product development and manufacturing. As mentioned, the current focus must shift to patient safety risk management.

Various challenging questions confront the Sponsor organization when optimizing the yields of their regulatory audit efforts:

- What strategy and tactics to implement at the enterprise and regulatory levels?
- To what degree and how should resources be allocated horizontally and vertically across the different risk areas?
- Where and when in the supply chain should the emphasis be placed?
- What document content details should be emphasized and to what depth of verification?
- What methods should be used to execute and report the verifications?

## Coarse Adjustment to Enterprise Risk Management

Before focusing the audit lens onto patient safety risk management, the coarse adjustment knob must be turned to sharpen the image of the entire enterprise risk management process. According to the Committee of Sponsoring Organizations of the Treadway Commission (COSO), enterprise risk management is a process, ongoing and flowing through an entity, applied in a strategy setting across the enterprise at every level and unit, designed to identify potential events that may affect the entity, and manage risk to be within its risk tolerance, to provide reasonable assurance regarding the achievement of entity objectives.<sup>28</sup>

The COSO framework for achieving the objectives of en-

terprise risk management is broken down into:

- **Strategic:** high level goals, aligned with and supporting enterprise's mission.
- **Operations:** effective and efficient use of its resources.
- **Reporting:** reliability of reporting in both financial and non-financial information.
- **Compliance:** compliance with the applicable laws and regulations.

An effective audit program will identify the targeted patient safety risk areas, but a step back to frame the big picture will ensure alignment and clarity of its objectives. Alignment is accomplished through periodic evaluations of audit plans against business objectives and risks, as well as a clear mission and role definition communicated throughout the organization.

To the enterprise, risk is the probability for loss, damage injury caused by an error, fraud, inefficiency, non compliance, or other type actions. The organization must perform an overall enterprise risk assessment to prioritize its auditing efforts and achieve a shared understanding among the various stakeholders. Annex II<sup>1</sup> of the ICH Q9 Quality Risk Management includes factors for consideration listed in Table E. Additional factors from the Healthcare Provider and the Patient also must be taken into consideration.

## Fine Adjustment to Patient Safety Risk Management

Once enterprise risk management is aligned and focused, the Sponsor can adjust its sights onto the patient safety risk targets. Audits are not only a regulatory requirement, but they make business sense, and should be carefully planned in terms of effort and method to derive decision making information from the medical product supply chains.<sup>29</sup> Moreover, the audit costs compound quickly, hence, planning will allow for efficient patient safety risk reduction.

Recent technology, increasing partnering, additional regulatory guidance, and commercial economic pressures have

No.	Factors for Determining Frequency and Scope of Audits
1	Existing legal requirements
2	Overall compliance status and history of the company or facility
3	Robustness of a company's quality risk management activities
4	Complexity of the site
5	Complexity of the manufacturing process
6	Complexity of the product and its therapeutic significance
7	Number and significance of quality defects (e.g. recalls)
8	Results of previous audits/inspections
9	Major changes of building, equipment, processes, key personnel
10	Experience with manufacturing of a product (e.g. frequency, volume, number of batches)
11	Test results of official control laboratories

Table E. ICH Q9 factors for determining audit scope and frequencies.<sup>16</sup>

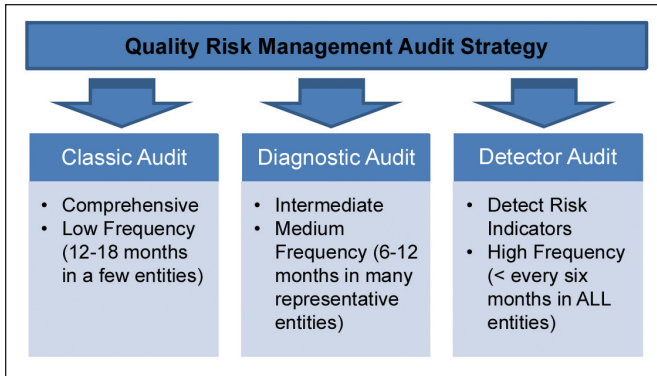


Figure 5. Three prong audit data collection, analysis, and detection strategy.

promoted risk management into the regulatory compliance limelight. Auditing expectations have leaped from traditional sampling of typical GxP risk areas and Corrective Action/Preventive Action plans to sophisticated approaches, partly real time monitoring in nature, combined with predictive analytics, continuous improvement, pattern assessments, and risk priority numbers. Combining the classic, diagnostic, and detector audit to balance cost and benefit efforts in risk management, results in a structured audit strategy using the right tools with the right timing as depicted in Figure 5.

To audit for patient safety risks of every medical product, at every step of each process at each location is unrealistic. Therefore, an up-to-date view of the patient safety risks for each entity according to geography, relevant processes, and medical product as shown in Figure 6 is more pragmatic. The Failure Mode and Effects Criticality Analysis Risk Priority Number (FMECA RPN) is an excellent quantitative method for establishing such prioritization. Sponsor groups are already engaging in such activities, but their center of attention is still on the risks of their medical products. They will need to extend their bandwidth to extract and assess the Healthcare Provider and Patient safety event data to

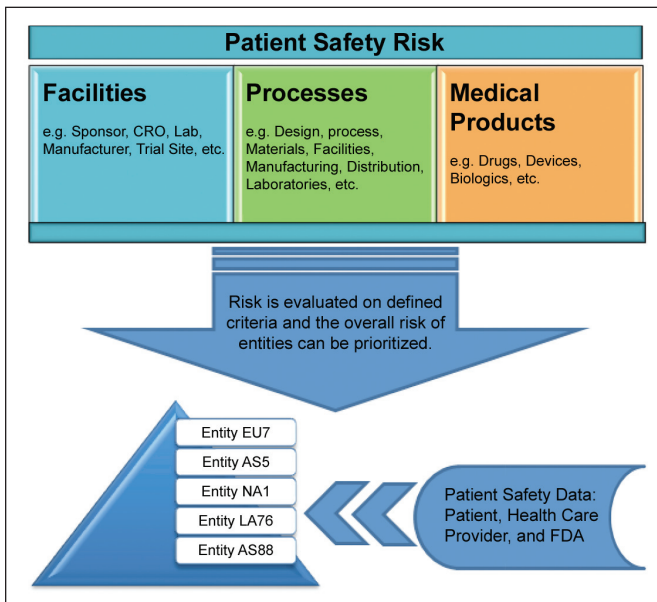


Figure 6. Entity patient safety risk prioritization.

gather indicators and/or other type of patient safety data to strengthen their own internal patient safety risk knowledge base. For example, some errors identified as preventable at the Healthcare Provider stage could possibly be redesigned by the Sponsor with a Poka-yoke or mistake proofing capabilities. Eventually, even real-time adjustments could be made to the manufacturing processes from event and effect data received from the patients.

## Determining Patient Safety Risk Criticality of a Patient Safety Risk Event

Risk criticality is determined by the likelihood of a patient safety risk event occurring and the severity of its impact. Figure 6 illustrates an example of a tool used for assigning a patient safety risk criticality value of Extreme, High, Medium, and Low for a particular risk event.

Numerous variations for assessing risk criticality exist and it would be essential that a standard for severity of impact be developed and used for patient safety risk criticality across the medical product supply chain. MedWatch Form 3500 criteria could be revised slightly to a standard scale of outcome and effect capture. By means of a check box, the current form captures adverse events outcomes that are serious in nature such as death, life-threatening, hospitalization, etc.<sup>30</sup> Establishing a 10 point severity of impact scale would help standardize the approach and allow the risk managers to automatically integrate the data into both their risk criticality assessments and their Risk Priority Number assignment.

Let's consider an example of the patient safety risk event of informed consent failure, i.e., informed consent not being executed to the regulations at a specific investigating site (entity) for a study of 1,000 patients over two sites in two countries. Table F provides a number of different guides that the risk manager could use to evaluate risk likelihood for the particular event.<sup>31</sup> These can be description based, time or probability based. Such practical guidance leads to a consistent assessment of likelihood across the various entities by different risk managers. Otherwise, the risk management process will lose its equilibrium and efforts will not be distributed

RISK = Severity * Likelihood (L, M, H, E)		Likelihood of Occurrence (Very Low = 1 to Very High = 10)										
		1	2	3	4	5	6	7	8	9	10	
Severity (1 - 10)	Catastrophic	10	M	M	M	H	H	H	E	E	E	E
	9	M	M	M	M	H		H	E	E	E	E
	Major	8	L	M	M	M	H		H	H	E	E
	7	L	M	M	M	M	H	H	H	H	E	E
	Moderate	6	L	M	M	M	M	M	M	H	H	H
	5	L	M	M	M	M	M	M	M	H	H	H
	Minor	4	L	L	M	M	M	M	M	M	M	H
3	L	L	M	M	M	M	M	M	M	M	M	
Negligible	2	L	L	L	L	M	M	M	M	M	M	
1	L	L	L	L	L	L	L	L	L	M	M	

**Risk Criticality Scores**

- Low (L) = 1 - 8
- Medium (M) = 9 - 36
- High (H) = 37 - 64
- Extreme (E) = 65 - 100

The entity's Event A has Medium Risk

Figure 7. Patient safety risk criticality assessment.

# Standardizing Patient Safety Risk Management

Rating	Description	General Conditions	Time Based Conditions	Probability Conditions	Informed Consent Failure
1					
2	Rare	Will probably never happen/recur.	Not expected to occur for years.	< 0.1 %	Consent not necessary/ special case complies with regulations.
3					
4	Unlikely	Do not expect it to happen/recur, but it is possible it may do so.	Expected to occur at least annually.	0.1 - 1 %	Clearly defined and documented informed consent process with responsibilities identified by individuals/roles.
5					
6	Possible	May happen/recur occasionally.	Expected to occur at least monthly.	1 - 10 %	Unclear process i.e. not documented. Responsibilities of who does consent is not documented. Risks to patient/subject not documented. Unclear areas on informed consent form.
7					
8	Likely	Will probably happen/recur, but it is not a persisting issue.	Expected to occur at least weekly.	10 - 50 %	Consent does not cover all aspects of the study/research. Inexperienced/inappropriate staff delegated to informed consent process. No explanation of recruitment process. No identification of potential risks or hazards. Subject/Patient required to consent the same day.
9					
10	Almost Certain	Will undoubtedly happen/recur, possibly frequently.	Expected to occur at least daily.	> 50 %	Prior instances of poor consenting process, execution and procedures. Documented in 483s or other finding sources - internal audits.

Table F. Various examples for assigning likelihood score.

according to the appropriate priorities. Using Figure 7, the risk manager would assign a rating of “Negligible” or “2” as the informed consent failure risk severity to the safety of the patient. If the likelihood of the informed consent failure would be described as “8” per the “Informed Consent Failure” guidance example provided in Table F, then the patient safety risk criticality ranking would be Medium (M) with an overall score of  $2 \times 8 = 16$ .

## Determining the Risk Priority Number (RPN)

Once criticality for a patient risk event has been determined, the next step is to establish its detectability as shown in Figure 8. Higher detection by controls and/or indicators will lower the detection score, i.e., a score of “1” is equal to almost certain that the event will be detected by some kind of key

indicators to a score of “10” where the event cannot or will not be detected as shown in Table G. For the informed consent failure example, if in our informed consent activity is paper based, then the Sponsor cannot detect the event. The informed consent failure will not be detected so its detectability would be a ranked as “10.” The overall RPN for the particular event would be equal to  $16 \times 10$  or 160.

The various risk events RPNs are combined and analyzed by entity, by process, by product, entity type, stakeholder, etc. Analogous to process control systems with critical process parameters, alarms also should be associated with the Risk Priority Numbers to ensure that the priorities remain up to date. Improvements in detection also will help reduce the priorities of certain activities such as the more expensive classic audits. Such an RPN structure should not only be ap-

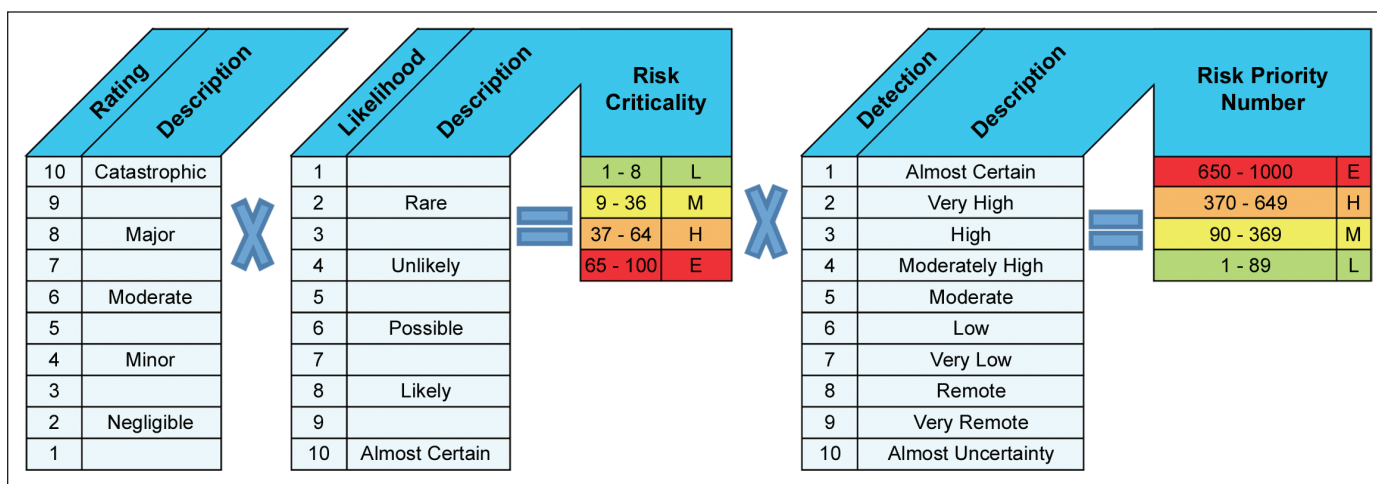


Figure 8. Patient safety risk priority number (FMECA RPN).

Rank	Detection	Likelihood of Detection by Indicators and Other Controls
1	Almost Certain	Controls will almost certainly detect a potential cause/mechanism and subsequent failure mode.
2	Very High	Very high chance the controls will detect a potential cause/mechanism and subsequent failure mode.
3	High	High chance the controls will detect a potential cause/mechanism and subsequent failure mode.
4	Moderately High	Moderately high chance the controls will detect a potential cause/mechanism and subsequent failure mode.
5	Moderate	Moderate chance the controls will detect a potential cause/mechanism and subsequent failure mode.
6	Low	Low chance the controls will detect a potential cause/mechanism and subsequent failure mode.
7	Very Low	Very low chance the controls will detect a potential cause/mechanism and subsequent failure mode.
8	Remote	Remote chance the controls will detect a potential cause/mechanism and subsequent failure mode.
9	Very Remote	Very remote chance the controls will detect a potential cause/mechanism and subsequent failure mode.
10	Absolute Uncertainty	Controls will not or cannot detect a potential cause/mechanism and subsequent failure mode.

Table G. Likelihood of detection ranking.

plied to the Sponsor, but extend to the Healthcare Provider and Patient.

## Conclusion

With modern technology, the medical product stakeholder's information boundaries are slowly eroding and enabling a convergence on patient safety communication. The patient safety data will be harnessed effectively and the next steps will be to ensure consistency in risk management across the medical product supply chain. The Patient along with the FDA, Healthcare Provider, and Sponsor, each have a critical role in increasing the strength of patient safety information.

The following actions must materialize for a uniform Patient Safety Risk Management paradigm to take shape:

1. The patient must be motivated to report timely and accurate adverse event related to the use of their medical products.
2. The FDA must regulate the shift from product to patient centric for the Sponsor.
3. The Sponsor must motivate sharing of patient safety data inputs from both the patient and Healthcare Provider. To make it possible, the Healthcare Provider, and Sponsor must establish a standard for communication of patient safety information across their different types of information networks.
4. The sprawling social type networks must be harvested to create a customer driven model and drive more reliable patient safety communication.

5. The Sponsor should extend and leverage various types of strategic regulatory audits to monitor the reduction of patient safety risks from the development of their products through to their intended use.
6. A standard methodology should be mandated for the collection of patient safety data indicators and events so that patient safety risks are managed uniformly in terms of severity impact, likelihood, and detectability, potentially, using the Risk Priority Number as a basis for comparison.

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## About the Author



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This article shows how a BPM-based Quality Management System optimizes the way to comply with today's evolving regulations and standards, while being even more competitive in the marketplace.

# Business Process Management (BPM) Based Pharmaceutical Quality Management Systems: A Win-Win Between Compliance and Competitiveness

by François Versini

**W**hile quality in healthcare has always been a priority, recent guidance, namely ICH Q8, Q9, and Q10, indicates a new direction for organizing the system that enforces and guarantees the quality. Many working groups in many countries have chosen this topic and are trying to establish an appropriate approach for this new direction. The purpose of this article is to explain the new concepts, demonstrate how such a system may be implemented, and present the potential opportunities of adopting this approach.

## Quality and Quality Management Systems under Scrutiny

In regard to product quality, problems such as stability or formulation are outlined on authorities' Web sites<sup>1</sup>; other articles question the quality of generics; others state that some fundamentals of quality management can be and should be enhanced, including traceability and data sharing throughout the supply chain and with the authorities.

In regard to global processes for quality assurance (company governance policies; corrective and preventive actions process, annual product review, clinical, or vigilance, etc.) there is information coming out that discusses new stringent expectations from authorities moving from end product control to process understanding.

At the same time and to support these products and product-related processes, attention is given to the information systems and the associated working methods to be deployed, including electronic documentation systems

for the procedures, events and actions tracking and management systems, information systems validation, etc.

And last, but not least, there is new international guidance (such as ICH) available meant to improve the quality system organization. These guidances, however, have generated a wide range of misunderstanding, comments, and advice from the different parties involved. This article provides three reasons why this is the case.

1. Individuals are not talking about the same topic. They are not using the same definitions or philosophies. Therefore, the first thing that needs to be done is to define the different layers of the Quality concept.
2. Individuals are not looking at the topic from the same angle, which gives them different perspectives of what is possible and desirable. Some of the concepts may be handled by other departments, instead of the Quality function. Therefore, it is important to define the Quality Systems essentials and what departments need to be involved. It is important for all individuals to understand that different functions need to work together to make this happen.
3. Individuals with no experience with this type of process can find it difficult to imagine what process-based documentation can look like. Therefore, instead of describing theoretical cases, this article will present figures inspired by real examples.

The following discussion will demonstrate a specific way to structure a Quality System in

the pharmaceutical industry, integrating the three following logics:

- **Logic of Compliance:** ensuring all requirements and priorities for health and patient safety are considered and to answer what the inspection systems are waiting for.
- **Logic of Competitiveness:** at the opposite of what is usually thought, compliance and performance are usually connected in a positive way. When compliance requests make a big investment necessary, it is the same rule for everyone, which means that it does not generate a competitive disadvantage to anyone. Also, Compliance gives the right to enter a market, thus creates value, and is always profitable in the long run. In addition, an improvement in the manufacturing process, for example, often brings an improvement both in terms of profit and in product consistency and quality control.
- **Logic of Capitalization of Competencies, Knowledge Management, Business Process Modeling, and Management:** a system is to be thought of as a systemic topic, built with a systematic approach, ensuring that what is done is solid and will be the basis for future steps, combining all of the company's dimensions.

People often oppose those dimensions, thinking that an effort in one of them will jeopardize the other.

"I don't have the time to think about optimizing that domain. I am not concerned by these topics, which are not being inspected. I need to focus on the certification in XX months." "We should develop a workgroup to optimize that domain, and we'll pass the chosen solutions through the quality department and regulatory affairs in the end to ask them if what we set up is acceptable." "Let us begin with this first step. We'll think about the rest later, we have no time to document it all..."

It is such a pity to function in compartmented departments, in compartmented objectives, whereas having everyone on board would result in better ideas for all departments and all objectives. Maybe a workgroup for optimization will find a way to achieve conformity through a simple process; maybe the quality person, if participating in the group, will say that the operational people have an exaggerated idea of the constraints and that a win-win solution for both inspectability and operations is possible; maybe being courageous enough to build a structured documentation will save a lot of time when preparing for inspections and give opportunities to optimize.

Experiences in industries like the automotive sector or the food industry show how much it pays off to follow that road. Seneca<sup>2</sup> stated: "It is not because things are difficult that we do not dare; it is because we do not dare that they are difficult."<sup>2</sup> The key is in the synergy. We must stop thinking these are efforts in addition to what we already do. These are efforts that replace other efforts that we had planned, and that allow us to eliminate far bigger efforts that we would have had to do. Do we prefer simple projects that generate complicated processes or projects that deal with complexity in order to generate simple processes?

## Compliance, Competitiveness, Competencies... a Challenge and a Potentially Dramatic Winning or Losing Strategy *What is Quality in the Pharmaceutical Industry and Elsewhere?*

The purpose of the Quality System in the healthcare sector is to maximize health and patient safety. An important objective is inspectability and auditability. Authorities have the power to decide whether the pharmaceutical company may continue its activity or not. Nevertheless, the inspection mustn't become the purpose as such; it is an objective and a tool, connected to the purpose, which is health and safety.

The best way to manage quality: *Plan, Do, Check, Act*<sup>5</sup> and *say what you do, do what you say*.<sup>9</sup> The firm creates documentation that illustrates what is done and the inspection body will conduct a two-step verification process, including confirming whether the documentation is compliant with the regulations and whether the practice is in line with the documentation. Then the inspectors and auditors will identify gaps and areas for improvement.

This is a proven way to manage quality. It is important, however, that the tool doesn't overshadow the objective. The documentation is not produced solely for the inspector. It must be a good representation of the actual practice, a good tool to train qualified individuals, an opportunity to improve, and to ensure that activities are aligned with the purpose.

Quality Assurance in the pharmaceutical industry has been very advanced for more than 40 years, essentially driven by this very high objective, health and patient safety, very detailed regulatory guidance, a very structured inspection system, an obligation for qualified individuals to take responsibility, and some very rigorous regulated processes.

Those elements have been the lever for continuous improvement and high compliance. Compliance will reach a new level in each and every silo in the industry as interfaces and global governance continue to improve.

The industry has now reached a turning point, particularly with ICH Q10, giving guidance for the Pharmaceutical Quality System, and GAMP 5, reaching a new maturity level for the compliance and validation of computerized systems. The new route is defined and designed to combine the advantages and experience from inside and outside of our industry.

The history of quality is a long one in the industrial world, from the Ford and Taylor time, through Deming and Juran, to Toyota and Welsh.<sup>3-8</sup> The following will provide a summary of some major elements which have a large impact on the pharmaceutical industry now and in the foreseeable future.

Quality was not a major subject before the beginning of the 20th century, as there were fewer products than customers. Even low quality products could find a market. The first priority was productivity. Nevertheless several quality tools have appeared at that time, even if mainly aimed at productivity, such as statistics and a form of process improvement. Ford<sup>3</sup> and Taylor<sup>4</sup> are the most well known examples.

Quality became a concern as soon as the quantity of manufactured products surpassed the number of potential customers. The first quality wave created quality laboratories

in the factories, which allowed workers to perform tests and sort products, thus minimizing the percentage of bad products reaching the customer. A second wave professionalized the “inspection type” control with an advanced way to use statistics and perform process control. The third wave built documented systems with instructions and procedures, allowing for audits and coordination. It ended up with building an assurance type of logic with prevention rather than correction, anticipation rather than reaction, e.g., auditing suppliers to verify, before selecting them, that they will be able to deliver the desired quality, and management reviews to plan and review what is important for quality, etc.

In fact, in the middle of the 20th century, quality evolved drastically, based on the principles imagined or re-worked by two American “gurus”: Deming<sup>5</sup> and Juran<sup>6</sup>; when Japan became a very dangerous competitor, managers from Europe and the US went there to see how the Japanese companies had transformed themselves from very low quality suppliers to best-in-class companies.

They discovered that one major root cause of this revolution was the fact that they had listened to the lectures of Deming and Juran, and had put into practice their ideas, while western countries had put their books with much respect on their library shelves.

One dilemma raised by Juran<sup>6</sup> in his conferences was the following: companies without a quality lab need to create one, but companies with a very advanced quality lab should work on downsizing it. An inspection step positioned after production may become an obstacle for defects prevention and production operators accountability. Such ideas are not to be implemented the same way by highly regulated sectors and classic businesses; nevertheless prevention and operators accountability are major concepts. Directly linked to these ideas and the way Japanese firms had implemented it, a “fourth wave” put human beings back in focus, by stating the following: “...it is with the ideas and the dedication of every operator that quality can be built and training people on quality and problem solving tools will allow for continuous improvement.”

By the end of the 20th century, the “Quality Management Systems” wave was aimed at:

- integrating all dimensions, e.g., Quality, Hygiene, Security and Environment (QHSE)
- improving the ways to design and develop products
- reducing the percentage of product defects to a very low number (Six Sigma)
- optimizing not only the product and the manufacturing process, but all processes of all departments, interfaces between all departments, and within the whole organization (e.g., Total Quality Management, Lean Six Sigma)

One main example of “Total Quality Management” success is Toyota<sup>7</sup>, and more recently what General Electric<sup>8</sup> achieved thanks to the Six Sigma methodology. These evolutions took place parallel to the rise of “Business Process Management,” which generalized to the company level the techniques that

were used in quality at the shop floor or departments levels. BPM brought the necessary tools to get rid of the functional silos, and making it possible, in far more efficient ways, to pilot the processes and the performance of a company.

Parallel to this evolution, the way to document the system also has been improved and it has reached a very helpful and recognized model, with ISO 9000.<sup>9</sup> That major standard has been taken as a template for other disciplines, such as environment, safety, etc. which makes it simple now to create an integrated management system combining all purposes without creating burden of documentation.

Why is this history of Quality so important? In order to better evaluate the importance of a concept, listing the obvious advantages is sometimes less relevant than analyzing the consequences of it being done poorly or not done at all.

Quality is all about doing things right the first time. This means that the process must be built in a perfect manner before performing it, checked and evaluated during the execution and afterward, and lessons must be learned from the results and the way it has been reached to improve it for the future and to build knowledge and competitive advantage. This is nothing new, it is the famous and enlightening *Plan, Do, Check, Act* of Deming,<sup>5</sup> but it is like a popular song: we remember the tune so well that we tend to forget the sense of the words...

## Quality Essentials

We will now consider the main issues at the product level, documentation level, and process and system level:

- **Product Quality:** this is the historical focus of the regulatory system in the pharmaceutical industry. It provided a very high level of requirements and achievements thanks to the hard work of pharmaceutical companies and the surveillance and inspection of the regulatory bodies.
- **Quality Documentation System:** the national regulatory codes and the “good practices” force pharmaceutical companies to describe how they answer the requirements in procedures and instructions, and to keep very well defined records on product and test data and on the traceability of compliance with the procedures.
- **Quality Management System and Processes:** all the processes and documentation set up to ensure the quality of the product and of the practices constitute a system. ICH Q8, 9, and 10 focus on creating a real Management Process, built on approaches, such as Business Process Management (BPM), Risk Management, etc., that combine all the historic strengths of the pharmaceutical industry with the enhancements of the concepts from other industries.

The following sections address the issues we typically face at these various levels.

## Product

At the product level, lack of acceptable quality is expensive: out of specification products that go to the bin, work on deviation or re-qualification to save it. We all heard the question “Why

do we have no time to do the things right, but we have the time to re-do them when they have been done wrong?"

Benchmark companies succeeded in getting out of the vicious circle of correcting instead of anticipating and preventing waste. Low product quality costs a lot. In addition, product quality is essential, an entrance barrier into the market. A company that can't prove to the authorities that the product quality is ensured loses its right to manufacture and commercialize products.

## *Documentation*

Why are our documentation systems often characterized by many long procedures and instructions with repetitions? Why are there often repetitions of the regulatory texts on one hand and description of equipment on the other hand and still the need for them to be completed by training and operational documents?

The answer largely lies in the way procedures are traditionally developed. When creating a new procedure – which can be for covering a new operation, closing an inspection gap, or coping with a new regulatory requirement, people may simply add one more procedure to directly fulfill the need. It may be regarded as too time consuming to analyze and simplify, and make an addition in a well-defined context.

This is a very short term view that ends up with a mixture of many long procedures and instructions that will require far more time for maintenance. Moreover, there is a high risk of inconsistency between all of these documents, which can end up causing other problems.

Furthermore, if we want to comply with an additional regulation in the future (for example, when we need to comply with the FDA in addition to the European GMPs or to produce a Medical Device in addition to drugs) it will be a huge task to determine which part is already as it should be and may be used, and which part is to be created.

Benchmark companies establish structured documentation that will comply with the expectations of inspection bodies and audit organizations, while minimizing the volume and the maintenance required, and optimizing the structure to make it useful and adaptable. Poor organization of the quality documentary system costs a lot in terms of duplication of effort for creating and maintaining documents, difficulty to prove compliance, and to adapt to new regulations and new strategies.

## *System and Process*

At a process and system level, there are other problems that will be further discussed.

The first problem is that people have very different views of what a process is, what a system is, and what model to copy. Many process approaches still have a limited ambition: to use the process representations to replace long texts in procedures. While this is a very good idea to do so, this is neither BPM, nor building a Management System. Benchmark companies build ambitious BPM approaches to ensure that they will cover what is essential to the company, both from compliance and competitiveness standpoints, and will represent the reality.

They then make an abstract of what is to be documented as a top to bottom quality system: first what is common to all and generic, then the specifics.

A Quality System not based on a process approach may be disconnected both from strategies and reality, and can turn into practices and documentations that aim at making inspectors happy rather than being useful and maximizing performance.

## ***The False Problem: What are the Boundaries of the Quality Function? The Strategic Subject: What is to be Managed in a Systemic Way?***

In different companies, the Quality Function can have a very different range of responsibilities. In the pharmaceutical industry, the first dilemma is how to connect the quality lab (which is an operational step within the integrated supply chain, after manufacturing and before warehousing) with the quality assurance part (which needs to be independent from manufacturing to organize and judge the quality of the whole chain).

Connecting them makes the person in charge at the same time the judge and the one being judged; on the other hand, it is comfortable because the people playing the two roles often have similar profiles. The decision must be made after balancing the pros and cons.

Moreover, Quality is often essentially seen as a manufacturing topic, whereas others think that the same principles and methods should be applied to development, commercial, as well as finance and HR. With the **Sarbanes-Oxley** law, we have the proof that the Quality management principles are to be applied in finance. There are now some pharmaceutical companies in which risk management becomes a combined quality, security/safety and finance/strategy approach, based on the corresponding international standards that are very similar; it becomes then a major management process serving the priorities of the executive committee.

Finally, the question arises whether or not a "process approach" should be run by the quality function? Should Quality take the lead on security and environment because systems should be organized similarly? Should quality work on all improvements, even the main "comex" objectives?

Some companies have a Quality function focused on the product in manufacturing, others create a Director for Quality, Hygiene, Security, and Environment, staffed in addition to project managers to work on any type of improvements. Some companies create two functions: quality keeps on the old scenario, and the second is called "progress" or "Six Sigma" or performance.

This article doesn't suggest one approach over another, as it will depend on the history and the nature of the company. However, organizations must develop a structure to deal with at least four key elements:

- **Risk Management and Action Alignment:** how the main risks for the company are brought to the attention of the executive committee; how all people in the company position their strategic, tactical, and execution actions

aligned with the decisions that have been generated this way.

- **Process Piloting, Information Systems Urbanization, Master Data Management:** how the main topics and information in the company are managed in one leveraged place and shared openly and protected when necessary.
- **QHSE Coordination:** how to leverage, for these four topics, the steps of the process, which are common (management responsibility organization, documentation, training, reviews, etc.)
- **Performance Improvement, both Continuous and Breakthrough**

Each separate company culture will determine whether or not to call this Quality, but no matter what a company calls it, the Quality function needs to exist. The discussion below will focus on what must be leveraged and piloted from a central function, and the most efficient tool to use to accomplish this. For the purpose of this discussion, we are calling it Quality.

## BPM based QMS

Figure 1 illustrates a Business Process Management-based Quality Management System, which is a combination of real examples from pharmaceutical companies that have implemented this new process. Since some of these companies adopted these approaches several years ago, we are able to evaluate the real life advantages gained.

Figure 1 shows an example Management System of a Pharmaceutical Company described as a BPM model. In order to clarify the representation and simplify the use of the modeling afterward, the model is structured as follows:

1. The middle is the main (critical) path (for example, produce product)
2. The top shows the processes that pilot the main path
3. The bottom shows support processes (for example, Information Technology)

Individual roles and departments may not be shown on the diagram since it is only aiming to describe the main flows. Thus the Financial Director, for example, may not be mentioned by name, but still plays a crucial role as both member of the Executive Committee and as head of the relevant support process.

The figure is not structured around departments, but on the activities that produce the main products, documents, and data. For example, Design and Develop doesn't mean the R&D department, but rather the process to transform an idea into a fully defined product, ready to be manufactured and commercialized. The process is the result of teamwork between Research, Development, Marketing, Regulatory Affairs, Quality, and some Industry and Logistics services that anticipate the downstream processes.

The figure should be used as a top level map with each domain being described in a lower level map. Each process is then described with a simple map which we will call an actigram, showing each element of inputs and outputs (product, document, information), constraints and objectives (requirements, goals, indicators) and resources and supports (roles, IT Applications, Material Resources). These are the objects that are the subject of the modeling and at the very heart of any Process project. All areas in the company must agree on the inventory list of these objects (what are the master data,

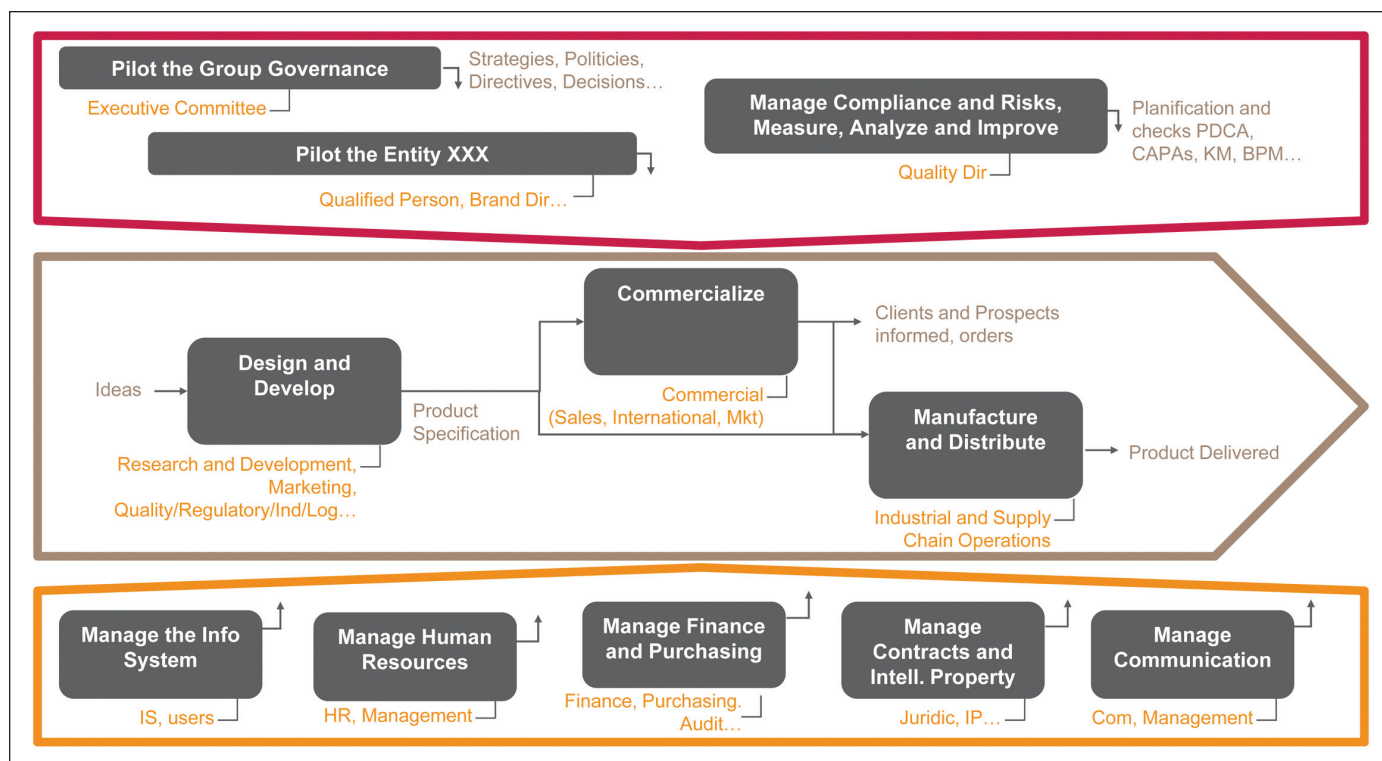


Figure 1. BPM model for the management system of a pharmaceutical company.

## Activities are presented as follows:

- First determined by Inputs - Outputs
- Under norms and constraints
- Supported by actors and resources

## The mapping is organized in three layers:

- First the concrete Execution
  - Major flow transforming inputs into outputs
- Piloted by Management Processes
  - Generation of Decisions, Objectives, Planning, and follow-up
- and helped by Support Processes
  - Transversal elements, human, information systems, and equipment

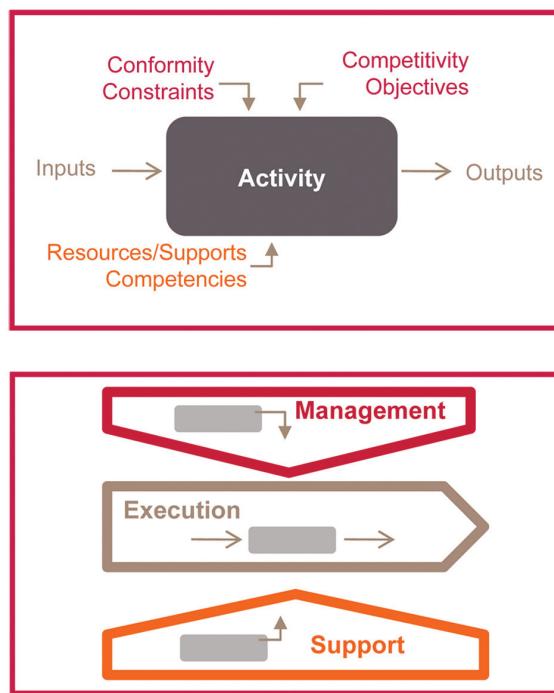


Figure 2. Representation and structuring rules: each activity in its environment, focusing on the what and the why.

main shared documents, the requirements, etc.) then in the representations that show the flows and the interrelations between those objects. Figure 2 summarizes the BPM principles.

Imagine the BPM project is advanced enough to cover its objectives for the company; how does it help with building an optimized Quality Management System? It is common practice to use the different levels of representation brought by BPM for the different levels of Quality Documentation, as shown in Figure 3:

- The general mapping and some actigrams may be imported in the Quality Manual.
- The appropriate logigrams may be imported inside the procedures and/or instructions.

It creates very efficient documentation. The Process representation aids navigation through the whole paperwork, allowing anyone – operator, manager, or auditor – to see the general picture then focus in on the appropriate area.

A major benefit is that the quality documentation is very close to reality, built with the real players, and focused on the essentials devoid of long sentences that may be interpreted several ways and focused on the main objects that are coherent throughout the whole company.

The project should adhere to the rule of modeling: first describe a generic model and then create versions of it to accommodate differences between some of the cases. Similar activities should be described by a unique model on which all involved people agree, and then create specifics for the differences between locations or departments, turning them

into slightly different versions from that generic model. BPM is the way to make it possible.

Quality benefits in many ways from such an approach. Plants or Development can create documentation far more compliant, easier to understand, and easier to maintain. Many examples show a reduction by a factor of two or three in the number of pages, and an inspection in the end that was far more fluid and positive.

The combined pyramid of process maps and quality documentation allows far more efficient audits, internal or external, and therefore improvement, thanks to the readability. Also a given improvement can be duplicated in all areas where it should be since it is easy to identify all areas which perform the same generic activity.

Finally, the main benefit is the capacity to really manage the important processes to combine all regulation types together, in an efficient system that answers all requirements and leverage throughout the organization.

This quality system has a direct and major effect on product quality: it makes it simple for all employees to know how they should perform their tasks in order to be compliant; it optimizes the quality assurance processes like CAPAs, deviations, etc.; and it ensures that all processes are managed. Based on these key elements, good control is possible.

It is always difficult to measure the improvement obtained through such a re-organization. Volume reduction of procedures is often 50% and maintenance effort reduction is often several man-years for large facilities. This is usually, however, a combined result with an implementation of an electronic data management system or a re-organization.

It is easy to imagine the gain obtained by the non duplica-

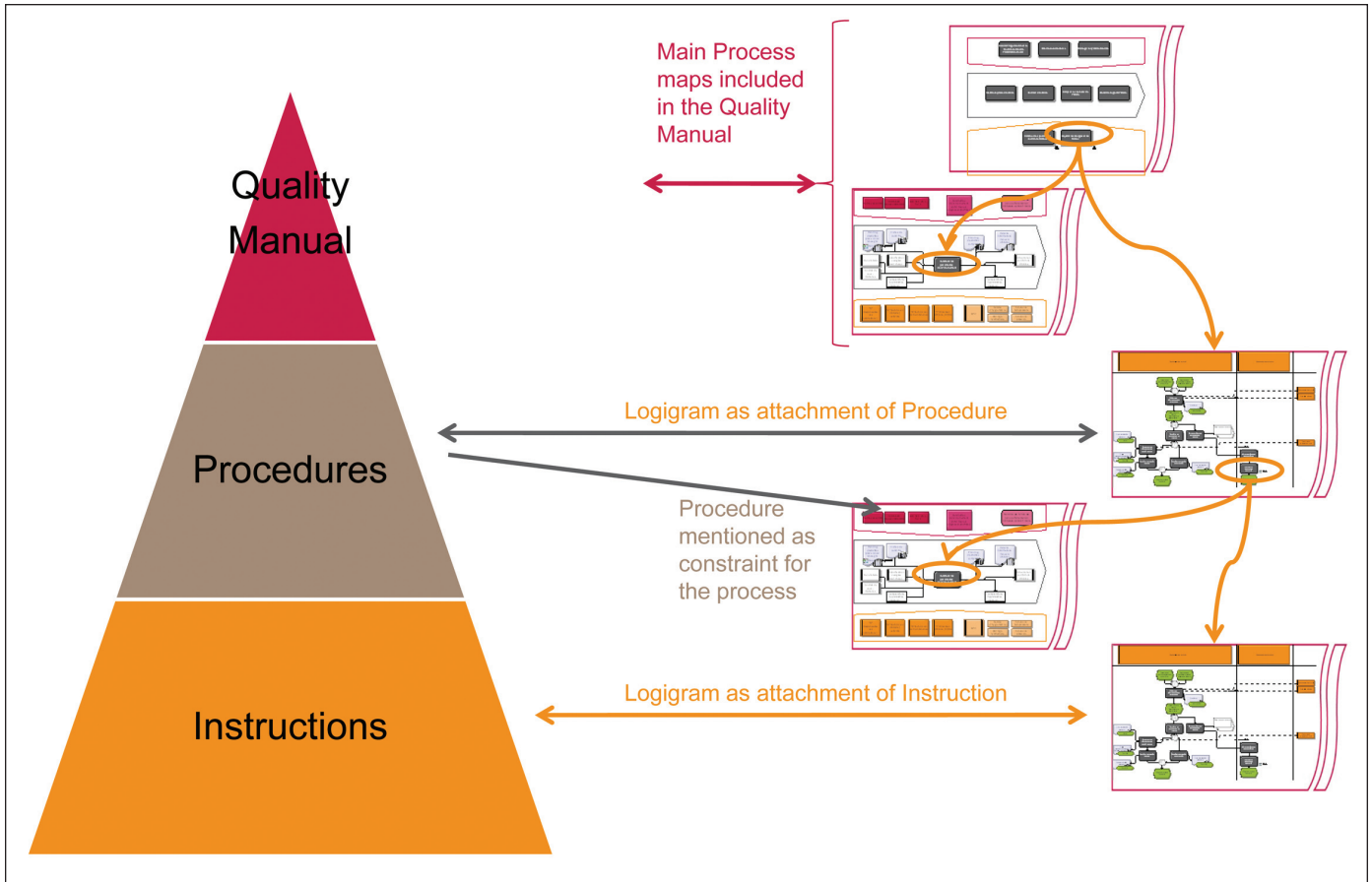


Figure 3. BPM and QMS: process maps show the why and the what, and structure the documentation detailed logograms describe the who, when, how.

tion: when a change is done somewhere, everybody benefits from it; and all consequences of non justified differences are eliminated. Such a system opens many synergies, and the gain for it will never be evaluated as such. It is becoming the normal way to organize quality in pharmaceuticals.

It is expected that having implemented ICH Q10 will be a criteria for reducing the frequency of inspections; it is not written, but this is the spirit, and it is very logical. When an inspector has verified a system according to ICH Q10 standards and then has inspected some details, he is far more comfortable about all the remaining perimeter than with a classical approach. Proof of its performance is given by positive inspections in areas where it was implemented and through the fact that the surrounding domains usually volunteer to implement an equivalent system. We shouldn't wait to get such benefits.

As a last example, Figure 4 shows how a map may at the same time be a logical extraction of the comprehensive representation of the management, execution, and support processes, and also position the chapters of the GMPs for a given plant. By extracting some of the lower level maps, it is easy and efficient to build a compliant documentary system.

### What's Next?

Let us conclude with some perspectives. The ideas developed above should become natural within a short period of time, as

ICH Q10 is being deployed. ICH Q10 is not, however, prescriptive on how to implement the principles. The given elements include ISO-type elements, such as creating a process mapping, management responsibility, and resource allocation.

As a result, there will be maps which will become tools for everyone. There will be some management processes which will be created and will change the way information goes up to the senior management and decisions are made on quality. There will be a new area of processes to be established for many pharmaceutical companies. The aim here is not to

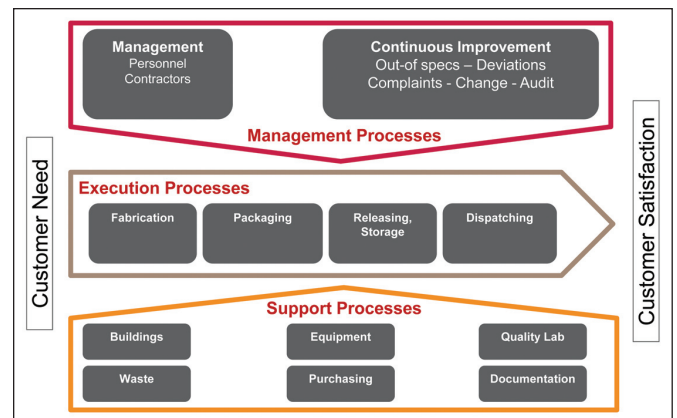


Figure 4. BPM model for a plant. Process mapping in relation with GMP classification.

explain what was written in ICH Q10, but to demonstrate the benefits for the pharmaceutical industry of implementing this new approach by illustrating some real life examples from other industries.

As a last image, I will discuss an example of a small plant, in which I was lucky enough to have my first job 22 years ago. The plant had been taken over by a large chemical company, which had brought over its own way to operate and manage. Among them, the “whole job concept,” meaning that it was normal to:

- go beyond the boundaries of the job
- think in a lateral manner
- stimulate teamwork to identify the potential safety accidents and potential quality accidents
- ask all employees to be vigilant on what could have gone wrong and suggest ideas to prevent that it ever happens again

Quality and Performance Workshops were held, including two day-quality tools trainings for 100% of the people, one of the tools being the process concept (not yet the whole BPM logic, but already including the idea to describe the “as-is” and the “to-be” in a workshop in order to solve problems).

The people were conscious that there had been a “cultural revolution” in order to be able to adopt those ideas. Before that change, they had been afraid to let one know what mistakes they made, there were no such initiatives to improve processes together, etc. Today, they are still ahead on those ideas since that “cultural revolution.” The process map they created seven years ago is one of the cleverest and most creative ones I’ve seen.

The result? They were small and they have been bought out several times. Each time, the buyer was planning to integrate the product of that plant in one of his big sites and then close the plant. Each time, after some months, the buyer was so astonished by the level of quality and the way people were working, that they never closed it and the plant is still there, standing as a reference.

They didn’t know that their Quality focus and know-how would be the key to their survival, but so it was. They did it because it was the best way to ensure that the product be at its best, that everybody gives his/her best contribution and be proud of what he/she does, that a competitive advantage be built and kept. And it did make it possible. A systemic way for Quality makes all this possible: a win-win between compliance, competitiveness, and capitalization of competencies.

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2. Epistulae morales ad Lucilium, Letters to Lucilium, Seneca, ca. 4 B.C.-65 A.D)
3. Henry Ford (1863 – 1947), founder of the Ford Motor Company, has been the sponsor of the mass production assembly line technique.
4. Frederick Winslow Taylor (1856 – 1915), an American mechanical engineer, is the father of scientific management, called after him “Taylorism.”
5. William Edwards Deming (1900 – 1993) American statistician, professor, author, lecturer, and consultant. He made popular the concept of “Plan, Do, Check, Act,” that he didn’t invent, but taught in his lectures to the Nippon Keidanren, the Japanese managers organization, during the fifties. The idea is to first think and establish the objectives and processes necessary to deliver the expected results (Plan), then implement the new processes (Do), then measure and analyse the new processes, comparing the results against the expected results (Check), then make changes and improve (Act), and come back to a next cycle of Plan, Do, Check, Act and so on. There are various definitions of the four steps, other names for the steps, and equivalent cycles with more steps, but the main idea is in these few lines.
6. Joseph Moses Juran (1904 – 2008) management consultant. In his books and lectures, he built the foundations and the frame for the concepts of Quality Management.
7. Toyota raised the Total Quality Management concept to a form of perfection with the “Toyota way,” including major ideas such as the “Lean Manufacturing” and Just In Time Production.
8. John Francis “Jack” Welch, Jr. (1935-...) CEO of General Electric between 1981 and 2001, took the opportunity of the “Six Sigma” method invented at Motorola’s to develop his company, in all businesses types and all departments of the company.
9. The ISO 9000 family of standards represents an international consensus on good quality management practices. It consists of standards and guidelines relating to quality management systems and related supporting standards. The first versions of the standard were initially very successful, but gave to it a reputation of being heavy and bureaucratic. Many people summarized the philosophy of Quality Assurance and ISO 9000 by saying “say what you do, do what you say,” meaning that the company needed to document clearly the activities that it had planned to perform and that it was really performing, so that an auditor could confirm that reality was in line with documentation, which was in line with the referential that the company wanted to comply with. The 2000 version changed drastically, incorporating ideas from BPM and EFQM : process based, focused on customer, performance and management. It is still very effective for the traditional Quality Assurance aims, but it adds very important dimensions, while allowing a far more simple, flexible and powerful format.
10. EFQM is a global non-profit foundation, which nurtures a network for innovative organizations and business leaders to share knowledge, experiences and good practice. EFQM is the custodian of the EFQM Excellence Model, which is




seen by many experts as the best management model ever thought. Companies that follow an EFQM approach are evaluated according to the best practices on 5 'Enablers criteria' (Leadership, Strategy, People, Partnership & Resources, Processes) and 4 'Results Criteria' (Customer, People, Society and Key Results). The modification between ISO 9000-1994 and ISO 9000-2000 is a convergence with some key ideas of EFQM, even if the two remain different: EFQM is an evaluation and benchmarking dynamic, while ISO 9000 is a standard against which to be audited and certified. EFQM meant "European Fondation for Quality Management," but is now a name that shouldn't be translated anymore.

### About the Author



**François Versini** became Quality Director for a midsize pharmaceutical Group 10 years after having endorsed that same function for a global business unit of an American chemical multinational company. In between, he also held positions in Logistics, Human Resources, and Production. He founded i3L, a consulting firm which provides support to health and life

sciences key players in conducting change management in terms of organization, quality, logistics, HR, and processes. i3L is an associated member of Product Life Group and this article has benefitted from several discussions with Dr. Erick Gaussens, Chief Scientific Officer of Product Life Group. He can be contacted by email: [fversini@integration3L.com](mailto:fversini@integration3L.com).

i3L, 8 rue Mirabeau, 81100 Castres, France. 

# An Eastern Experience – Japan Affiliate on Tour in the US

by Osamu Matsumoto and Michael Lucey

A valuable and well regarded service provided by the Japan Affiliate to its membership is the US Pharmaceutical Plant Tour, an event organized on an annual basis. The Tour is invariably combined with (mandated!) participation in ISPE's Annual Meeting, which in 2010 was held in Orlando, Florida. With this in mind, the Plant Tour Organizing Committee focused on pharmaceutical plants located in the general vicinity of the US East Coast.

The Committee, comprising Messrs O. Matsumoto, S. Nakamura, and M. Akutagawa, who serve on the Affiliate's Board, together with Japan-based members Mason Waterbury and Michael Lucey who took the lead in coordinating with candidate plants, allowed itself a lead-time of six months, recognizing that ample time is required for approaches and formalities to proceed and for acceptance of the visits to be obtained.

Ultimately, the 20-member Tour party, comprised of 15 industry representatives and the five planning members, visited six pharmaceutical plants during the five days from 1 to 5 November. Details of the plant tour were compiled into a report and developed real time while on the road by the industry representatives. Reporting was later made at the Affiliate's Winter Meeting in December, in Yokohama, Japan, partly to encourage future generations of US Plant Tour participants.

## Pfizer

At Pfizer's core bio-plant located in Andover in the suburbs of Boston, Massachusetts, the Tour had an opportunity to closely observe the bioreactor line. Through the helpfulness of an interpreted pre-meeting after lunch, Pfizer described its aims of cost reductions by manufacturing standardization and acceleration of product development.

## MannKind Corporation

As a biopharmaceutical company located in Danbury, Connecticut, whose business ranges from drug design and development to commercial production, MannKind was a double winner of the 2010 Facility of the Year Award for both Process Innovation and Equipment Innovation. Using the company's proprietary Technosphere technology, MannKind has developed an inhalant called Afrezza. Following an explanation of the Afrezza production process, the group was shown the manufacturing line. It was noted with interest that QbD and PAT had been adopted for production management.

## Johnson and Johnson

Johnson and Johnson's Sterile Process Technology Center is located in Raritan, New Jersey. As a technology hub for the Johnson and Johnson Group, the Center provides guidance on optimal sterilization methods, studies sterilization methods for new medical equipment, and provides sterilization training



Plant tour group at Johnson & Johnson's Sterile Processing Technology Center.

and related seminars. The facility is a "one-stop sterilization center" with a full range of sterilization equipment.

## Merck

Located in West Point, New Jersey, Merck's facility is the largest-scale pharmaceutical plant in North America. The group was shown the vaccine production line where Merck clarified that its process is characterized by the production of safe vaccines, applying ultra-filtration technology. Additionally, the opportunity was provided to observe the utilities which support the production system.

## Biogen Idec

Located in Research Triangle Park, North Carolina, the bio-product production plant is the winner of 2010 Facility of the Year Award for Operational Excellence. Having six bioreactors with a capacity of 15 m<sup>3</sup>, the plant was once the largest-scale bio-plant in the world. The group was guided right up to the bioreactors and invited to observe culture conditions directly through a viewing window.

\*\*\*

In addition to the visits to the pharmaceutical plants, the



Plant tour group at Biogen IDEC in North Carolina.

*Continued on page 3.*

## Revision of EU Annex 11 and Chapter 4

by Sion Wyn, ISPE Technical Consultant

The EC has announced a new revision of EU GMP Annex 11 *Computerized Systems*, and consequential amendment of EU GMP Chapter 4 *Documentation*. These will come into operation by 30 June 2011.

Annex 11 has been revised in response to the increased use of computerized systems and the increased complexity of these systems. The Annex defines EU requirements for computerized systems, and applies to all forms of computerized systems used as part of GMP regulated activities.

EU GMP Chapter 4 requirements on generation, control, and retention of documents have been revised in the light of the increasing use of electronic documents within the GMP environment, and in the light of the Annex 11 revision.

A significant addition to the revised Annex is a new clause on quality risk management, which states:

*Risk management should be applied throughout the lifecycle of the computerized system taking into account patient safety, data integrity, and product quality. As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerized system.*

The revised Annex also states that regulated companies should be able to justify their standards, protocols, acceptance criteria, procedures, and records based on their risk assessment.

The risk management approach adopted is very much in line with ICH Q9 Quality Risk Management and the ISPE GAMP 5 Guide – *A Risk Based Approach to Compliant GxP Computerized Systems*.

The Annex is harmonized with GAMP 5 life cycle terminology such as the use of Project Phase and Operational Phase,

and uses GAMP 5 terminology for roles and responsibilities such as System Owner and Process Owner. There is also good match between the operational requirements and the topics covered in the GAMP Good Practice Guide – *A Risk Based Approach to Operation of GxP Computerized Systems*.

Enhanced and clarified requirements covering suppliers and service providers have been included, reflecting the increasing role of IT service providers, and the increased dependence on supplier activities and documentation.

One aspect that is certain to generate discussion is the requirement that quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request.

Other interesting aspects include the need for:

- an up-to-date inventory of GMP systems and their functionality
- documented adequacy assessments for automated testing tools and test environments
- periodic evaluation of systems to confirm that they remain in a validated state and are compliant with GMP

Requirements covering electronic records and signatures are broadly in line with current US FDA expectations and interpretation of 21 CFR Part 11.

An initial draft revision was released for public consultation in April 2008. There was significant industry feedback, including substantive and detailed comments from the ISPE GAMP Community of Practice (COP). Most of the issues raised by the GAMP COP have been addressed in the final revision.

The revised Annex 11 adopts a risk-based approach, and is generally aligned with current industry good practice. 


## ISPE Releases GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems, Second Edition

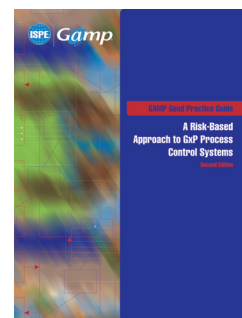
*Guide updated to align with recent regulatory and industry developments*

ISPE released the GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems (Second Edition) on 18 February 2011. The Guide, which provides guidance on how to achieve process control systems that are fit for intended use and meet current regulatory requirements, has been significantly updated to align with the concepts and terminology of recent regulatory and industry developments.

Concepts addressed by the new Guide include the International Conference on Harmonization (ICH) Guidance setting out expectations for the application of science- and risk-based approaches to drug development and manufacture supported by pharmaceutical quality systems and ISPE's Product Quality Lifecycle Implementation® (PQLI®) global

initiative for a practical approach to implementation of ICH guidances Q8 (R2), Pharmaceutical Development, Q9, Quality Risk Management, and Q10, Pharmaceutical Quality System. FDA cGMPs for the 21st Century Initiative and other emerging industry standards also were influences as the Guide was developed.

The new Guide is available for purchase in book form and as a downloadable PDF. The cost of the document is US\$145/€115 for ISPE Members and US\$405/€45 for non-members. More information can be found at [www.ISPE.org/GuidanceDocs/GAMP-GxP-Process-Control-Systems](http://www.ISPE.org/GuidanceDocs/GAMP-GxP-Process-Control-Systems). 



# What are the benefits of being a CPIP?

by Niels Guldager, CPIP

Pharmaceutical industry colleagues have often asked me the following question in one form or another: "What do I get out of spending time and resources on obtaining the CPIP certification?"

My answer is that based on my CPIP certification experience, the benefits fall in three categories – 1) expansion of work opportunities, 2) improved industry perspective, and 3) a roadmap for structured career planning. In my book, the last category – the career roadmap – has the potentially largest impact for long term payback. So with this perspective I would also say that the big value comes from the activities in the certification process more than the diploma itself.

The CPIP certification process gave me a framework for first mapping my general pharmaceutical industry knowledge against a benchmark (take 30 minutes to do the example test on the CPIP Web site) and then resources (the study guide) and a motivation to explore and improve in knowledge areas that did not score so well. The career roadmap arrived courtesy of the credential writing activities that inspired me to reflect on previous achievements and


*"In my book, the last category – the career roadmap – has the potentially largest impact for long term payback."*

see them in a new light (provided by the credentials framework). In short, the career roadmap: Where have I been, where can I go from here? And what roads do I need to take – or maybe avoid?

The time spent preparing for the computerized test is where my industry perspective was expanded. It is not possible, nor necessary to study for in-depth knowledge of all fields. However, spending time on areas most likely to improve overall perspective – as identified in the example test results – is manageable. So the benefits of being a CPIP in this regard are that you get some general knowledge as starting points for cooperation and communication with colleagues specializing in other areas.

Being a CPIP has expanded my range of work opportunities due to the

quality management, risk assessment, and continuous improvement mindsets highlighted in the credentials. Going through the credentials process is an excellent introduction to these topics. The time spent on obtaining the CPIP has clearly prepared me for working with these industry transforming approaches to a greater extent. The certification process provided me a mindset and general orientation – and prepared me for taking on new opportunities.

A somewhat unexpected benefit is the networking side of things: A very open, well connected and highly professional network of CPIP certificate holders is starting to develop. It is simply a great community and as the certification program gains momentum, I expect it to become a very strong industry network. 



## An Eastern Experience – Japan Affiliate on Tour in the US

*Continued from page 1.*


group also traveled to Xcellerex, a short drive from Boston. The company's services as a disposable bioreactor manufacturer were first outlined, followed by a viewing of equipment on the premises.

A distinctive feature of the Plant Tour is the opportunity each year to exchange greetings with members of local Chapters. The 2010 Plant Tour featured two such events: one hosted by the Boston Chapter, in Cambridge, Massachusetts, and the second by the Delaware Valley Chapter, in Philadelphia, Pennsylvania. Bonds of friendship were established at the receptions.

The Plant Tour organizers are deeply appreciative for the kindness extended by the pharmaceutical companies who so readily accepted the visits to their plants, and for the hospi-

talities of the US Chapters who arranged the heart-warming social events.

This year, 2011, marks the 10th anniversary of the establishment of the ISPE Japan Affiliate. As a part of a planned commemorative program to coincide with the regularly scheduled Annual Meeting in Tokyo, a tour of a Japanese pharmaceutical plant is planned for 15 April, at the end of the 13 and 14 April seminar-style events.

Finally, it should be said that the US Plant Tour registrants of yesteryear are not forgotten. Efforts are made to expand the network of ISPE members by holding reunion gatherings of plant tour participants; in fact, there will be a joint reunion in June 2011 for those who joined the 2008, 2009, and 2010 plant tours. With the further kindness of accommodating hosts in the US, that number will grow in the years to come! 

## 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.

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Alfa Laval Inc., 5400 International Trade Dr., Richmond, VA 23231. (804) 222-5300. See our ad in this issue.

## Cleanroom Products/Services

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NNE Pharmaplan, Vandtarnsvej 108-110, 2860 Søborg, Denmark. +45 4444 7777. See our ad in this issue.

## Dust Collectors

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

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

## Micro Leak Detection Machines

Bonfiglioli Pharma Machinery, Via Rondona, 31, 44018 Vigarano Pieve (Fe), Italy. Tel: +39 0532715631 Fax: +39 0532715625 WEB: www.bonfigliolipharma.com Email: h.carbone@bonfiglioliengineering.com. Manufactures of Laboratory or High Speed Leak Testing Machines for ampoules, vials, blister packs, BFS, HDPE containers and any other type of pharmaceutical packaging.

## Passivation and Contract Cleaning Services

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

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AdvantaPure, 145 James Way, Southampton, PA 18966. (888) 884-6981. See our ad in this issue.

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

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Emerson, 8000 W. Florissant Ave., St Louis, MO 63136. (314) 553-2000. 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.

# Advertiser's Index

AES CLEAN TECHNOLOGY .....	35
ALFA LAVAL .....	96
AZZUR GROUP LLC .....	94
BAUSCH + STROEBEL MACHINE .....	25
CAL-CHEM CORP .....	61
CAMFIL FARR AIR POLLUTION CONTROL .....	2
COLE-PARMER .....	29
COMMISSIONING AGENTS .....	7
CRB ENGINEERS AND BUILDERS .....	3
DAGARD .....	59
EI ASSOCIATES .....	69
ELETTRACQUA SRL .....	27
EMERSON PROCESS MANAGEMENT .....	11
FIKE CORPORATION .....	51
FLEXICON, A MEMBER OF THE WATSON-MARLOW PUMPS GROUP .....	13
FREWITT SA .....	59
FRISTAM PUMPS USA .....	9
GE ANALYTICAL INSTRUMENTS .....	41
IMA LIFE .....	75
IMA S.P.A. .....	15
INTELLIGEN INC .....	43
JIM CRUMPLEY & ASSOCIATES .....	94
MAR COR PURIFICATION .....	19
MECO .....	5
NEWAGE INDUSTRIES INC .....	57
NNE PHARMAPLAN .....	48-49
OPTIMA GROUP PHARMA .....	17
PARTICLE MEASURING SYSTEMS INC .....	37
PERFEX CORP .....	39
PHARMACEUTICAL ONLINE .....	89
PLASCORE INC .....	57
PROPHARMA GROUP .....	61
REED EXHIBITIONS .....	87
ROBERT BOSCH GMBH .....	77
SAINT-GOBAIN PERFORMANCE PLASTICS .....	31
SARTORIUS STEDIM BIOTECH GMBH .....	33
SKAN AG .....	65
TELSTAR TECHNOLOGIES .....	21
TOPLINE PROCESS EQUIPMENT CO .....	53
VAISALA INC .....	45
WESTFALIA SEPARATOR INDUSTRY .....	23

## International

### ICH

#### ICH Celebrates 20 Years with a Refreshed and Revitalized New Visual Identity<sup>1</sup>

ICH's new logo has been designed with a view to representing the letters "I," "C," "H" in a manner which speaks to the benefits of harmonization for better global health. This has been achieved through the embodiment of the letters in an abstract human form. The principle color of the logo is blue, a color often synonymous with healthcare, and which adds an air of vitality and wellbeing to the depicted abstract figure. Purple was chosen as being complimentary to blue.

The new ICH logo also includes the slogan "Harmonization for Better Health," which further emphasizes the benefits of harmonization for better global health and is also reflective of ICH's Terms of Reference.

### PIC/S

#### PIC/S Adopts Revision of the Explanatory Notes for Industry on the Preparation of a Site Master File (PE 008-4)<sup>2</sup>

The aim of these Explanatory Notes is to guide the manufacturer of medicinal products in the preparation of a Site Master File that is useful to the regulatory authority in planning and conducting GMP inspections. The document can be found at <http://www.picscheme.org/bo/commun/upload/document/pe008-4sitemasterfile-copy1.pdf>.

## Europe

### European Union

#### A Council of Europe Convention to Fight against Counterfeit Medical Products<sup>3</sup>

The Council of Europe Committee of Ministers adopted the MEDICRIME Convention which, for the first time, criminalizes the counterfeiting, manufacturing, and supplying of medical products placed on the market without authorization or without being in compliance with security requirements.

The MEDICRIME Convention is the first international criminal law instrument to oblige States Parties to criminalize:

- the manufacturing of counterfeit medical products
- supplying, offering to supply, and trafficking in counterfeit medical products
- the falsification of documents
- the unauthorized manufacturing or supplying of medicinal products and the placing on the market of medical devices which do not comply with conformity requirements

#### EDQM Strengthens International Collaboration<sup>4</sup>

The European Directorate for the Quality of Medicines and Healthcare (EDQM, Council of Europe) is strengthening its collaboration with renowned international organizations in the field of medicines by signing Memorandums of Understanding with the National Institute of Food and Drug Safety Evaluation (NIFDS), Korea Food and Drug Administration, and the Chinese National Institute of Food and Drug Control (NIFDC).

#### European Medicines Agency Facilitates Interaction Between Small and Medium-Sized Enterprises (SMEs)<sup>5</sup>

The European Medicines Agency has launched a public SME registry providing information on companies which are registered as SMEs with the Agency. The registry aims at facilitating and promoting interaction amongst SMEs. In the first phase, this registry will include contact details of individual companies, their area of activity, and headcount. In the second phase, available from the end of March 2011, this registry will also include information on the company pipeline and product profile.

#### European Medicines Agency and European Centre for Disease Prevention and Control Agree to Enhance Cooperation<sup>6</sup>

The European Medicines Agency and the European Centre for Disease Prevention and Control (ECDC) have signed a working arrangement, which aims to enhance cooperation and mutual consultation between the two Agencies on areas of common interest.

The new arrangement, which came into force on 16 December 2010, outlines a number of initiatives to ensure that the two Agencies make best use of their resources while avoiding duplication of effort and overlaps in their activities. It includes:

- the exchange of information on vaccines, antimicrobial resistance, and antiviral medicines
- monitoring the benefit-risk balance of vaccines
- collaboration on "substances of human origin," such as the use of human tissue or cells in medicines
- participation in meetings and joint projects

#### Committee for Medicinal Products for Veterinary Use (CVMP) Publishes New Draft Strategy on Combating Antimicrobial Resistance<sup>7</sup>

The Committee for Medicinal Products for Veterinary Use (CVMP) at the European Medicines Agency has published for public consultation its latest strategy on combating the threat of antimicrobial resistance related to the use of veterinary medicine for the period 2011-2015. The strategy highlights the importance of keeping effective veterinary antimicrobials on the market while minimizing risks to animals or humans arising from their use and emphasizes the need for prudent use of antimicrobials. The strategy encourages both an EU-wide and global approach to combating antimicrobial resistance in order to reach the stated goals and objectives. The public consultation is open until 31 March 2011. Comments received will be considered when preparing the final strategy for adoption by the CVMP. The strategy can be found at [http://www.ema.europa.eu/ema/doc\\_index.jsp?curl=pages/includes/document/document\\_detail.jsp?webContentId=WC500100649&murl=menus/document\\_library/document\\_library.jsp&mid=0b01ac058009a3dc](http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500100649&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc).

#### EU Releases Revised Annex 11 on Computerized Systems<sup>8</sup>

The EC has announced a new revision of EU GMP Annex 11 Computerized Sys-

tems, and consequential amendment of EU GMP Chapter 4 Documentation. These will come into operation by 30 June 2011. Annex 11 has been revised in response to the increased use of computerized systems and the increased complexity of these systems. The Annex defines EU requirements for computerized systems, and applies to all forms of computerized systems used as part of GMP regulated activities. EU GMP Chapter 4 requirements on generation, control, and retention of documents have been revised in the light of the increasing use of electronic documents within the GMP environment and in the light of the Annex 11 revision.

## European Medicines Agency Publishes Final “Road Map to 2015”<sup>9</sup>

The European Medicines Agency has published its final “Road Map to 2015,” coinciding with the 16th anniversary of its inauguration on 26 January 2011.

The “Road Map to 2015” sets out the Agency’s vision in further developing its role as a European public health agency in the field of medicines. Building on the achievements made by the previous road map initiative between 2005 and 2010, the new road map proposes three priority areas for future actions to strengthen the Agency’s role in protecting and promoting human and animal health in the European Union:

- **Addressing public-health needs** by stimulating medicines development in areas of unmet medical needs, neglected diseases, and rare diseases, and for all types of medicines for veterinary use; facilitating new approaches to medicines development; applying a more proactive approach to public health threats where medicines are implicated.
- **Facilitating access to medicines** by addressing the high attrition rate during the medicines development process; reinforcing the benefit/risk-balance assessment model; continuing to improve the quality and the regulatory and scientific consistency of the outcome of the scientific review.
- **Optimizing the safe and rational**

**use of medicines** by strengthening the evidence base in the post-authorization phase to enable better regulatory decision-making; enhancing patient safety by avoiding unnecessary risks to patients as a result of the use of medicines; becoming a reference point for information on medicines

## EDQM Begins Development of a Demonstrator of Its Future “TRACK AND TRACE” System<sup>10</sup>

As part of its anti-counterfeiting strategy, the EDQM has initiated an ambitious project for a “Track and Trace” system for medicines, open to any manufacturer marketing medicinal products in any of the 36 Member States of the European Pharmacopoeia. The project has now reached Phase 2 in which a demonstrator (live demo) will be developed.

The live demo is to be shown as a proof of concept to authorities from the 36 Member States, to business stakeholders from the supply chain, and to patient organizations during workshops taking place from the fourth quarter of 2011, mainly at the EDQM premises in Strasbourg. During these workshops, the features of the EDQM system will be demonstrated and discussed, and the concept and the live demo will be fine-tuned so that the development of the future working system meets all expectations.

## Germany

### BfArM Publishes Advice on Harmonization of Product Information Texts for Medicinal Products with Identical Active Substances<sup>11</sup>

For the benefit of patient safety and improved compliance, it is desirable to have harmonized pharmacological and medical statements in the Gebrauchs- und Fachinformation (PIL and SmPC).

Therefore, the BfArM recommends harmonization of purely national authorizations for products with identical active substances by adopting any missing indications and dosages. This should be reported via a Notification of Variation pursuant to Section 29 sub-

section 2a AMG and can only be done if the added or changed indications do not belong to another therapeutic area (therapeutic area is defined as the third level of the ATC code). It is also recommended that the necessary harmonization of the medical statements concerning side effects, contraindications, and warnings be reported via a Notification of Variation pursuant to Section 29 sub-section 1 AMG. In doing so, you would also meet the requirement that the PIL and SmPC pursuant to Sections 11 and 11a AMG are kept at the latest scientific levels.

The BfArM intends to give preference and accelerate the processing of such Notifications of Variation, especially if the PIL and SmPC are completely harmonized with the reference product, provided that patent restrictions are not infringed upon.

## Malta

### Maltese Medicines Agency Launches “Know Your Medicines” Web Site<sup>12</sup>

The Maltese Medicines Agency launched a consumer/industry Web site entitled “Know Your Medicines.” It provides links to information on regulation, safety, supply chain, taking medicines, and more. The site can be found at <http://www.medicinesauthority.gov.mt/knowyourmedicines.htm>.

### The Maltese Medicines Authority Receives Three Awards for Good Practice and Quality Initiatives in People Management<sup>13</sup>

The Medicines Authority received three awards at the Malta People Awards. It was recognized for employee engagement, the level of excellence it registers in the learning and development of its employees, and for offering equal opportunities.

The Medicines Authority was awarded for engaging its employees in the overall strategy and operations of the organization. It involves its people in its decision making, mainly through high quality staff meetings throughout the year and theme related committees and working groups. It conducts a staff satisfaction survey on a regular basis so as to identify the needs and expectations



of its people in a structured manner and so that highlighted opportunities for improvement are taken into consideration.

## Asia/Pacific

### China

#### Chinese SFDA Moving Notice<sup>14</sup>

Effective 13 December 2010, the Chinese State Food and Drug Administration (SFDA) moved from A38, Beilishi Road, Xicheng District, Beijing. The new contact information is as follows:

Address: Building 2, No. 26 Xuanwumen West Street, Xicheng District, Beijing  
Postcode: 100053  
Telephone: 68313344

#### The Inaugural Conference of the 10th Chinese Pharmacopoeia Commission and the 60th Anniversary Ceremony of Chinese Pharmacopoeia held in Beijing<sup>15</sup>

The Inaugural Conference of the 10th Chinese Pharmacopoeia Commission and the 60th Anniversary Ceremony of Chinese Pharmacopoeia was held in Beijing on 23-24 December 2010. The tenth Chinese Pharmacopoeia Commission, which was established in accordance with the Drug Administration Law of China and the Constitution of Chinese Pharmacopoeia Commission, is the technical organization responsible for organizing the formulation and revision of national drug standards. It has an executive board and 23 professional committees, and consists of 348 experts and scholars in such fields as clinic, scientific research, teaching, manufacturing, inspection, and management closely related to the work on drug standards, including 28 academicians from the Chinese Academy of Sciences and the Chinese Academy of Engineering.

#### Three Government Agencies Jointly Issue Notice on Strengthening the Supervision of Prepared Slices of Chinese Crude Drugs<sup>16</sup>

To further intensify the supervision to the prepared slices of Chinese crude drugs and promote the sound development of traditional Chinese medicine,

the State Food and Drug Administration, the Ministry of Health, and the State Administration of Traditional Chinese Medicine recently jointly issued a notice, which specified relevant requirements on strengthening the supervision of prepared slices of Chinese crude drugs.

### Malaysia

#### Malaysia Publishes Guidelines on Good Distribution Practices<sup>17</sup>

These guidelines are used as a standard to justify status and as a basis for the inspection of facilities, such as manufacturers, importers, and wholesalers. All manufacturers, importers, and wholesalers of registered products/notified cosmetics and its related materials are required to adopt proper distribution and store management procedures appropriate for the distribution and storage of registered products/notified cosmetics and its related materials destined for the consumer. These procedures should include the management of personnel, premises, facilities, and adequate documentary procedures that preserve the safety and quality of the material, product or cosmetic.

## North/South America

### Canada

#### Summary Report: Stakeholder Consultations on the Good Manufacturing Practices (GMP) Inspection Program Review<sup>18</sup>

Health Canada is currently conducting a review of its Good Manufacturing Practices (GMP) inspection program for drug establishments in an effort to make the program more risk-based. Further to this review, Health Canada undertook face-to-face and online stakeholder consultations during the Fall of 2009. This report provides a summary of the feedback that was received online and during face-to-face sessions. The report can be found at [http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gmp-bpf\\_rpt-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gmp-bpf_rpt-eng.php).

### USA

#### US FDA Publishes Advanced Notice of Rulemaking on Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies<sup>19</sup>

The US Food and Drug Administration (FDA) is seeking comment on whether to amend the regulations governing Good Laboratory Practices (GLPs). The Agency decided that to require a GLP quality system for all facilities/laboratories, as well as to more completely address nonclinical studies as they are presently conducted, the Agency would need to modify the existing regulations. The Federal Register notice can be found at <http://edocket.access.gpo.gov/2010/2010-31888.htm>.

#### Joshua Sharfstein Leaves US FDA<sup>20</sup>

Joshua Sharfstein, the Deputy Commissioner of Food and Drugs and second in command at the US FDA, resigned from the agency in January to take the top public health job for the state of Maryland. His 21-month tenure at FDA was marked by an increased focus on drug safety.

#### US FDA Launches Web Site to Help Regulated Industries Save Time, Resources<sup>21</sup>

The US Food and Drug Administration (FDA) today introduced a new Web resource called FDA Basics for Industry ([www.fda.gov/FDABasicsforIndustry](http://www.fda.gov/FDABasicsforIndustry)) to help companies and others save time and resources in their interactions with the agency. The website includes basic information about the regulatory process, including information that is frequently requested by industry.

#### US FDA Warns Public of Continued Extortion Scam by FDA Impersonators<sup>22</sup>

The US Food and Drug Administration (FDA) is warning the public about criminals posing as FDA special agents and other law enforcement personnel as part of a continued international extortion scam.

The criminals call the victims – who in most cases previously purchased drugs over the Internet or via “teleshops” – and identify themselves as FDA special agents or other law enforcement officials. The criminals inform the victims that purchasing drugs over the Internet or the telephone is illegal, and that law enforcement action will be

pursued unless a fine or fee ranging from \$100 to \$250,000 is paid. Victims often also have fraudulent transactions placed against their credit cards.

The criminals always request the money be sent by wire transfer to a designated location, usually in the Dominican Republic. If victims refuse to send money, they are often threatened with a search of their property, arrest, deportation, physical harm, and/or incarceration.

## US FDA Updates Process Validation Guideline<sup>23</sup>

In the Federal Register of 11 May 1987 (52 FR 17638), FDA issued a notice announcing the availability of a guidance entitled Guideline on General Principles of Process Validation (the 1987 guidance). Since then, they have obtained additional experience through regulatory oversight that allows them to update recommendations to industry on this topic. This revised guidance conveys FDA's current thinking on process validation and is consistent with basic principles first introduced in the 1987 guidance. The revised guidance also provides recommendations that reflect some of the goals of FDA's initiative entitled "Pharmaceutical CGMPs for the 21st Century – A Risk-Based Approach," particularly with regard to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality system tools and concepts. This revised guidance replaces the 1987 guidance, and can be found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>.

## Guidance Agenda: New and Revised Draft Guidances CDER is Planning to Publish During Calendar Year 2011<sup>24</sup>

In accordance with Good Guidance Practices, the US FDA has published a guidance agenda listing the new and revised draft guidances Center for Drug Evaluation and Research (CDER) is planning to publish during calendar year 2011. The Agenda can be found at <http://www.fda.gov/downloads/Drugs/>

[GuidanceComplianceRegulatoryInformation/Guidances/ucm079647.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079647.pdf).

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