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Just in Time. An Approach for a cGMP Fill-Finish Facility

by Andrew Cunningham

This article presents a detailed narrative on the design drivers and delivery methodology for Genentech's recently completed fill-finish facility in Hillsboro, Oregon.

Designing and constructing a technically complex yet efficient, fully integrated fill-finish facility is no small task. The timeframe can be long, the costs can be high, and the stakes with numerous stakeholders involved, can be even higher. But this case study of one biotherapeutic company's new fill-finish facility in Hillsboro, Oregon, provides practical insights and steps for success for "just in time" delivery of a fully operational and cost-effective ground-up manufacturing facility in a shorter timeframe than typically witnessed by industry standards. The end goal of this project was to bring a licensed fill and finish facility online to ensure reliable supply of product to patients through innovative design, sustainable technologies, and effective use of capital. By all accounts, the "just in time" process and mindset facilitated this, laying the groundwork for a shift in the way the industry approaches and completes complex projects.

Background

Prior to constructing the new fill-finish facility, the company had three existing manufacturing facilities online, all of which were in northern California. The building of the new facility was driven by the company's need to address specific fill and finish operational conditions: lack of supply chain capacity; the risks associated with all operations concentrated in a single, high-risk seismic zone; and operational inefficiency, due to production in multiple facilities. In addition, locating in Oregon provided a favorable tax climate as a single-sales factor state, which bases its sales tax upon profit apportioned to revenue of in-state sales relative to total sales. When licensed, the facility will be used for the filling and packaging of commercial biotechnology therapeutics from bulk drug substance and will assume commercial filling operations from another of the company's facilities

The facility was to be designed and constructed in two years with qualification and licensure taking an additional 18 months. Planning for the project began in 2006. Forward-looking in scope, the company required that the facility include space for expansion to accommodate increased production and to be responsive to future needs and new product lines. The facility had to meet

Figure 1. The construction sequence of the facility was governed by completing B5 first, followed by B4, utilizing the high bay space for material storage followed by the manufacturing, utility, and administration buildings.

current and unforeseen regulatory requirements for both international and United States markets, and be capable of processing both liquid and lyophilized biotherapeutic products on an annual basis.

Other goals for the project were to build only what is required to support the company's immediate fill and finish needs, employ lean principles with limited redundancy throughout the process, minimize on-site inventories based on high turnover rates and shortened cycle times, and integrate off-the-shelf, demonstrated technologies. Leveraging equipment technology to minimize construction costs and improve quality control to satisfy multiple markets was an important tenet of both the design and engineering phases of this project.

Meeting Conditions, Achieving Goals

Part of the facility's fast-track success was the clear vision company executives laid out before initiating the design of the facility, as well as the initial engineering work the company completed on the front end; this was crucial in adhering to the fixed budget the company set for the new facility. With the high-level scope of the facility already mapped out, the design teams began to develop the basic design and core elements, breaking the big picture into smaller pieces of a puzzle.

In relation to the fill-finish facility, "just in time" is indicative of both the lean manufacturing practices utilized within the facility, as well as the design and construction processes. It also incorporates strong partnering with local government for fast-track approvals and ensuring excellent relationships and adequate high skilled local labor. As the design process overlapped with the construction, as soon as information became available, it was handed to construction crews for implementation. Due to the speed of the construction timeline, the project was essentially divided into smaller pieces, defined by construction trade.

While the goal was to complete construction of the facility within 24 months, the timeline was driven, in part, by Oregon's climate, where the rainy season lasts November through February; in short, the building needed to be watertight by the end of October 2007. Additionally, toward the conclusion of the Basis of Design, the company added a distribution center to the project, which corporate executives required to be completed first to satisfy immediate supply chain requirements for storing and shipping finished product being produced by Contract Manufacturing Organizations (CMOs).

This presented an interesting challenge. Given the six-month lead on steel at the time and the constrained overall schedule, a steel order was placed in March 2007, using an estimate of the gross tonnage needed for the project, while final plans were still being developed. With the mill order in process, the design team began focusing on the detailed structural design in line with the intended construction sequence. In tandem with this effort, the architectural team focused on the exterior envelope design, developing alternate options for the review of company executives and the City of Hillsboro. The City successfully partnered with the company, allowing fast track approvals at each stage of the project. In addition, the local Labor Council collaborated early on to provide highly skilled trade labor. Ultimately, working in close conjunction with the subcontractors, the exterior skins of the buildings were erected in quick succession to the completion of the steel frame, moving sequentially from (Figure 1 - building aerial) Building 5, the distribution center; to Building 4, the warehouse; then to Building 2, the three-story cGMP-manufacturing facility at the center of the campus; and finally Building 3, a utility building, and Building 1, the main office administration area. From initial ordering of steel to commencement of exterior envelope, the process took five months.

While team leaders were assigned for every technical and functional area of the facility, they relied on the expertise of their consultants and vendors, allowing subcontractors to work within the cost models and design parameters to provide available goods and materials.

Regular meetings, including a minimum of 17 standing weekly meetings, allowed work groups to collaborate, troubleshoot, and prioritize issues within the larger scope of the project. These meetings were organized in a hierarchy of management; project managers and major decision-makers came together in one meeting; work groups, such as those for structural engineering and architecture in another; and design process engineers in yet another. This allowed issues and concerns to move laterally as well as vertically without slowing down certain parts of the ladder with unnecessary information and details. In all, by eliminating handoff points, minimizing work-in-progress staging areas, and passing control of the plan details to specialized design teams, the overlap of the exterior construction and design-bid-build phase of the process manufacturing facilitated an integrated workflow to ensure on-time delivery.

Project Statistics

- Five months from start of design to groundbreaking
- Goal: 24 months from concept design to mechanically complete; actual time: 22 months
- Designed 1,500 square feet per day
- 17 weekly standing meetings covering company's core team review, facility, project management, process, Civil, Structural and Architectural (CSA), mechanical, electrical, plumbing, site, design team coordination, multiple trade discussions, individual work groups, and intermittent all hands meetings
- 1 million construction hours worked
- 520 highly skilled and motivated trade workers on site at height of construction
- Local government collaborative accelerated approval process
- Mechanically Complete, Operationally Qualified (MCOQ) in 4.5 months within the given time frame.

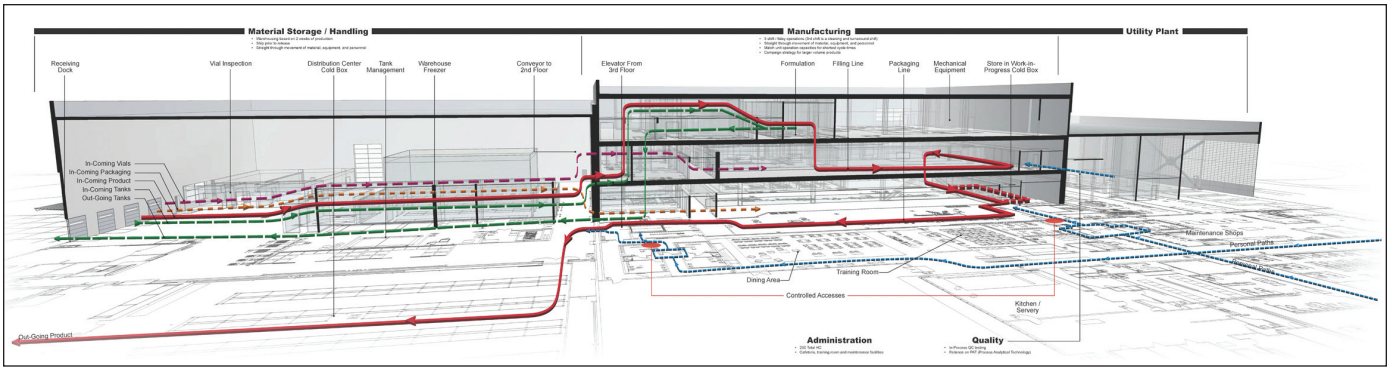

Figure 2. The uni-directional flow of the finished product is represented by the red line with raw product and materials entering through the warehouse, moving into the three-level manufacturing building and then stored in the distribution center prior to being shipped.

Additionally, commissioning and qualification reviews were started early in the design process with the company's quality assurance group actively involved in the development of the plans; as such, there was no direct hand-off from design-build to the validation process. Validation occurred as an integrated part of the design and construction process, where Factory Acceptance Tests (FATs) were leveraged as part of the validation strategy.

As previously mentioned, the company had three specific operational goals to achieve with the construction of the fill-finish facility. How these goals were achieved is outlined in detail.

Supply Chain and Operational Efficiency

Supply chain and operational efficiency are inextricably linked within the project as evidenced by Building 2's top-to-bottom workflow schematic - *Figure 2*. At a high level overview for this article, supply chain relates to the global supply of product to patients around the world, from raw material supplies delivered to the facility for processing or use in the manufacturing process, and distribution of finished product from the facility to patients. Operational efficiency is the internal organization within the facility and the work patterns of people, raw materials, products, or waste streams in support of the broader supply chain.

Location Risks

To mitigate the location risks associated with having all the company's original manufacturing facilities in an active seismic zone, among other factors, Genentech conducted an extensive site analysis and selected Hillsboro, Oregon as the facility's home. The location offered the ability to serve the West Coast market and remain in proximity to the company's main campus in California. A suburb of Portland, the location provided a high quality workforce, good business relationships, and a great place to live for facility staff. The community also had a welcoming, collaborative political environment conducive to the project's fast-track approval process, and offered tax incentives and rebates for the use of energy-efficient technologies and training programs.

General Design for the Facility

Design studies revealed the need for a 300,000-square-foot, three-story, super-block building, a single building that housed all the facilities the company needed under one roof, instead of multiple buildings scattered around the campus. This design accommodated a single, continuous, straight-through process of materials, equipment, and personnel, as well as matching unit operation capacities for shortest cycle times. Manufacturing also required a campaign strategy for larger volume products.

In addition to manufacturing, the building needed to contain warehouse and distribution spaces, a quality control laboratory, administration offices, and a central utility building. Massing the building into one super-block reduced the travel and circulation time between different areas of the building. It also condensed the building's footprint to save construction dollars.

Product Flow

The diversity of the company's biotherapeutics portfolio proved an interesting challenge; the design needed to accommodate flexibility in vial sizes, along with capacity. To respond to the supply chain capacity issues, the new facility was sized to accommodate three production lines with mixed 3cc to 100cc vial capacities. The facility's manufacturing sector included two filling lines with shell space provided for a future syringe line and two future freeze dryers. The manufacturing process moves materials, equipment, and personnel in a simple uni-directional flow, reducing the chance for cross-contamination. This allows for the product to move in one direction through the fill-finish process rather than backward and forward in an inefficient manner.

At the company's California headquarters, where the manufacturing process was long housed, operations were developed and spread out through the site, creating inefficiencies. By contrast, the new fill-finish facility's efficiency begins at the gate with a rational flow of vehicles onsite to assist with clear security checkpoints in and out of the facility. As for materials, upon arriving at the receiving dock at ground level, frozen product is moved via elevator to the third-floor freeze-thaw area and formulation space, and vials after inspection are delivered to the second floor.

Once the product is formulated, it moves down to the second-floor filling line (Figure 3); this process design element leverages gravity feed, a critical component so that every last drop of product is utilized. Following inspection, the product then moves down to the first floor where the filled vials move to the packaging line. Prior to the packaging line, Work in Progress (WIP) cold storage boxes are available for filled vials awaiting packaging; this eliminates the need to temporarily transport the product to the cold box in the distribution center at the end of a shift. The finished product exits through the cold box to the shipping area of the distribution center; so all materials, raw and finished, enter and exit through the same side of the super-block building.

Figure 3. The fill line incorporated depyrogenation through capping within the isolator, including sterile stopper loading and automated lyo loading/unloading with all controls through an HMI.

Delivery at a Glance

Delivery Goals

- A single point of responsibility for budget and scope control – integrate general contractor into process
- Facilitate early shipping of product – design and construct distribution center in 16 months
- Schedule required interior construction to proceed in winter – complete the building exterior before rainy season
- Phased validation of equipment to support licensure – sequential handover of process systems
- Maintain the aggressive construction schedule – integrate undefined long lead items into the building

Delivery Strategy

- Approved plan to meet function and budget – early review and fix plan layout
- Quality Assurance Approval – sign off on process and equipment flows
- Best value delivery team – bid individual scopes based on URS/design packages
- Accelerate and motivate workforce capacity to meet schedule – engage multiple design-build subcontractors to develop scope
- Stand alone design packages – identify construction sequence
- Communication strategy – robust meeting schedule
- Integrated design team – Building Information Modeling (BIM)/roundtable meetings/review process
- Ability to control cost; individual budgets were allotted to different parts of the project, such as the exterior skin, the landscape, etc., which gave the contractor and designer a better perspective on the money available and what could be done with it.

Operational Efficiency

Process designed to maximize operational efficiency by building in:

- Single Point Location
- Production Capacity
- Flexibility
- Quick Batch Turnaround
- Equipment Technology

Right-Sizing

To support the just-in-time methodology of the facility, staging areas were efficiently sized, circulation zones were created, and equipment and effective personnel adjacencies were established. For instance, fill suites and inspection areas were positioned adjacent to each other with view windows to facilitate easy communication and monitoring of the process, and the facility was designed so FDA inspectors can easily view the technical areas without needing to gown up.

The adjacent warehouse was right-sized for supply expectations to keep a two-week supply of raw materials; this minimizes on-site inventories based on high turnover rates and shortened cycle times. This also fulfills the company's goal of risk mitigation, be it a shortage of products and raw materials or a localized breach, such as an earthquake in the area of the company's headquarters, without stockpiling product.

Planned Expansion

On the north side of the building, expansion space was allotted to accommodate two additional production lines. This was a critical component of the company's recent merger with another major pharmaceutical company. Prior to acquisition, a supply agreement between the companies committed this firm to producing fixed quantities of three specific pharmaceuticals sold throughout the world by the acquiring company. Additionally, in 2007, the partner company completed a fill-finish plant in Switzerland. These sister facilities were designed to be compatible with one another and serve as back-up should either need to go offline.

Operations required three shifts per day with a five-day work week. The third shift was responsible for cleaning and turning around the production area for use during the following day's first and second shifts.

Figure 4. Isolator technology provides improved user comfort, due to reduced gowning requirements, while maintaining critical environmental control.

Technology Solutions

Technology plays a large role in any complex pharmaceutical manufacturing facility, and at this location, it is an integral part of the design. One of the company's initial goals was to leverage off-the-shelf, demonstrated technologies to both minimize construction costs and improve quality control to satisfy multiple markets, which were important tenets of both the design and engineering phases of this project. It also required entrusting subcontractors, equipment vendors, and other partners to take the lead on individual components and systems to assist in streamlining the facility.

Design

In determining the needed technology for the facility, an early and detailed definition of the equipment URS was developed by the company's process engineer leads; the vendors then provided solutions and the project team helped to integrate all the needs. Validation and qualification were phased by system as each building block became mechanically complete.

Maintaining sufficient resources and leveraging the Factory Acceptance Test (FAT) process to expedite IQ/OQ accelerated the turnover process.

Figure 5. Inspection lines are visually connected to the fill suites to ensure ease of communication. Within the inspection suite, there is the capability for both automated and manual inspection.

Isolator Technology

To reduce the size of the class 100 areas, isolator technology was integrated into the facility. Isolator technology ensures environmental control and reduces contamination risk during aseptic processing. Key features of this filling system include mass flow technology and a filtration skid that can be cleaned and sterilized in place. In addition to accommodating vials, isolator technology offers lyophilization capability - *Figure 4*.

Because the last facility the company built utilized Restricted Access Barrier Systems (RABS), isolator technology was new to the firm. Based on this, every effort was made to thoroughly understand potential product implications so the isolators could be utilized to their fullest capacity. Grade A isolators in the fill suites minimize personnel gowning time and maximize operators comfort. The facility has segregated integrated isolator fill lines with one liquid/lyophilization line providing overlap fill operations.

Additionally, isolator technology offered numerous cost benefits, including lower fill room air classification with reduced HVAC costs and less environmental monitoring. Contamination risks are also reduced, eliminating human intervention in a critical zone and increasing sterility assurance. Isolator technology also hastens turnaround time for cleaning, sterilizing, and parts change-out.

Quality Controls

Quality control is absolutely critical in the pharmaceutical industry as is knowing where your product has gone once it heads out the door. Operational requirements for ensuring quality include in-process testing. At the fill-finish facility, fully automated inspection lines were built in to the ends of the fill lines; manual inspection is also an option. The rate for the auto-inspect line is equivalent to the fill rate; the semi-automated line is 30 vials per minute. By comparison, the manual inspection line moves at a rate of five vials per minute - *Figure 5*.

Additional quality controls include the use of SAP technology to track filled and finished products awaiting shipment from the distribution center's cold box. This provides a clear record of the product and its status should quality issues occur.

Other Solutions

The just-in-time nature of the operations required minimizing space requirements and maximizing labor efficiencies, other technological solutions included equipment integration and streamlined production efficiency. For instance, high bay storage racks served by wire-guided forklift trucks keep raw materials consolidated in a smaller footprint. A direct supply of vials moves from the warehouse through a conveyor system to the fill area, reducing handling. The facility was designed to be paper-free; digital controls and the use of digital tablets allow supervisors to be close to the production line rather than working in remote offices. With the knowledge that

Figure 6. The main arterial circulation street in the administration building provides natural daylight into the interior spaces along with providing visual connections between the lab and office areas.

staff would be working in controlled areas, combined with the restrictive winter climate, it became important for the facilities' culture to provide open, interactive spaces - *Figure 6*. The main spine through the administration building and large cafeteria seating area, named the Great Hall, with its fireplace and capability for large-screen projection, are envisioned as key social hubs to provide the workforce with a refuge for relaxation - *Figure 7*.

Budget and Savings

In total, including land, fees, construction, equipment, design, and in-house staff costs, this fill-finish facility cost $400 million. Relative to industry standards, this price point is within the bounds of what is expected for a project of this size and scope.

To create a target budget, first the scope of the project was established based on satisfying the company's operational and business needs; from there, high-level area requirements and equipment lists were developed. A fair market value was then assigned to needs to determine a target budget. Through the early stage of the project, the overall needs and scope were refined before fixing the final goals, resulting in the actual budget to further develop the project. By employing lean principles in the development of the building and operational needs, the project was engineered to deliver best value.

Figure 7. The Great Hall was conceived to provide a collaborative and community building environment incorporating multiple amenities. Functions include the cafeteria seating area, training room break out space, viewing windows in the manufacturing building, and a fireplace with a large format projection screen.

To reach "best value," changes needed to be made along the way. This project was set up with a budget by system; a fixed amount of money was allotted to the exterior skin, the finishes, the landscape, and more. This compartmentalization made for more efficient decision-making during design and construction and helped strike a balance between budget and schedule.

Some times budget ruled, and sometimes schedule. For example, it may have cost a bit more to get the distribution center up and running in 16 months, but the benefits outweighed the costs so schedule was the driver there. Additionally, more time could have been spent in designing the structural system, but it was critical to get steel fabrication and erection started so the building could be made watertight before the winter rains. This resulted in using steel that was readily available and not specifically rolled for the project, which had schedule benefits. Conversely, some items of equipment could have been procured cheaper, but given the operational needs or quality goals, there was value in spending more. Prior to final sign-off on the interiors, the project had to save $6 million, resulting in cost cutting of some of the systems and finishes in the building. Here cost became the driver in hitting an established budget.

All this begs the question: What were the cost savings in this fast-track approach? Initial savings were realized for the design portion of the project. The company solicited a bid for only design early in the process before deciding to go design-build, saving the company more than $10 million. Other savings achieved relate to the schedule; the project could not have been achieved in the same time frame if a sequential design-bid-build strategy was implemented. For example, by getting the distribution center done well before the completion of the remainder of the facility, the company was able to start shipment of product sooner. While there may not have been cost savings identified in construction, there were enhanced occupancy benefits resulting in revenue.

Lessons Learned for Success

In the end, design and construction of the facility was completed in less than 22 months, two months prior to the final deadline and nearly eight months faster than the industry average - *Figure 8*. At the peak of construction, there were more than 520 workers on site. These workers surprised even the company's longtime project staff with their capacity to work through the most severe weather to "get their job" done in furtherance of the project. It is a true tribute to the collaboration with the local trades that this project was delivered ahead of schedule.

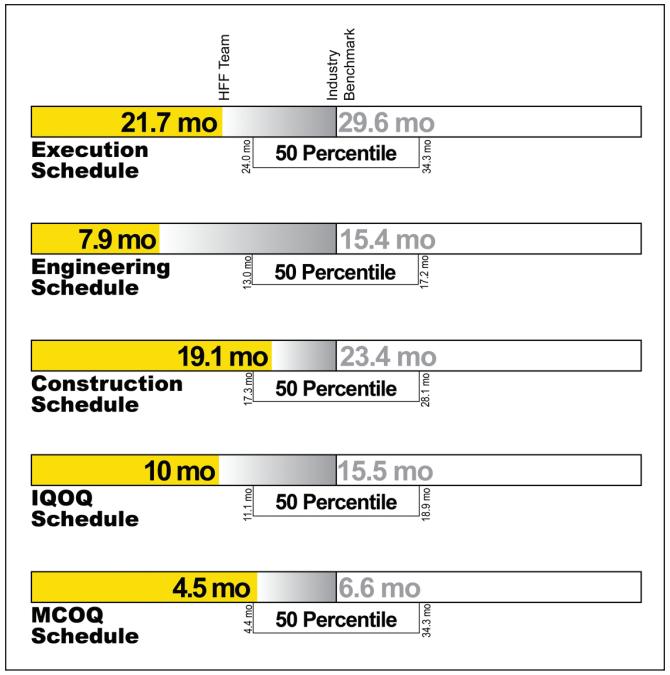

Figure 8. The design-build relationship facilitated an accelerated delivery process resulting in completion within the top 80th percentile of industry standards

The facility has already shipped more than one million vials of biotherapeutics through the distribution center, which has been fully operational since July 2008. While commissioning and qualification reviews were started early in the design process and occurred as an integrated part of the design and construction process and FATs leveraged to validate equipment before coming onsite, full validation of the facility's system remains ongoing as planned for in the original schedule.

In support of the accelerated pace of work, the tight turnarounds, and the sheer number of decisions made across all levels, the following are seven lessons that helped all parties involved achieve success:

1. A Team with a Can-Do Mentality

In its team selection process, quality, their ability to meet regulations, and price were only cursory parameters for the evaluation and selection of design and construction partner. The company sought designers and a contractor who would be collaborative and innovative in the way they worked and how they worked together. In order to create solutions in a fast-paced project, it is critical to have a team approach rather than a number of individual groups working in separate silos. For solutions to be explored and options presented to the client, all team members had to be working toward a common goal, not at odds with one another. Included in this team approach were regular defined interaction and updates with both local government and labor trades to keep them aware of and to advance project goals and schedule deadlines. In the end, the chosen contractor, which had never done a facility of this magnitude, was selected as it brought the best value to the table with all these parameters, but particularly innovation and collaboration in mind.

2. Clear Project Goals and a Strategic Vision

In a visioning session at the start of the project, the facility director explained the building's function of producing cancer-curing therapeutics and cited examples of how products produced in the facility would save lives. The notion that the faster the building was completed, the more lives could be saved was a powerful one. This single act identified that it wasn't just about building a building, but coming together as a group to provide a solution to improve the quality of patients' lives. The facility director's continued involvement in creating a project vision was critical to buy-in by the local community. To that end, there were many clearly identified milestones along the path, which were shared with key community stakeholders to keep them aware and help guide the process, chart progress, and maintain budget control. If any of these items began to deviate from the desired course, a recovery plan was put in place to realign the goal.

3. Clear Decision-Making Process

In a project of this size, there were many disciplines and people required to execute all the necessary tasks; it was important to make sure that no one person became a bottleneck in the process. Sometimes there may be competing goals, be it from a budget, schedule, or function point of view. The project structure was organized with tiered levels of decision-makers, corresponding to the various discipline groups ranging from process equipment to quality to construction and design with strong alignment and interactions with legal, corporate relations, and government affairs. Within each corporate engineering group, various levels of oversight existed with one level reporting up to another should a decision not be attainable. Ultimately, the company's core team had the ability to sanction changes and resolve project-defining issues.

4. Clear Roles and Responsibilities

Given the scope and schedule of the project and once the basis of design was defined, it was imperative that a "divide and conquer" approach was adopted. The design disciplines operated in work groups to develop each of the scopes, and then met on a regular basis as a large group to collaborate and review interdisciplinary coordination. Each group had a clear development schedule with milestones that were tied into the integrated construction strategy.

5. Balance Cost vs. Function for all Design Solutions

Although the phrase 'least cost scope' was repeatedly used, it also was imperative to align the budget allocation with the functional requirement. Not all items were created equal and having a hierarchy of equipment, spaces, finishes, and materials to work with not only resulted in a judicious use of resources, but also added to the richness and variety of the environment. Designing appropriately was as critical as maintaining budget.

6. Phased Sequencing and Schedule Execution

A key strategy was having the contractor engaged early in the process as a single point of contact that understood the project goals and drivers. The design team collaboratively designed the schedule with the contractor to benefit these goals. This resulted in a distinct approach to engage the construction process, harnessing the abilities of the team to hasten the overall schedule and meet the vision by allowing a fast acceleration of the workforce.

7. Flexibility in Solutions

Satisfying a fast-track schedule requires flexibility with the design solution, budget application, and schedule impact. The team worked to balance all these items, while still addressing the least cost scope directive. Function was a key driver in all decisions, along with availability of resources, be it material or labor.

Given the complex nature of this fill-finish facility, these same seven tenets easily can be applied to any construction project for coordinated delivery in a time-constrained manner.

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This article presents a case study focusing on the design and optimization of a large scale biopharmaceutical facility using process simulation and scheduling tools.

Design and Optimization of a Large Scale Biopharmaceutical Facility Using Process Simulation and Scheduling Tools

by Abdelaziz Toumi, Christian Jürgens, Carmen Jungo, Bernd A. Maier, Victor Papavasileiou, and Demetri P. Petrides

Introduction

The global competition in the biopharmaceutical industry and the increased demand for affordable and effective medicines has shifted the industry's focus on manufacturing efficiency. Therefore, process development and design are gaining importance. For new products, it is crucial to minimize market entry time without compromising product and process quality. This is particularly true for biopharmaceuticals for which it is commonly said that "the process makes the product" and process changes are very difficult to implement after the regulatory approval of a new product.

Process development scientists have a short time window to optimize the process of a promising new molecule. Similarly, engineering teams face challenges within the design and construction of new production lines and facilities required for manufacturing newly developed products. The challenges of both groups can be lessened by the use of appropriate computer aids, such as process simulators and production scheduling tools.[1,2,3,4]

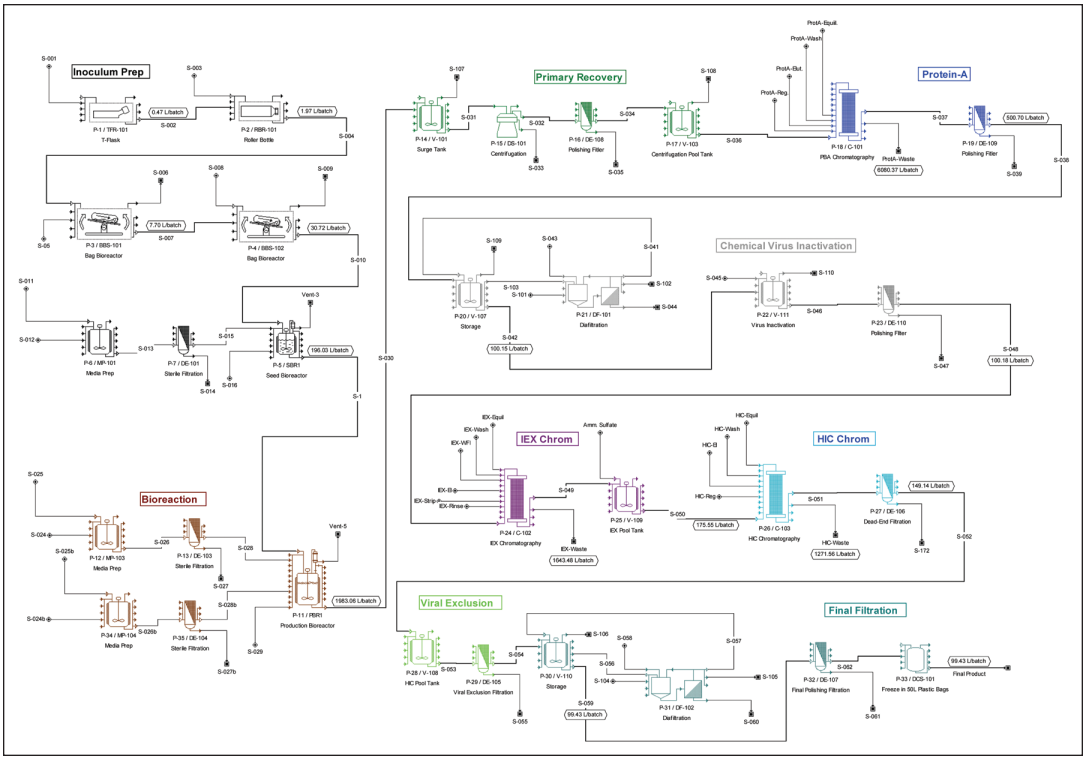

Figure 1. Monoclonal antibody production flowsheet.

The objective of our Large Scale Biotech (LSB) project was to support the design of a new production facility at an existing manufacturing site of Merck Serono (Vevey, Switzerland). The plant will initially be dedicated to the parallel production of two different molecules, a Monoclonal Antibody (MAb) and a fusion protein. Additional MAb and related molecules from the Merck Serono pipeline are expected to be manufactured in the same facility in the future. The limited space available for the construction of the new facility made the design very challenging and the project highly complex. A computerized process model was developed at an early stage of the basic design phase of the project to support all design activities and facilitate scenario analysis and evaluation. This article describes the strategy followed for the development of the model, the challenges faced, and the benefits derived from this effort.

Monoclonal Antibody Production

Monoclonal Antibodies (MAbs) are large protein molecules used to treat a wide variety of illnesses, such as rheumatoid arthritis, psoriasis, Crohn's disease, transplant rejection, and a variety of cancers. They constitute the fastest growing segment in the biopharmaceutical industry. More than 20 MAbs and fusion proteins are approved for sale in the United States and Europe[5,6] and approximately 200 MAbs are in clinical trials for a wide variety of indications.[5,7] The market is growing by more than 15% per year and is expected to exceed $30 billion in 2010.[8,9,10,11]

Figure 1 displays the flow diagram of a typical MAb process. The left-hand-side of the diagram displays the seed train (for inoculum preparation) and the production bioreactor(s). Such processes include several cell expansion steps as well as two to three seed bioreactor steps to expand the volume of the inoculum. Cell growth and product formation in the production bioreactor takes usually 11 days. Considering the time for cleaning and turnaround activities, the overall cycle time of the production bioreactors that operate in fed-batch mode is around 14 days. That includes some idle time to synchronize the cycle time and to accommodate batch to batch changes in fermentation time in a way that a fixed amount of batches are produced every week. After a production bioreactor run is completed, primary recovery is initiated, which typically includes centrifugation for cell removal followed by filtration. The purification part of the process that follows usually includes three chromatography steps, dia-filtration/concentration steps, and virus removal/inactivation steps. The overall product recovery yield is around 70 to 80%.

Such processes utilize a large number of buffer and cleaning solutions (usually 20 to 30) that must be prepared on time and be ready for delivery when required by the main process. The preparation and storage of such buffers involve a large number of tanks. Most of the tanks are used for the preparation and storage of multiple solutions and require cleaning after each use. Estimating the number and size of such tanks is a challenging task during the design of such facilities. Figure 1 does not display buffer preparation and holding activities. However, such activities were taken into account in the models developed for the needs of this project.

Our design project involved the modeling and optimization of a facility equipped with two production lines, each capable of producing a different MAb. Each line includes four production bioreactors feeding a single purification train. The two production lines have their own independent main equipment, but share tanks for media and buffer preparation. They also share all utilities, such as steam, Water for Injection (WFI), Highly Purified Water (HPW), waste collection, and treatment systems, etc.

Process Simulation Tools – Evaluation and Selection

Computer-aided process design and simulation tools have been used in the chemical and petrochemical industries since the early 1960s. Simulators for those industries have been designed to model continuous processes and their transient behavior. However, most biopharmaceutical products are produced in batch and semi-continuous mode. Such processes are best modeled with batch process simulators that account for time-dependency and sequencing of events. In the mid 1990s, Aspen Technology, Inc. introduced *Batch Plus* (now called Aspen Batch Process Developer) a recipe-driven simulator that targeted batch pharmaceutical processes. Around the same time, Intelligen, Inc. (Scotch Plains, New Jersey) introduced *SuperPro Designer*. The initial focus of SuperPro was on bioprocessing. Over the years, its scope has been expanded to include modeling of small-molecule Active Pharmaceutical Ingredients (APIs) and secondary pharmaceutical manufacturing processes. In 2005, Intelligen introduced *SchedulePro*, a production planning and scheduling tool. SchedulePro also functions as a modeling tool that facilitates design, debottlenecking, and capacity analysis of multi-product facilities that operate in batch and semi-continuous mode.

Discrete-event simulators also have found applications in the pharmaceutical industry, especially in the modeling of secondary pharmaceutical manufacturing processes. Established tools of this type include *ProModel* from ProModel Corporation (Orem, Utah), *Arena* and *Witness* from Rockwell Automation, Inc. (Milwaukee, Wisconsin), and *Extend* from Imagine That, Inc. (San Jose, California). The focus of models developed with such tools is usually on the minute-by-minute time-dependency of events and on animation of the process. Discrete event simulators are often used to evaluate the impact of variation on step duration and random events, such as equipment failures and process delays. 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. For instance, BioPharm Services, Ltd. (Bucks, UK) have created an Extend-based module with emphasis on biopharmaceutical processes.

Microsoft Excel is 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 Excel that capture the

time-dependency of batch processes. This is typically done by writing extensive code (in the form of macros and subroutines) in Visual Basic for Applications (VBA) that comes with Excel. *K-TOPS* from Biokinetics, Inc. (Philadelphia, Pennsylvania) belongs to this category.

Engineers at Merck KGaA (the parent company of Merck Serono) have had experience with chemical/pharmaceutical process simulators like Batch Plus and planning tools like *Orion-Pi* from Axxom Software AG (Munich, Germany) and *SimPlan* from SimPlan AG (Munich, Germany). Batch Plus was initially considered for the project, but it was not finally adopted because of its limited bioprocess modeling and advanced scheduling capabilities. Instead, SuperPro Designer and SchedulePro were selected because the combination of the two tools satisfied both the modeling as well as the scheduling objectives of the project. SuperPro Designer can effectively model the bioprocess recipes, which can then be exported to SchedulePro to generate representative production schedules for the combined operation of the two production lines, thus enabling visualization of the utilization of shared resources, such as buffer preparation tanks and utilities. Another reason for the selection of these tools was the fact that SuperPro and SchedulePro had already been adopted by the research and engineering departments at the Vevey site of Merck Serono where the new facility was going to be constructed. The adoption of common tools by multiple departments created a common platform of communication among the various teams and provided assurance that the start-up and handover phases would be smooth.

Building a Model in a Batch Process Simulator

The first step in building a simulation model is always the collection of information about the process. In this case, draft versions of process descriptions and block flow diagrams, which contained information about material inputs and operating parameters, were available. Missing data forced the team to make assumptions after consulting with the operations department. Rough estimates were used at the start of the project for unknown process parameters and operating times. As the project progressed, the assumptions were updated several times and were thoroughly documented in order to comprehend and track the development of the various models.

The steps of building a batch process model are generally the same for all batch process simulation tools. The best practice is 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 (Figure 1) is developed by putting together the required unit procedures and joining them with material flow streams. Operations are added to unit procedures (see next paragraph for explanation) and their operating conditions and performance parameters are specified.

In SuperPro Designer, the representation of a batch process model is loosely based on the ISA S-88 standards for batch recipe representation.[12] A batch process model is in essence a batch recipe that describes how to a make a certain quantity of a specific product. A single basic processing step is called a "unit procedure" as opposed to a "unit operation," which is a term used for continuous processes. The individual tasks contained in a procedure (e.g., Transfer in, Ferment, Transfer Out, CIP, etc.) are called "operations." A unit procedure is represented on the flowsheet with a single icon that represents the main equipment used. Figure 2 displays the dialog through which operations are added to a vessel unit procedure. On the left-hand side of that dialog, the program displays the operations that are available in the context of a vessel procedure; on the right-hand side, it displays the registered operations for the edited procedure. The two-level representation of processing tasks (operations in the context of unit procedures) enables users to describe and model batch processes in detail.

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 obtained by the material 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 not 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. For certain types of equipment, minimum size requirements also are taken into account in order to satisfy constraints, such as minimum stirring volume in vessels.

The outputs of batch process simulators include the following:

- visual representation of the entire process
- material and energy balances
- sizing of equipment and utilities
- estimation of capital and operating costs
- process scheduling and cycle time analysis

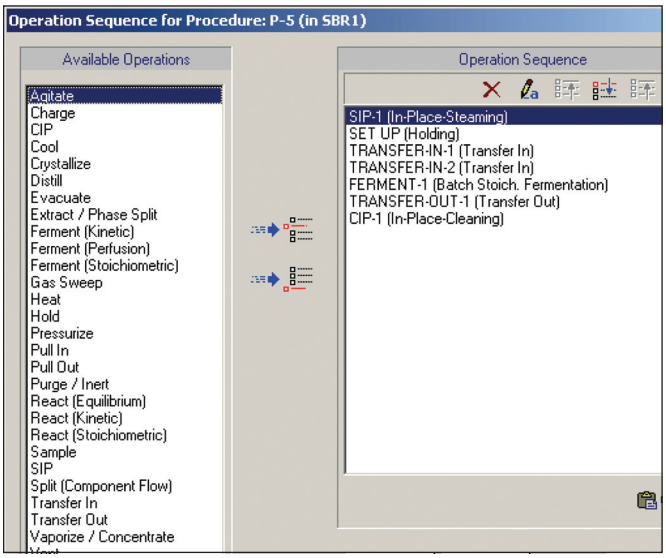

Figure 2. Specifying the operations of a unit procedure.

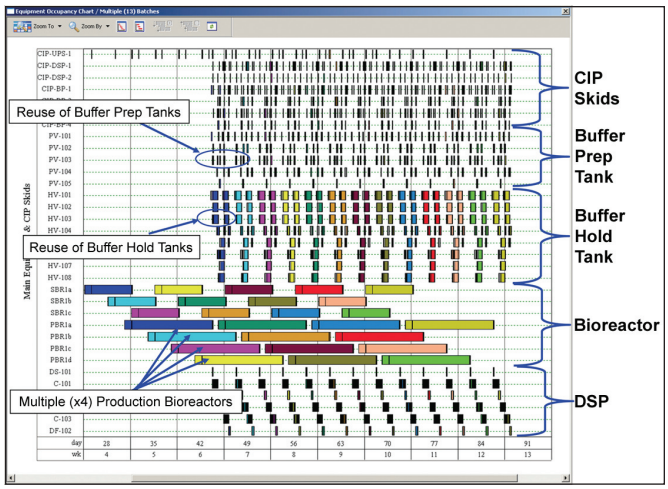

Figure 3. Equipment occupancy chart.

- throughput analysis
- environmental impact assessment

With respect to process scheduling and cycle time analysis, the results are typically visualized with Gantt charts that display equipment occupancy as a function of time - *Figure 3*. Equipment items grouped by type are listed on the y-axis and time is on the x-axis. The horizontal bars in the chart represent occupancy of the corresponding equipment by a procedure during a time interval. Different colors are used to represent different batches. Multiple bars of the same color on the same line represent reuse of a piece of equipment within a batch, while bars of different colors correspond to activities (unit procedures) of different batches. Scheduling conflicts arising from overlapping activities that share the same equipment are displayed with multiple lines (one for each conflicting activity) and exclamation marks on the y-axis. This type of chart enables engineers to resolve scheduling conflicts and optimize the cycle time of the process.

Modeling the Multi-Product Facility

After the SuperPro Designer models had been developed, the individual process models (recipes) were exported to SchedulePro for the generation of the multi-product model. Within SchedulePro, scheduling information imported from SuperPro Designer related to processing tasks can be expanded in the following ways:

- For every procedure, an equipment pool (instead of a single equipment) can be declared representing the list of alternative equipment that could potentially host that procedure.
- Auxiliary equipment (e.g., rinse in place skids and transfer panels) can be assigned, possibly through pools to operations.
- Flexible delays (i.e., the ability to delay the start of an operation if the resources it requires are not available) can be declared, thus relaxing the rigidity in executing a recipe.
- The general availability of resources in time can be declared through a calendar.

All these extra features proved very useful especially in modeling the media and buffer preparation tasks. The multi-product model offered us the ability to represent and visualize the demand of shared resources, such as media and buffer preparation tanks, utility generation systems, and bio-waste treatment systems. The structure and boundaries of the multi-product model are shown in Figure 4.

As soon as the multi-product model was constructed, it was used to answer a wide variety of questions concerning utility and raw material consumption, potential scheduling conflicts, and plant capacity issues.

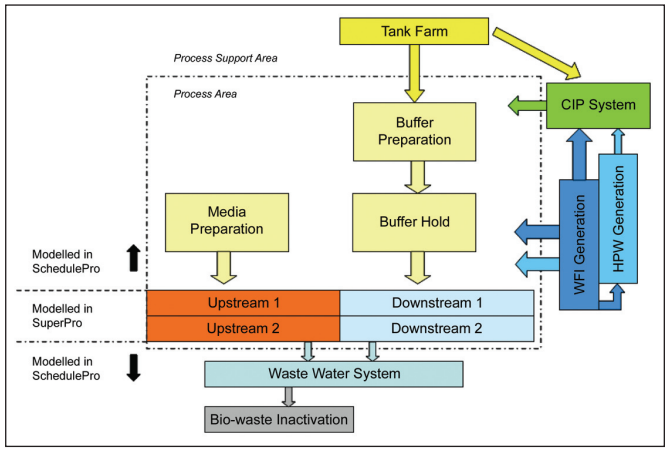

Figure 4. Structure and boundaries of the multi-product model.

Challenges Related to Model Development and Validation

The processes that were analyzed in this project have been developed using a platform technology approach that aims to standardize the number and the sequence of the production steps as well as the media and buffer solutions used. All process parameters that affect product quality (e.g., bed height of chromatography purification steps) were fixed by the end of process development. Such process parameters were not altered during the scope of this project. Instead, the focus was on engineering parameters that affect capital cost and capacity (e.g., number and size of vessels for buffer preparation and storage, requirement for transfer lines, cleaning skids, etc.).

Keeping the models up to date proved to be quite challenging because the design of the facility underwent many changes. The collection of information concerning changes in the processes and the general plant design is a tedious and time-consuming task, due to the fact that many people are involved. It would be advisable, for future practitioners, to develop an appropriate information workflow and change-management process that includes the simulation team, thus enabling the members of the simulation team to have constant access to the latest process and plant information.

The validation of the model was based on information that was available to the team (e.g., process description, op-

erational experience based on past runs, analytical results, etc.). The validation of the process parameters was based on batch records from previous runs carried out by the process development department. Values from existing processes were used as a first approximation for operations that are similar in other bioprocesses, such as buffer/media preparation and CIP/SIP activities.

The modeling of the buffer preparation area was one of the most challenging tasks of the simulation. That was due to the fact that many constraints had to be taken into account - *Figure 5*. In terms of main equipment, this area included several buffer preparation vessels. The list of auxiliary equipment included three closed powder transfer systems and two Rinse-in-Place (RIP) skids. The model included interfaces to the utilities that are used in buffer preparation and an interface to the tank farm. The preparation of the 40 different buffers required by the two processes was represented with 40 different recipes. The large number of buffers required, even though platform technology is adopted, is due to the different physical properties of the two products (the first product is a monoclonal antibody and the second is a fusion protein). Modeling of buffer preparation and hold activities was particularly challenging because it involved numerous connectivity constraints. For example, if a certain ingredient from the tank farm was required for the preparation of a certain buffer, but not all preparation vessels were equipped with a supply line from the tank farm for this certain ingredient, then some of the preparation vessels could not be used for preparing that specific buffer. These constraints were modeled by specifying appropriate equipment pools for the various buffer preparation procedures.

The handling of shift constraints also was quite challenging. Since certain areas of the production facility were planned to operate in a two-shift-mode, appropriate outages (downtime) had to be specified for the involved equipment, and flexible delays had to be added to some of the operations. Using flexible delays, the tool was able to automatically shift the start of an operation (or interrupt an operation) in order to accommodate facility downtime and/or unavailability of required resources. The tool also is able to handle material supply, utility, and personnel constraints. However, such constraints add to the complexity of the model and increase the computation time significantly. If a problem is over constrained, the tool may even fail to generate a meaningful solution.

Discussion of Results

The models were mainly used to size shared resources (e.g., utilities and media/buffer preparation tanks) and evaluate various capacity scenarios. The impact of different shift patterns on equipment demand for buffer preparation also was evaluated. Using such tools it is easy to quantify the trade-off between labor cost and capital investment when management wants to decide whether buffers should only be prepared during the day shifts or around the clock. The former option involves lower labor cost, but higher capital investment. However, it also constitutes a solution of higher inherent capacity. More specifically, if product titers increase

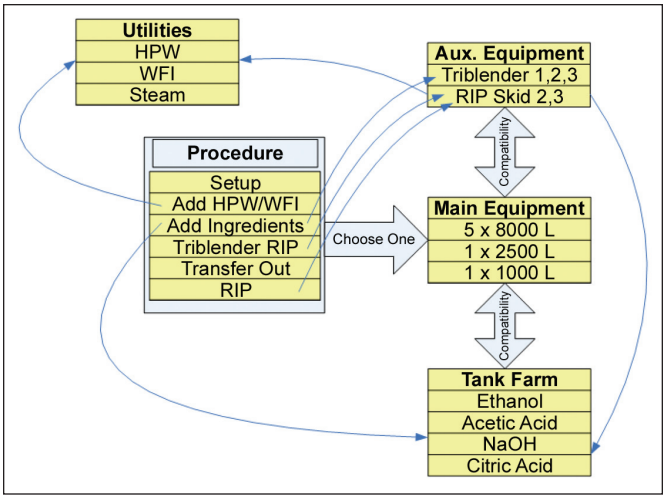

Figure 5. Buffer preparation constraints.

in the future and there is a need for reduced purification cycle times, the plant may switch to a three-shift operation for buffer preparation in order to accommodate the increased demands of the purification trains.

Sizing of WFI systems is simplified considerably using these tools. 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. Plant capacity may be limited by any of the following:

- The plant cannot, on average, consume more water than the still can generate.
- The peak demand cannot exceed the capacity of the circulation system.
- The surge vessel must be large enough to maintain capacity during peak demand.
- Periodic circulation loop sanitization cycles may interrupt all WFI draws.

Process simulation can provide reasonable estimates for the sizes of the still, the surge tank, and the pumping capacity of the circulation loop. Figure 6 displays the demand of WFI for

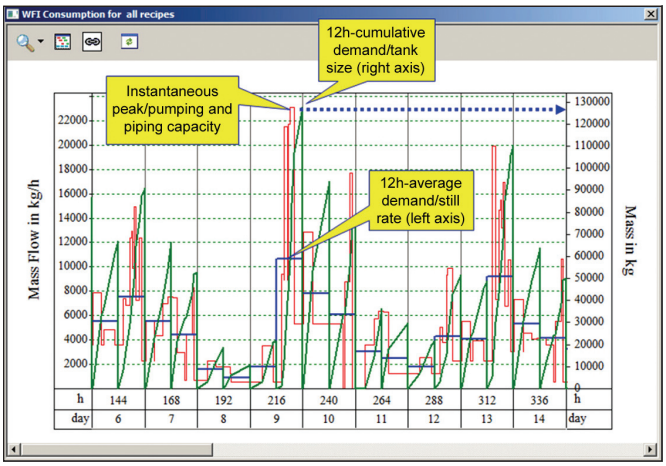

Figure 6. Instantaneous (red lines), 12-h averaged (blue lines), and 12-h cumulative (green lines) WFI demand as a function of time.

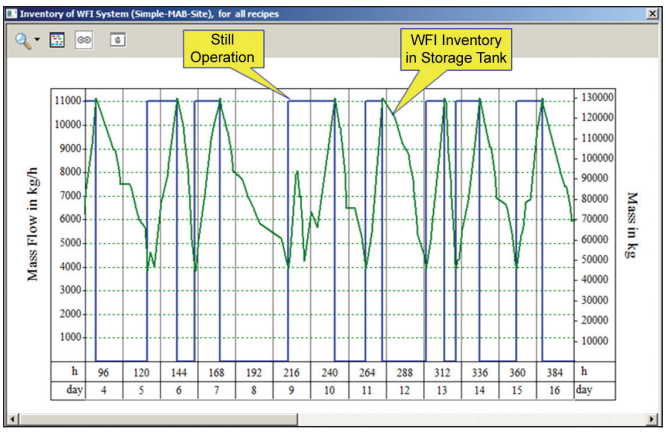

Figure 7. WFI inventory (green lines) and operating frequency of still (blue lines).

such a plant. The chart shows the instantaneous (red lines) and the 12-h average (blue lines) demands. The chart also shows the 12-h 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 (23,000 kg/h). The peak 12-h average rate provides an estimate for the still capacity (10,600 kg/h) and the corresponding 12-h cumulative peak is an estimate of the surge tank capacity of 128,000 L. 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 7 displays the inventory profile of WFI in the surge tank (green lines) for a tank size of 130,000 L and a still rate of 11,000 L/h. The still is turned on when the level in the tank falls below 35% and it remains on until the tank is full. The operation rate and frequency of the still is depicted by the blue step-function lines.

Sizing of bio-waste treatment systems can be handled in a similar way. Such systems typically involve two tanks that alternate in operation periodically (while one is receiving, the other is treating a batch of waste material). The peak cumulative amount for the alternating period indicates the minimum capacity of each tank.

The tools also were used to analyze the impact of buffer

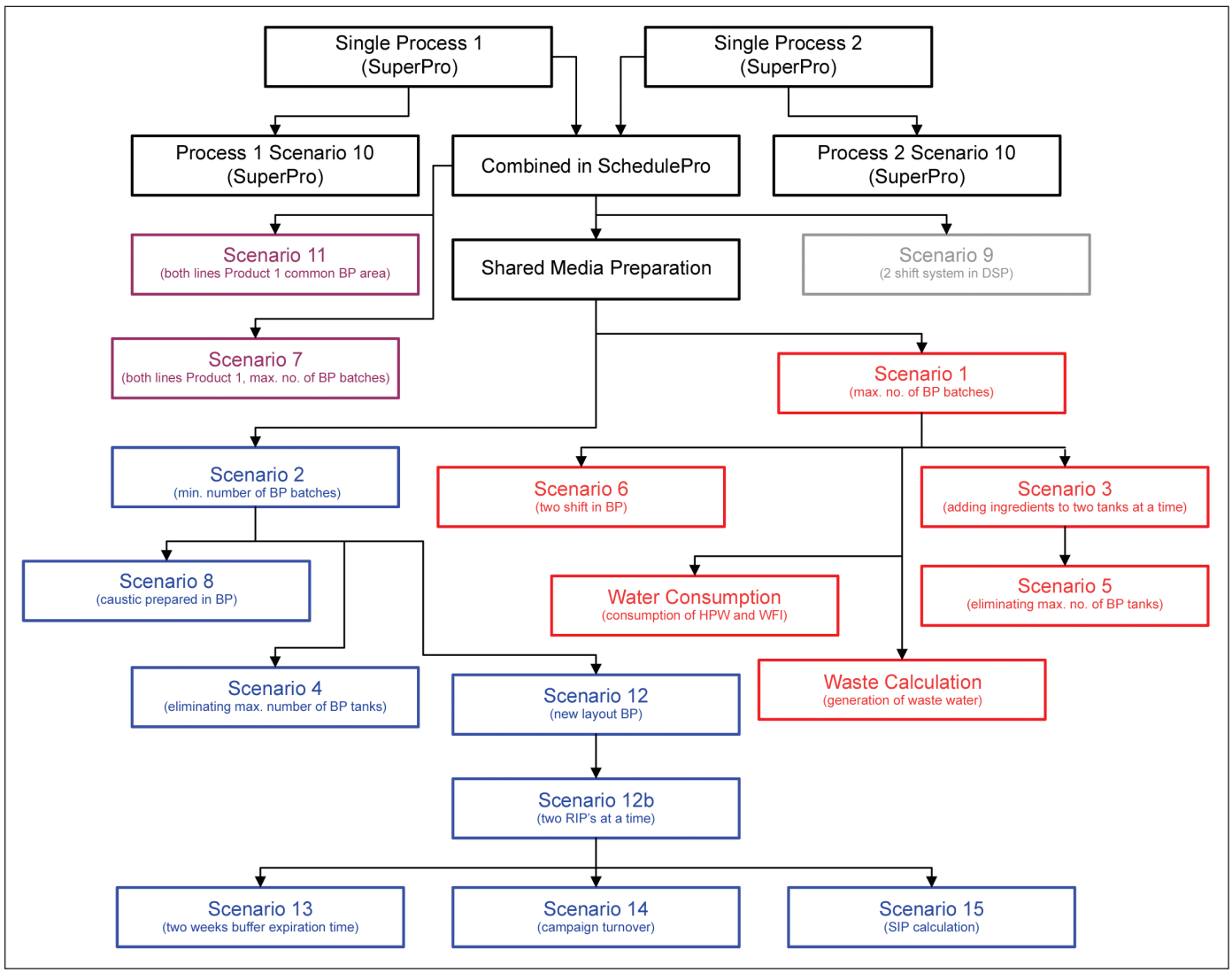

Figure 8. File diagram representing the evolution of the scenarios: Buffer Hold (BH), Buffer Preparation (BP), Rinsing in Place (RIP), and Sterilization in Place (SIP).

expiration times, shift patterns, equipment sizes, and number of equipment items. Approximately, 35 different scenarios were evaluated during the project and most of the scenarios included major model updates. As the project evolved, the team's understanding of the processes, the facility, the underlying links, and constraints improved, and the knowledge gain was used to improve the models. Figure 8 shows the evolution of the models up to scenario No. 15.

As mentioned before, the initial stages of the project focused on the development of the SuperPro models of the two processes (one for each product). The SuperPro models were then combined in SchedulePro to generate the first multi-product model. Next, a rough model representing media preparation was added to the multi-product model. Two different options for buffer preparation and holding were evaluated. Option number one involved refilling of the buffer hold tanks after every batch of the corresponding main process. That led to a set of scenarios where the maximum number of buffer preparation batches was performed (red scenarios in Figure 8). Option number two involved the preparation of larger buffer batches that could supply multiple batches of the main process. That led to a set of scenarios where the minimum number of buffer preparation batches was performed (blue scenarios in Figure 8). The final design evolved out of the blue set of scenarios.

The simulation of the process support areas was quite challenging and required an iterative approach. The buffer preparation area was initially represented with a simplified model. Next, minimum cycle times for each process were specified and the tool was used to generate feasible solutions. Experienced manufacturing engineers were then asked to evaluate the results and confirm that the generated solutions would work out in practice. For questionable solutions, improvements were proposed involving rearrangement of existing equipment or installation of additional equipment. Then, the changes were incorporated into the model and feasibility was checked once again. That worked very well for the buffer preparation area and valuable results were gained from the model. The final model also contained constraints for the delivery lines, the Rinse-in-Place (RIP) skids, the powder transfer systems, the connectivity to the tank farm, and the personnel resources, including shift patterns.

Using the model, a number of potential bottlenecks mainly associated with cleaning equipment and delivery lines were identified and resolved. Capacity analysis enabled the team to identify a number of opportunities for equipment savings. That approach worked especially well for areas with multiple parallel equipment items, such as media and buffer preparation. When analysis revealed that spare capacity existed, resources were gradually removed from the equipment pool and feasibility rechecked. That eventually resulted in infeasible situations. Addition of an extra resource item led to the optimal solution.

Return on Investment

Table A summarizes the subjects that were analyzed and the benefits that were derived from the use of simulation tools. The core of the analysis was done during a period of 12 months. Besides the financial aspects, there were additional benefits that are hard to quantify, but are equally valuable. The common language of communication that process simulation brings to the different stakeholders was probably the most important qualitative benefit. The members of the various teams involved with plant design and operations were able to communicate effectively despite the fact that they were looking at the plant from different points of view: engineering vs. operations vs. maintenance. It was recognized that the graphical presentations generated by such tools helped stakeholders to visualize the problems and come up with solutions more efficiently.

Model Lifecycle Management and Hand-Over to the Operations Team

The simulation work was intended to support the engineering team during the detailed design phase. However, the simulation model continues to live and evolve in the operations

No.	Subject	Initial Approach	Benefits
1	Vessels for the buffer preparation area	The initial number had been estimated using basic engineering assumptions and conservative design.	The detailed model enabled the team to eliminate one 2,500 L and two 8,000 L tanks, resulting in savings of more than $1.2 million (€0.85 million).
2	Sharing of the bulk filtration unit	The initial design assumed a bulk filtration unit for each production line.	Simulation showed that sharing of the unit by the two production lines is feasible, leading to savings of $1.4 million (€1 million).
3	Sizing of HPW and WFI supply systems	The initial design was based on overall averaged demand without taking into account the demand as a function of time.	The detailed simulation model enabled the team to size these systems more accurately.
4	Sizing of waste treatment systems	The initial design was based on simplified spreadsheet models.	The detailed simulation model enabled the team to size these systems more accurately and reduce capital expenditures.
5	Tank farm sizing	In the plant, basic chemicals are stored in the tank farm. The number of tanks and their sizes had been estimated using crude spreadsheet models.	The detailed simulation model enabled the team to size the tanks and the delivery lines more accurately and confirm the reliable supply of these chemicals to the production lines.
6	RIP routing in buffer preparation and holding areas	The initial piping design for this area was so crowded that the simulation team had been asked to evaluate the impact of an alternative piping design which uses fewer pipes and couples the usage of two RIP stations.	The process simulation model showed that this is achievable even with additional rinsing of the tri-blender (a closed introduction system for buffer preparation).

Table A. Subjects analyzed and benefits derived.

department. The detailed model, which constitutes a virtual plant, was handed over to the operations team to help in preparing the personnel for the start-up of the plant and its "routine" production schedule.

The model developed in SchedulePro by importing the SuperPro Designer recipes of the two processes will be transferred into the new production facility and serve as a basis for the scheduling of the future production activities. However, many details included in the model are not necessary for on-going scheduling purposes and lead to long calculation times (several minutes) every time a new production schedule is generated. Currently, a new "simpler" model is under development in SchedulePro to support the scheduling of the future production activities. Less detail will be specified in each unit procedure; for example, the typical operations of a chromatography cycle (e.g., load, wash, elution, regeneration, etc.) will be lumped into a "cycle" activity and consequently a chromatography procedure will be represented as a sequence of the following events: equilibration, cycle-1, cycle-2, … cycle-n, and sanitization. Similar simplifications will be implemented in the procedures that represent buffer preparation and holding activities. The simplified model is intended to be used by the operations department to:

- plan the activities during the start-up of the new production facility
- analyze the bottlenecks at full production capacity
- analyze and schedule changeovers (change from one process to another on a production line)
- consider the impact of equipment maintenance on production schedule
- analyze the influence of a failure or delay of one step on the following steps of a batch and on the scheduling of subsequent batches
- understand interdependencies between shared areas and production lines

Conclusions

When applied early, simulation tools can support plant design and technology transfer and can facilitate the communication between the engineering and operations teams. In this project, process simulation was started early during basic engineering and valuable results were obtained from the process modeling effort. The insight that modeling provided for the design of the support areas, such as buffer preparation and holding, utilities, and equipment cleaning requirements, was of particular importance. In general, process simulation tools, such as SuperPro Designer, are useful for understanding and improving a process whereas process scheduling tools, such as SchedulePro, are beneficial for estimating equipment and utility requirements for multi-product facilities. Scheduling tools also facilitate production planning and scheduling of operating facilities on an on-going basis. Future practitioners are advised to apply process simulation tools as early as possible in a project. That way, more synergies can be achieved. The use of process simulation in this biopharmaceutical project was a success. It provided additional insights on how a design could work in reality. The final models have been handed over to the operations team to be maintained and for future use. The scheduling models can be used for production and maintenance planning as well as scheduling in the future. They might also prove valuable for bringing new products into the facility. The SuperPro process models might serve as basis of decision making for future process changes.

References

1. Petrides, D., Koulouris, A., and Lagonikos, P., "The Role of Process Simulation in Pharmaceutical Process Development and Product Commercialization," *Pharmaceutical Engineering*, January/February 2002, Vol. 22, No. 1, www.ispe.org.
2. Petrides, D., Koulouris, A., and Siletti, C., "Throughput Analysis and Debottlenecking of Biomanufacturing Facilities, A Job for Process Simulators," *BioPharm*, August 2002.
3. Petrides, D., and Siletti, C., "The Role of Process Simulation and Scheduling Tools in the Development and Manufacturing of Biopharmaceuticals, *Proceedings of the 2004 Winter Simulation Conference*, Ingalls, R.G., Rossetti, M. D., Smith, J. S., and Peters, B. A., eds., pp. 2046-2051.
4. Tan, J., Foo, D.C.Y., Kumaresan, S., and Aziz, R.A., "Debottlenecking of a Batch Pharmaceutical Cream Production," *Pharmaceutical Engineering*, July/August 2006, Vol. 26 No. 4, pp. 72-82, www.ispe.org.
5. Pharmaceutical Research and Manufacturers of America, Biotechnology Research Continues to Bolster Arsenal Against Disease with 633 Medicines in Development, PhRMA 2008 survey, www.phrma.org.
6. Walsh, G., "Biopharmaceutical Benchmarks 2006," *Nat. Biotech*, 24(7) 2006:769-775.
7. Farid, S.S., "Established Bioprocesses for Producing Antibodies as a Basis for Future Planning," *Advances in Biochemical Engineering / Biotechnology*, (2006) 101: 1-42, published online 8 June 2006.
8. Pavlou, A.K., Belsey, M.J., "The Therapeutic Antibodies Market to 2008," *European Journal of Pharmaceutics and Biopharmaceutics*, 59(3) 2005:389-396.
9. Jagschies, G., "Where is Biopharmaceutical Manufacturing Heading?," *BioPharm International*, 21(10), October 2008.
10. Farid, S.S., "Economic Drivers and Trade-Offs in Antibody Purification Processes," *BioPharm International,* http://biopharminternational.findpharma.com/biopharm/Downstream+Processing/Economic-Drivers-and-Trade-Offs-in-Antibody-Purifi/ArticleStandard/Article/detail/633295, 2 October 2009.
11. Low, D., O'Leary, R., Pujar, N.S., "Future of Antibody Production," *Journal of Chromatography*, B 848(1), 2007:48-63.

12. Parshall, J., Lamb, L., Applying S88 – Batch Control from a User's Perspective, Instrument Society of America (ISA), Research Triangle Park, North Carolina, USA, 2000.

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This article presents some helpful "tips and suggestions" regarding building capital projects in China.

"East is East and West is West" – Managing Capital Investment Projects in China

by Jerry Hourihan and Gordon Lawrence

Introduction

"Help one another, for we are all in the same boat."
Chinese Proverb

More and more project management professionals from North America and Europe are finding that their work is taking them eastward to China. The authors of this article are two such professionals. In the spirit of the Chinese proverb quoted above, we offer this article containing some "tips and suggestions" based on our experience of recent capital investment projects in China, in which we have been involved.

The article is intended for those project professionals who may have many years of experience of building in places such as Europe or North America (hereinafter referred to as "the West"), but who have never worked in China before and may be faced with just such a challenge in the near future.

The Basics Still Apply

The first thing to remember is that just because the project will be built in China, it does not mean that the basic rules of successful projects do not apply. These rules are just as important here as anywhere else in the world. They are:

- ensuring clarity of business objectives at the start
- achieving a good level of front-end definition before committing funds for detailed engineering, procurement, and construction
- ensuring clarity of team organization, roles, and responsibilities

These three key areas are still vital and must not be forgotten.

Getting a Bigger Bang for Your Buck

One business reason given for setting up in China is the knowledge that building a facility there is less expensive than building a similar facility in the West. However, the arguments start when one begins to discuss just how much cheaper it may be to build in China.

Location adjustment figures can range from well below 40% up to around 80% of the cost of a similar facility in the USA,[1] depending on facility type and geographical location within China.[2] The "International Construction Cost Index," published by Faithful and Gould[3] currently indicates that a simple "light industrial" facility[4] in Shanghai should cost approximately 59% of the cost of a similar facility in Chicago, Illinois.

In our experience, the more a facility is based on simple building structures and the more that it is possible to source equipment locally, the greater the capital cost saving when compared with a similar facility in the West. However, as the need for complexity in the facility construction increases, through a need for specialized architectural room finishes, complex HVAC systems, or complex, specialized process equipment, the cost increases and the difference between China and the West reduces.

In addition, the other deciding factor in the capital cost is the location. Those facilities built in or near the east coast, developed cities of Beijing, Shanghai, and Guangzhou will likely cost more than a similar facility built further west.

Front-End Design

Home-Based or In-Country?

An early question that will arise for the project team relates to the strategy for designing the project; namely, should the front-end design be done in the owner's home country/region or in China?

Home-Based

The advantages to the owner of doing the front-end design in the home country/region are that one:

- is likely to have a greater knowledge of the strengths and weaknesses of the contractors available to bid for the design
- can potentially keep a closer eye on design quality
- can probably expect transparent, "Western" style project control practices
- can delay the time when one has to relocate team members as (very expensive) expatriates to China

However, there are generally two major potential disadvantages to doing the front-end design at a remote distance from China.

1. Since any facility will need to be compliant with local design laws and operating norms, it is necessary to employ a design contractor that can demonstrate either in-house knowledge of Chinese rules and regulations or can demonstrate that it has a partnership with a Chinese Local Design Institute (LDI)[5] that can provide such knowledge.
2. If the project is a "brownfield" expansion of, addition to, or upgrade of an existing facility, the design team will still need frequent and extended access to the site to survey the existing facility and to discuss and coordinate the design with end users. Hence, the design budget will require considerable funds for accommodation and for travel to and from the proposed construction site.

In-Country

If one opts to do the design in China, one avoids the two disadvantages listed above. However, one immediately has to relocate the owner team members to China with all the expatriate costs that entails. Perhaps more importantly, one also has the decision of whether to employ an international design contractor (e.g., one from Europe, North America, Singapore, Australia, Korea, or New Zealand) who has offices in China or to work directly with a Chinese LDI. The decision to choose an international contractor is usually driven by the desire to retain at least some of the quality control advantages of working in one's home country/region, while avoiding the need to commit a large owner team to supervise and monitor the LDI. (However, there is another issue to consider in using international contractors. The more expats used by the contractor, the more expensive the team, and the less cost advantage gained. We found that those international contractors that had taken the time to train local staff, while imposing international working procedures, held the cost advantage. We also found that while many of these contractors had secondary/pharmaceutical experience, fewer of them had bulk/active pharmaceutical ingredient experience).

Which to Choose?

As we have shown above, each strategy has advantages and disadvantages. The important thing to consider is how the strategy fits your particular project. We have used both home based and China based strategies. In our view, if the owner has only a small team (which he inevitably does), the better strategy is to do at least conceptual design on a home-based basis and preferably, basic design as well. Then, when you do eventually move to China, work with the LDI through an international contractor that has China experience.

Why Do You Need an LDI?

No matter which strategy is used, before the end of Basic Design, an LDI will need to be involved. This is due to complex system of design authorization and government permits that are required for every project, specifically, the need for an authorized design house to stamp (or "chop" in the local slang) design packages to confirm they have been designed in compliance with regulations. In order to be authorized to "chop" drawings, a design contractor needs to be licensed and registered by the relevant local Chinese authority. In practice, the only companies who currently have such approval are LDIs.[6] Consequently, even if the front-end design is carried out in the home country/region, an LDI will still need to be employed to review and approve the design, submit the permit application to the authorities, and "chop" the approved drawings.

Government Permits

Every country has certain permits and approvals that are required in order to proceed with designing, building, and operating a facility. However, the permit requirements in China are much more complex, and due to the fast pace of development in China, subject to revision/modification at unexpected intervals.

Understanding the Permits and their Sequence

Permit requirements in China occur at every stage in the project process, from the initial decision to invest, through design, engineering, procurement, construction, and commissioning, up to and including start of operations. They also require one to work with numerous government agencies. Hence, it becomes clear that any project team needs an LDI that is experienced in knowing which permits are required and when. Table A shows an early draft of a permit list for one of our smaller projects. We provide it purely as an example to indicate the scale of the issue. (To claim it is a comprehensive list would be foolhardy on our part). This project did not need the full range of permits because it was an expansion of an existing building, not a new site or a new building.

Understanding Regional Interpretations of Permit Regulations

In addition, there can be slight variations in the interpretation of the regulations from region to region. Consequently, it is important to have an LDI that is not only knowledgeable about the Chinese permit system, but also about how that system is enforced in the specific region in which you are building. Space does not permit us to go into details, but we experienced several instances where designs had to be modified because of differences in interpretation of regulations from one region to another.

Managing the Timelines for Permit Applications

It is important that the various permits are correctly represented in the project schedule in order to set a realistic timeline.

What Permit is Needed For	Permit Title
Permits to Proceed with Project	- Project Verification - Business License - Environmental Impact Assessment - Project Permit - Encourage Industry Permit
Permits to Recover VAT and Gain Customs Exemption	- Master Equipment List (MEL) Preparation - MEL Customs Registration – City Authorities - MEL Customs Registration – Regional Authorities - MEL Customs Registration – Provincial Authorities
Permits to Proceed with Engineering	- Preliminary Design Package (PDP) for the Planning Bureau - Registration of LDI with City Authorities
Planning Permit	- Planning Bureau Permit
Approval of Engineering	- Construction Drawing Design Audit - Fire Fighting Design Certificate - Lightning Protection Design Certificate
Permits to Proceed with Construction	- Construction Permit (Construction Bidding Registration, Safety Permit, Quality Permit) - Approval to Break Ground - Registration of Construction Supervision Contractor - Registration of Construction Quality Supervisor - Cement Funds Approval - White Ant Prevention Certificate - Land Planning Permit
Approval of Installation	- Fire Fighting Installation Certificate - Lightning Protection Installation Certificate - Construction Quality Bureau Approval - Construction Planning Re-Measure Certification - Electrical Power Requirement Approval - Special Equipment Final Acceptance Certification - Special Equipment Registration - Construction Safety Record Certification - Construction Environment Certification - Acceptance of Project Archive
Permits to Proceed with Operations	- Project Completion Certification

Table A. An example (for illustrative purposes only) of some of the permits required.

Several of the permit applications are almost certainly going to be on the "critical path" of the project schedule. Consequently, it is vital to closely manage the permit application process, including preparation of applications, application submissions, and (hopefully) receipt of approvals. To manage the various permits, the following steps should be taken:

- Set up a "Permits Team" with responsibility for coordinating and progressing permit applications.
- Appoint one person from within that Team with single point responsibility for keeping track of progress of all permits.
- Keep a register of all permits.
- Hold regular meetings of the "Permits Team" to monitor progress, maintain the permit application schedule, and be prepared to take action when obstacles arise.

Preparing the Permit Application

Any application will frequently go through several reviews by the relevant Bureau and it is important to maintain a task-list, identifying all comments received from the Bureau reviews. All of the comments must be reviewed, and where appropriate, dealt with in a timely fashion. Even though it may not be obvious that the Bureau is reviewing these items, at some stage, usually just before final approval, the Bureau will assuredly check that they have been addressed.

Submitting the Permit Application

Even though it is acceptable for the owner firm to have the contractor/LDI prepare the permit application, it is advisable to have someone from the owner organization act as the interface with each Bureau, rather than leave it entirely to the contractor. In this way, the owner demonstrates to the bureau that the owner attaches importance to the application.

Construction Permits and Overlapping of Engineering and Construction

In Europe and North America, it is common practice to overlap detailed engineering and construction work by around 20 to 30%. In China, this is a less accepted practice. The ideal approach from the point of view of the Chinese authorities is that you should finish all your design details and submit them for approval in one package, followed by a single approval for construction. We discovered that any deviation to this approach requires negotiation with the applicable Bureau with no guarantee of success. Since construction cannot start until the permit is received, and the permit cannot be applied for until a considerable quantity of the detailed engineering is complete, this should be accounted for in your timeline.

Working with an LDI

It should now be clear that the project will need to employ an LDI at some stage during design or detailed engineering. So what are some of the issues associated with dealing with a LDI?

Registration of the LDI

China is divided into different provinces, each with its own specific regulations, similar to state versus federal regulations in the USA. Consequently, when choosing an LDI, it is important to ensure that not only is the LDI authorized to "chop" design drawings, but that their authorization is registered with the local regional authority. As an example, drawn from our own experience, an LDI previously registered for work in Shanghai, which was hired to work on a project near Suzhou (80km from Shanghai), had to re-register with the Suzhou authorities. The Shanghai registration was not valid.

Pharmaceutical Experience

A lot of the process engineering work performed by LDIs in the past was in the chemical and petrochemical industries. Consequently, there may be a lot of experience among the LDI staff in civil and structural disciplines, power, mechanical/rotating equipment, and large bore pipework, but less experience in small bore specialized pipework, control and instrumentation, specialist HVAC for clean areas, and specialist architectural finishes for clean areas. It is important to assess the level of experience early on in dealing with the LDI, and where necessary, bring in additional expertise to reinforce the weaker areas.

"Constructability" Experience

In our experience, it is not common for the LDI design staff to visit the site or deal with practical design issues on site. Their normal method of working is to prepare a design remotely from the construction site and "pass it over the fence" to the construction team. This can lead to problems with:

- reluctance to visit the site to survey existing facilities for a revamp project
- poor design "constructability"
- poor estimating of material quantities for cost estimates, and a tendency to focus only on the main items and not on the small details, which are required along with the main items
- lack of efficiency in resolving construction technical queries
- a tendency to repeat design errors in the design office that were previously unearthed at the construction site

Drawing Quality and Document Control

The review and approval of drawings prior to issuing, as well as document numbering and control may not be to the standard you typically expect. You may find you need to spend time ensuring this is of an acceptable standard.

Design Flexibility

It appears that Chinese clients make few changes during execution and in general leave it to the LDI to make design decisions. This can manifest itself in an unwillingness on the part of the LDI to show flexibility in dealing with client requests for changes in project priorities or design.

Project Control Practices

Perhaps because LDIs are used to a more "hands off" approach from clients, there may be a reluctance to demonstrate project schedules and project progress in the form you are used to. However, by judicious questioning, you may find more progress has been made than first appears.

Value for Money

In general, if the above points are evaluated properly, LDIs in China offer good value for money.

Procurement

As on any project, efficient working of the procurement team is a key aspect of project success. Strong procedures and clear workflows are normally necessary to remain compliant with your company finance rules.

Equipment Procurement

Choosing Vendors

There is an obvious cost benefit in sourcing some or all of your process equipment in China. However, as with purchasing anywhere, it is important to specify the design and fabrication quality that you expect to receive. In China, as in other parts of the world, the vendor may well be willing to offer a low price, but it may be because he cannot offer the design complexity or the quality of finish that you require. Therefore, it is important to thoroughly vet potential vendors before including them on any bid lists. The vetting process should include visits to the workshops, not just desk surveys. This all takes time and it needs to be allowed for in the project schedule.

Obtaining Quotes

When preparing a good quality ±10% cost estimate, it is usual to obtain firm quotes for all major and long lead items of equipment and budget quotes for the lesser equipment items. However, in our experience, Chinese vendors are very often reluctant to provide firm, detailed quotes for use in cost estimates on projects that are not yet approved. The issue seems to be that they do not wish to "waste time" providing a detailed quote for a project that may not be approved for several more months (if at all). The attitude seems to be "come back when you're ready to place the order." This can be a serious issue for cost estimate accuracy. Even getting a quote can require the purchasing officer to expend considerable effort with the vendor. To turn that quote into even a good budget standard will take a lot of time and effort from the engineer and the purchasing officer to try and "expedite" the vendor into bringing his quote up to a reasonable standard.

In addition, whereas in the West, a budget quote can generally be relied upon to be at the high end of the likely final cost; in China, there is a tendency to provide low early quotes in the expectation that this will encourage you to continue discussions.

Fabrication Quality

In any location around the world, it is important to inspect equipment during manufacture. China is no exception. You

must be prepared to invest adequate time and resources in an inspection program tailored for your project needs. In addition, it is important to ensure that all inspectors engaged for such a role are reliable. In one example, we received poor quality equipment despite numerous works inspections. The problem was traced to the inspector failing to adequately fulfill his role.

Delivery

There is a saying in English, "The squeaky wheel gets the grease" (i.e., the one that shouts loudest gets what he wants, whether he is the most deserving or not). We have heard of situations where an order which one thought was on time, is suddenly several weeks behind. Upon investigation, one discovers that another customer has come in, paid a premium, and been allocated "your" materials in the workshop, while you are now returned to the back of the workshop queue. In China, you may find that you need to put more effort into expediting than you are used to.

Importation Permits

As with engineering and construction work in China, the importation of equipment requires various permits to be considered, and if required, applied for. As an example, in order to obtain a customs duty waiver on some equipment (and until recently, in order to recover Value Added Tax (VAT) as well), it is necessary to provide lists to the relevant authorities of equipment that is being bought and imported. These lists need to be relatively accurate in terms of supplier and the cost of the item if the full waiver or refund is to be obtained. Ideally, these lists need to be submitted well before expected order placement, in order to receive approval before the order is placed. But this needs to be balanced against the fact that you may not have accurate equipment costs until late in the basic design phase, at which point you wish to place orders immediately. Again, this potential area for delay needs to be planned into the schedule.

Bulk Materials

When ordering bulk materials in the West, unless schedule is an overriding concern and orders need to be placed early, it is common to ask the construction contractor to supply the material. In theory, this removes the burden of supply from the owner, removes the risk of claims for delay due to non-arrival of material, and opens the potential for obtaining cheaper materials since the contractor can buy "in bulk." However, this strategy is less successful in China for two reasons:

1. The contractors may feel that their cash flow situation will not allow them to buy large quantities of expensive material.

2. Unless the owner puts a lot of effort into quality control, the contractors may provide sub-standard material.

As a consequence, you may be forced into buying bulk material whether you want to or not.

Construction

Construction Management

As with projects anywhere in the world, it is important to try and appoint the construction management team early so that they may be involved in constructability reviews of the design before it reaches site. When getting ready to actually move to site, finding mid-level construction supervisors with the necessary multi-discipline coordination experience is, in our experience, difficult.

Choosing your Contractors

Permits…Again!

When choosing construction contractors, the issue of permits arises again. Ideally, any construction contractor shortlisted should have a good, working relationship with the relevant local government bureau (e.g., The Fire Protection Installation Contractor should have a good relationship with the local branch of the Fire Prevention Bureau). This can help smooth communication when trying to obtain permit approvals. It is then a good idea to listen to the contractor's advice with regard to dealing with that Bureau.

Manage the Relationship

It is very important to develop good relations with the higher management of the individual contracting companies. If difficulties do arise, this can matter more than the precise details of the contract agreement signed by everyone at time of award.

Nomination of the Main Contractor

Chinese regulations require that one construction contractor be nominated as the "main" contractor. This in itself is not a major issue. However, problems arise if one then wants to start a second major project on a site where a "main" contractor is already in place on an earlier project. Trying to nominate a different "main" contractor for the second project may be difficult.

Choice of Quality Control Contractor

Ensuring that construction quality standards are upheld is an important job on any construction site. In China, the appointment of a quality control contractor (a "Jianli" in the local jargon) is mandatory on larger projects. The Jianli's role, although paid by the owner, is to ensure that regulatory codes and government quality standards are adhered to. It is in your interest to choose a good contractor for this role. In one example, testing by our Jianli demonstrated that some pre-formed piles were not to specification, despite having been supplied with certificates showing they were to the correct specification. The contractor replaced the piles at no extra cost.

Working with your Contractors

Progress Measurement

In our experience, there is a tendency by contractors (both LDIs and construction contractors) to avoid giving bad news until the last moment. Consequently, it is necessary to actively seek out the real situation regarding progress and potential

issues if you are to avoid surprises and delays. Bad news will not usually be offered voluntarily. This results in the owner needing to retain active and persistent project engineers and project controllers on the team to constantly seek out the "true" status.

Re-Negotiation of Terms

One big surprise for a Westerner is the discovery that renegotiation of the elements of contractual agreements post-award is regarded as a reasonable practice by contractors, especially if the commercial outcome begins to look less attractive to them than originally envisaged.

Workforce

Skilled Labor

The impression that many Westerners have is that construction workers in China are in plentiful supply. The reality is that unskilled workers are in plentiful supply, but skilled workers, such as welders and pipefitters, may be harder to find.

Construction workforces in China frequently consist of migrant labor, who move to the more prosperous Eastern regions from the less developed regions of the far West. Many of those workers may previously only have had very limited experience of anything other than farm work. Because the workers are usually migrants, they tend to live in a "camp" environment, away from their families and to return home infrequently, sometimes only once a year.

Working Week

Firms will very often prefer a work week of 10 hour days, seven days a week. Consequently, the owner's construction supervision team needs to plan their shifts for regular weekend cover. This can add considerably to the owner team supervision costs.

Public Holidays

Project professionals from Western countries are aware of the need to plan around major holiday periods, such as Christmas, New Years, or Thanksgiving. But when working in China, the most important holiday to remember is Spring Festival, also known as the Lunar New Year (or in the west, Chinese New Year).

The time chosen by migrant workers for their once yearly visit home is inevitably Spring Festival. The festival is generally sometime around the last week in January or first week in February.

You should expect ALL work in both the design office and on the construction site to halt for at least the first week (think of it as you would the Christmas/New Year period). In addition, since this is very often the only time of the year when the migrant workers get an opportunity to return home, you should anticipate construction work to be impacted for up to three weeks in total.

In addition, there are the following two other issues to be aware of, leading up to the Chinese New Year:

- Contractors may come with demands for additional payment against progress accounts although the progress may not be fully substantiated by measurement. This appears to be driven by cashflow concerns because this seems to be the main payment point to their immigrant workforce.
- The cost of basic commodities, such as steel and concrete tend to rise for about two to three months before the Chinese New Year and go down again afterward. This appears to be driven by higher demand for the materials, driven in turn by the cultural practice within the Chinese construction industry of setting achievement targets to be reached by the Chinese New Year.

Harvest

Finally, it is important to recognize that since the migrant workers come from remote farming villages, they are very often required back in their home villages at harvest time. The loss of up to 25% of your labor force for two to three weeks during harvest time is to be expected (and remember, rice crops can be harvested two or even three times per year).

Construction Safety

The safety of the workforce is of paramount importance to any project manager. We believe and experience shows us that it is possible to run a safe site in China. The important

Figure 1. An illustration of good construction safety in China – note the good use of personal protection equipment.

issue in China, as in other parts of the world, is to show from the start that the owner (not just the managing contractor) is serious about safety. You may hear many stories about poor safety in China, but with vigilance on the part of the owner, you can control the situation. Figure 1 illustrates good use of personal protection equipment on site. We accounted for more than eight million workhours without a lost time accident.

Commissioning and Qualification

We originally hoped that qualified Commissioning and Qualification (C&Q) staff could be recruited locally. There are local firms with experience of more general utility and chemical type commissioning, but we found a severe lack of people with experience of pharmaceutical commissioning and qualification. The explanation given for this was that historically, the foreign operating companies would bring in their own expat team, thus, preventing the local workforce from gaining experience in this field. Consequently, it is necessary to bring more expats in than you might expect to carry out C&Q work. If you want a local team for the future, you should expect to have to spend time training them.

Changes in Government Regulations

China is developing fast. As a consequence, the rules and regulations can change with very little warning. When discussing project risks, make sure you consider the potential effect of regulatory changes. Cost forecasts can be thrown completely by a change in the rules part way through project execution. Here we cite two recent examples that affected projects that we worked on:

- In mid-2008, the regulations surrounding "social burden overheads" (health insurance, pension, sick pay, etc.) for construction workers were changed. The regulations were changed for the very laudable purpose of improving the working conditions under which construction workers worked. However, the effect on construction hourly rates charged to owner firms was that the rates increased by 50% or more within the space of a few weeks (Figure 2 shows how wage rates increased in that period[7]).
- In December 2008, a change in the regulations was announced that would restrict the ability of firms to reclaim VAT paid on process plant items. This effectively added approximately 17% to the cost of all process plant items not yet bought on the project. (We learned about this change purely by chance, reading an article in the local English language newspaper.)

Owner Team Presence

Communication is a major issue for any owner on a project in China; both communicating to the contractors what the owner wants done; and communication in terms of having eyes and ears to understand what the contractors are doing.

The Cultural Challenge

Language is obviously the first considerable barrier for a Western expat to overcome. Even though you may have a good

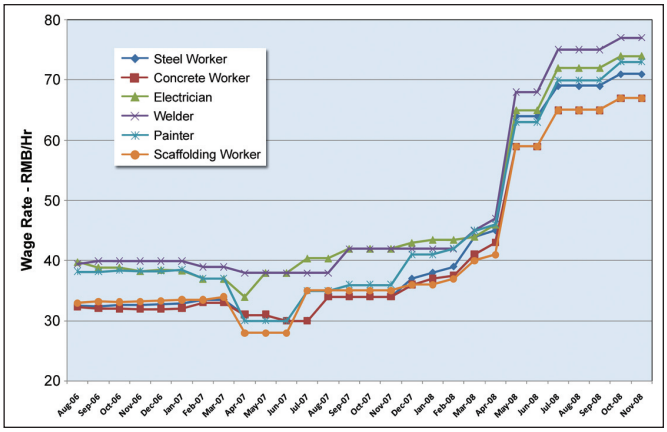

Figure 2. Wage rate data for construction labor in the Shanghai region showing the jump in wage rates in 2008.

interpreter, this does not necessarily mean that your point of view is being relayed word for word. Even after overcoming the language barrier, being heard and being understood are two very different issues. You will need to discuss a topic from several different angles before you can be sure that what you are trying to communicate is understood. Finally, negotiation of everything is a part of everyday life and you must be ready to expend time and effort in this area particularly to ensure that neither side loses face.

"Boots on the Ground"

In our experience, any owner organization needs to recognize that assigning only a small owner team will increase communication difficulties. Assigning more contractor expats is only a partial solution and comes with a similar cost penalty to increasing the owner team. Stringent supervision and time-consuming involvement is required from the owner in order to ensure the required quality and execution in a timely manner. In our experience, empowerment is generally not readily accepted and the most expedient method of management is "command and control."

Conclusions

For a foreigner, working on a construction project in China does present challenges. Many of these challenges are common to working in any foreign country. However, a few are unique to China. For example, a higher level of effort is required to deal with the permit system and a higher effort is required to expedite and deliver equipment and materials than we have encountered in other countries. Nevertheless, China is a fascinating country and with an open-minded attitude and a willingness to learn from new experiences, we believe that working in China can be a rewarding opportunity for any foreigner.

References

1. Remembering that the USA in turn is cheaper than some parts of Europe, such as Switzerland.
2. We cross checked our "gut feel" via a "vox-populi" of the members of the Pharmaceutical Committee of the Construction Industry Institute (www.construction-institute.org).

This Committee comprises heads of cost estimating and control departments from several major pharmaceutical firms. In addition, we are aware of studies carried out by such highly regarded research firms as Independent Project Analysis (www.ipaglobal.com), which have come to similar conclusions.

3. Faithful and Gould, "International Construction Intelligence," Volume 20, Issue 4.
4. The International Construction Cost Index is based upon a nominal 13,900 m^2 (150,000 ft^2) manufacturing building, but it excludes the contents of that building, such as process plant, furnishings, etc. It also excludes design and engineering costs. Hence, it reflects only the on-site construction cost of what we have referred to in this article as a "civil and concrete" based structure.
5. Indigenous local engineering contractors, who are often still state owned.
6. A few western contractors that have been based in China for some time seem to now be beginning to investigate the possibility of becoming directly licensed themselves. However, to the best of our knowledge, this initiative is still in its infancy.
7. These data are supplied by the Shanghai Construction Institute.

About the Authors

Jerry Hourihan recently relocated to Switzerland, after more than three years of living in China. He was the Senior Project Manager of a major new production and development facility on a Greenfield site in Changshu about 70 km outside of Shanghai. This is the largest capital investment by Novartis in China to date. Hourihan has more than 30 years of experience in project work in locations, such as Ireland, the US, Switzerland, and most recently in China. This also includes a period of eight years as Head of Engineering for the Novartis site in Ireland. Since late 2008, he has taken up the role of Head of Project Controlling in Novartis' corporate projects group, dealing with all major capital investments around the globe. Hourihan's original background is mechanical engineering. He can be contacted by telephone: +41-61-69 63725 or by email: jerry.hourihan@novartis.com.

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This article provides the background and current status of ISPE's Product Quality Lifecycle Implementation (PQLI®) initiative, including the development of an ISPE PQLI Guide Series.

PQLI Roadmap: Product Design, Development, and Realization, a Science- and Risk-Based Approach to Implementation – An Overview of ISPE's First PQLI Guide

by Christopher J. Potter, John C. Berridge, and Contributing Team

Introduction

One of the key deliverables for PQLI for 2010 is the release of the first in a series of ISPE PQLI Guides. The first Guide entitled, "PQLI Roadmap: Product Design, Development, and Realization, a Science- and Risk-Based Approach to Implementation," will give an overview and top level roadmap for subsequent separate PQLI Good Practice Guides, covering various topics.

The Guides will provide the industry with "how to" options for introducing the science- and risk-based approaches from the ICH guidelines Q8(R2), Q9, and Q10 into developing and manufacturing products and processes (product realization).

The PQLI Roadmap will give an overview of the application of Quality by Design (QbD) to product realization. Subsequent PQLI Good Practice Guides will describe the relationship possibilities between Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs), options and opportunities for using design space, and development of control strategies. A case study developed by a PQLI team will be used to exemplify some of the options and this will be issued as a separate Guide. A Guide describing the application of science- and risk-based approaches to existing products also will be developed. Using the already-developed and published case study entitled, "A-Mab: A Case Study in Bioprocess Development," alternative approaches and some other considerations to development and introduction to manufacturing of a monoclonal antibody product will be discussed in a separate Guide devoted to biotechnology.

Subsequently, Guides will be produced on important topics relevant to introduction and operation of a modern pharmaceutical quality system particularly supporting products and processes developed using enhanced approaches.

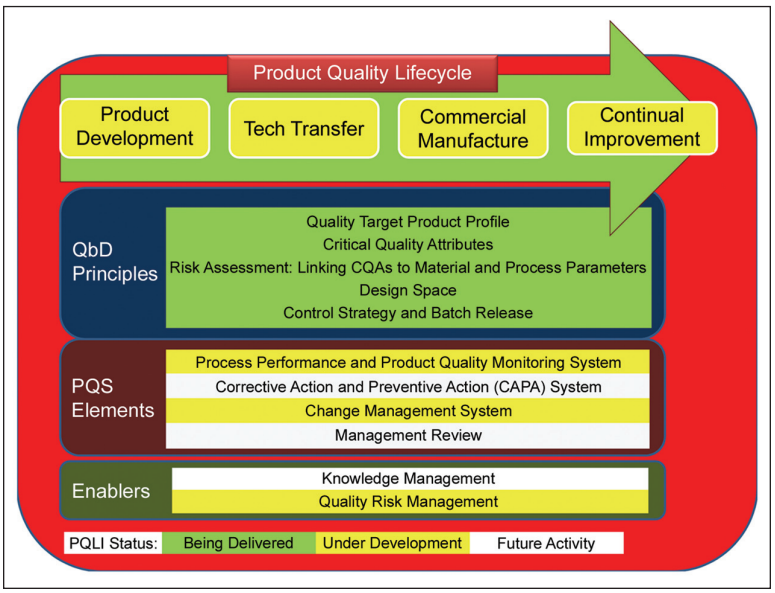

Figure 1. The strategic themes, structure, and status of PQLI.

Overview of PQLI

ISPE launched its Product Quality Lifecycle Implementation (PQLI ®) initiative in June 2007 to help industry find practical, science- and risk-based approaches to the global implementation of recent ICH guidelines. Through PQLI, ISPE is spearheading options to assist in the implementation of ICH guidelines, in particular, Q8 (R2) (pharmaceutical development),[1] Q9 (quality risk management),[2] Q10 (pharmaceutical quality system),[3] and imminent Q11 (development and manufacture of drug substances). ISPE is working with industry and regulatory leaders worldwide to support pragmatic and practical implementation of the guidelines based on sound scientific, engineering, and business principles.

Key goals of PQLI include the provision of a technical framework starting with a series of PQLI Guides, which will include explanatory documents supported by illustrative examples and references to case studies in the public domain, explaining options for implementation of enhanced science- and risk-based approaches to product realization, and its continual improvement. PQLI recognizes that there is no one way to implement the ICH guidelines, rather there are many perfectly satisfactory ways to address the concepts that are described, and the Guides will reflect this important concept.

PQLI uses, where appropriate, output from discussions and interactions in many forums, meetings, and presentations, for example, from regulators' presentations, ISPE and other similar organizations' meetings and workshops, and EFPIA, PhRMA, Japan PMDA work.

The principles from ICH Q8 (R2), Q9, and Q10 are applicable to new products and processes emerging from the innovative industry, and additionally, it is also considered that these principles could be applied to existing products, and potentially to generic or branded-generic products.

Current Status of the Initiative

PQLI encompasses three strategic themes given in Figure 1. Topics relating to Quality by Design (QbD) principles have been developed. An overview of the direction of the PQLI Initiative will be presented in the first Guide entitled, "PQLI Roadmap: An Overview of Product Design, Development, and Realization, a Science- and Risk-Based Approach to Implementation." A case study illustrating how the key concepts can be applied to product realization will be published as a separate Guide. The series will include a Guide explaining how science- and risk-based approaches could be applied to existing products. Throughout the PQLI Guide Series, there will be references to other case studies and relevant publications, which are in the public domain. These parts of the series will be published in 2010.

PQLI is now expanding to help in the implementation and/or operation of a modern pharmaceutical quality system using the concepts outlined in Q10. The first two topics are Process Performance and Product Quality Monitoring System, and Change Management. In line with PQLI processes, these topics will be discussed and developed at the ISPE Conference co-sponsored with the FDA in Washington in June. From this Conference, further detail will be generated as output for publication as potential additional Guides. Updates of the PQLI program will be issued in due course and progress can be followed in the PQLI section of the ISPE Web site.

PQLI Good Practice Guides

Some phrases and concepts used in ICH guidelines, such as "critical" as applied, for example, to Critical Quality Attributes and Critical Process Parameters, and Design Space as defined in Q8 (R2),[1] and Control Strategy as defined in Q10[3] are judged to require further discussion and explanation to assist in their routine application and use. Consequently, the topic initially called "criticality" as applied to Critical Quality Attributes and Critical Process Parameters, and other topics, Design Space and Control Strategy, were selected by the PQLI program as the first to be given further attention and explanation. Initial thoughts related to these concepts were published for comment.[4,5,6]

Feedback was received on the first three papers from both industry and regulators. This feedback recommended that Criticality, Design Space, and Control Strategy needed to be presented in an integrated way to show clearly how these concepts fit together to demonstrate effectively the application of QbD principles described in ICH Q8(R2), Q9, and Q10. There were other technical comments, which have resulted in our revising some of the explanations in the original papers.

Consequently, the PQLI Guide Series will include overview roadmap or "bridging" guidance relating to development of a product and its process or processes using the enhanced approach, and subsequent introduction to commercial manufacturing (product realization) with the establishment of the state of control (control strategy). The series will include a case study to illustrate this overview, and additional explanatory Guides on Critical Quality Attributes and Critical Process Parameters (CQA/CPP), Design Space, and Control Strategy. Another Guide will include an example of Continual Improvement of Process Performance and Product Quality dealing

Unit Operation	Element of the Dissolution CQA	What to Control	How to Control
High Shear Wet Milling of Drug Substance	Dissolution	Drug Substance Particle Size	High Shear Wet Milling Time
	Dissolution Algorithm	Drug Substance Particle Size	Particle Size by Focussed Beam Reflectance Method
Dispensing of Excipients for Drug Product Process	Dissolution Algorithm	Magnesium Stearate Specific Surface Area	Analysis of Material Attribute in Excipient
Final Blend	Dissolution Algorithm	Lubrication Time,	Time
Compression	Dissolution Algorithm	Tablet Hardness	Use Compression Force as a Surrogate for Hardness

Table A. Table showing examples of elements of unit operations impacting on dissolution CQA and associated algorithm

with the application of science- and risk-based approaches to an existing product, which was based on a paper[7] containing three case studies.

Content of the PQLI Guide Series

The PQLI Guide Series is a comprehensive discussion of the concepts underpinning enhanced product and process understanding and how to use this enhanced understanding to the benefit of the company throughout the lifecycle of the product. The series considers the totality of a drug product realization, including some aspects of development of the API, the selection of excipients, the choice of the manufacturing process, identification of the CQAs and CPPs, technology transfer and implementation into commercial manufacturing, and much more. Through practical examples, extended and focused discussion, and a comprehensive case study, the vital principles outlined in the ICH guidelines are translated into practical opportunities and application.

The following gives more detail of the content to be covered in the PQLI Roadmap and subsequent PQLI Guides:

The lifecycle of a pharmaceutical product is defined in Q8 (R2) as:

All phases in the life of a product from the initial development through marketing until the product's discontinuation.

A schematic of how this could be achieved using QbD principles is given in Figure 2 and the PQLI Guide Series uses this as a high-level guide and explains in detail examples of the science- and risk-based steps. While this figure was developed by EFPIA[8] to apply to drug products, the same principles are equally applicable to the development of the active ingredient.

Q8 (R2) gives guidance on the flow from developing and defining Quality Target Product Profile to Continual Improvement. Figure 2 gives the impression that product/process development and continual improvement are linear processes. However, in practice, development and continual improvement processes may consist of several parallel activities and are typically iterative and the iterative nature is represented in Figure 3 for a drug product. In addition, Figure 3 shows the relationship between formulation and process development of a drug product, and the application of quality risk management as described in ICH Q9. More detailed explanation of the iterative nature of formulation and process development is discussed in the PQLI Guide Series.

In summary from Figure 2, a Quality Target Product Profile (QTPP) is proposed, which is a defined[1] as "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product." During development of a new product, the QTPP could evolve and be refined as the project development process progresses. For example, when developing a simple tablet, the strength(s) to be submitted and included in a QTPP may not be finalized

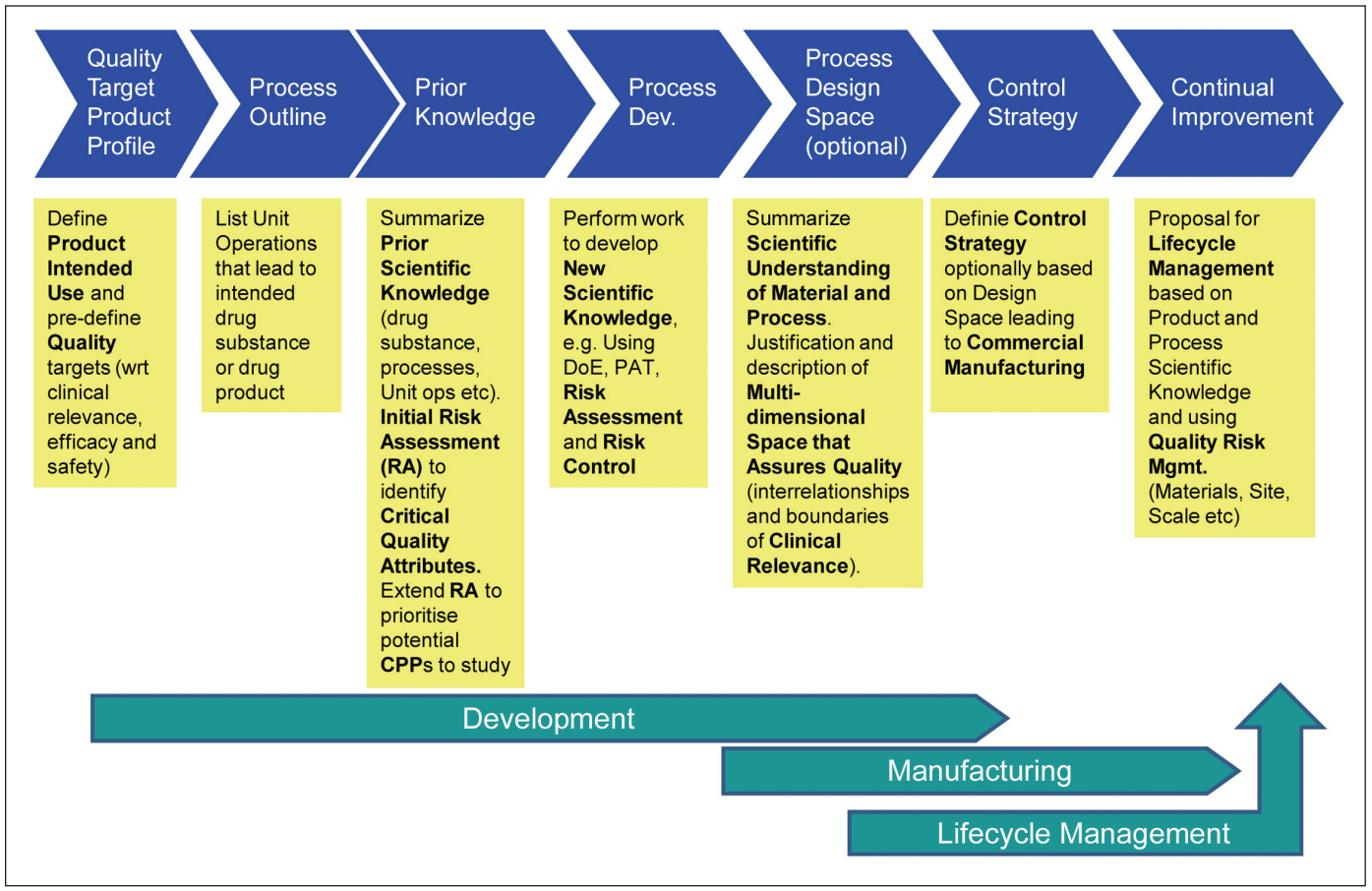

Figure 2. Application of QbD through a product's lifecycle (from EFPIA model).

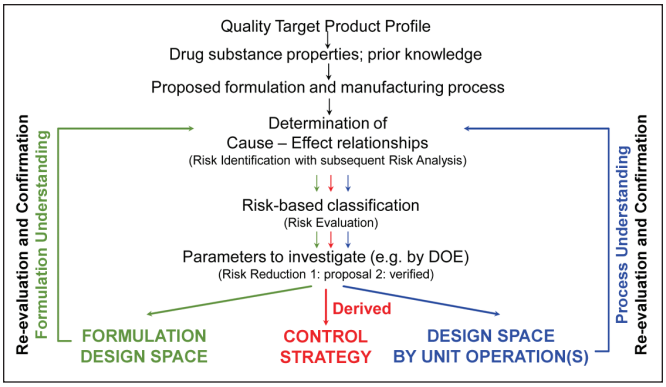

Figure 3. Iterative approach.

until after completion of Phase 3 clinical studies. A QTPP could be considered a qualitative and quantitative description of the design goal. The Guide Series shows how the QTPP enables a putative product and manufacturing process to be proposed, perhaps with several options, which may require experimental data to enable decisions to be made between options. Company strategy, prior knowledge, and experience of a process or availability of equipment and facilities also could influence the choice of manufacturing process. The case study exemplifies how these factors were brought together in the selection of a manufacturing process for an oral solid dosage form.

The PQLI Guide Series gives examples and explanation of application of quality risk management steps to product and process design. The case study explains the risk management steps as applied to drug product formulation and process development as outlined in Figure 2, giving examples of risk assessment (identification, analysis, and evaluation) leading to risk control (reduction and acceptance), which essentially are the studies designed to understand interactions with the intention of reducing risk.

The Guides on CQA/CPPs and case study will describe how prior knowledge can be used for example in a cause and effect analysis (risk identification and analysis) to prioritize (risk evaluation) as a continuum of quality attributes based on a "harm to the patient" or "severity" risk ranking to determine which are potential Critical Quality Attributes (CQAs) - *Figure 4*. These three risk steps constitute risk assessment.

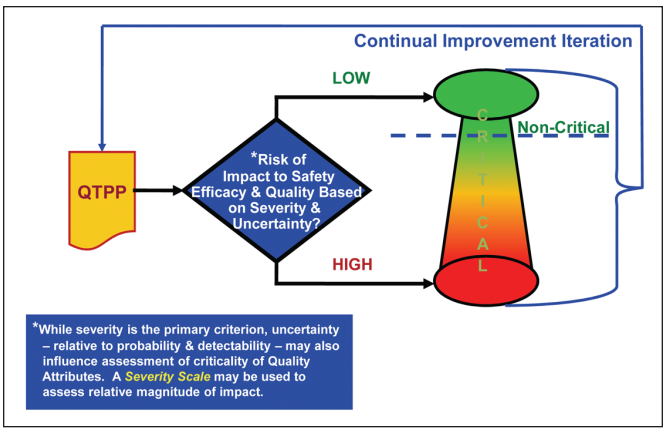

Figure 4. Quality attribute continuum of criticality.

Potential product CQAs could be modified as development progresses. For example, at the start of development of a controlled release product, quantitative in vitro drug release acceptance criteria, and selection of an appropriate dissolution medium are frequently not known. These are often developed in parallel with development of the formulation. The PQLI Guide Series will exemplify how qualitative or semi-quantitative acceptance criteria for CQAs could change as development progresses.

Prior knowledge also may be employed, for example, using Failure Mode, Effects, and Criticality Analysis (FMECA) to assess the combination of "severity," "probability," and "detectability" to prioritize the evaluation of the potential Critical Process Parameters (CPPs) and Material Attributes (MAs) whose variability may impact potential product CQAs (risk assessment). The PQLI Guide Series will give examples of how to derive a list of potential CPPs and MAs to study, showing how this list will have a continuum risk level. Furthermore, examples will be given of how factors to study are taken from this list and included in statistically-designed studies showing examples of how ranges of factors to study could be chosen. In risk management terms, execution of studies is considered risk reduction and review of the results of these studies could lead to risk acceptance or recycling through the risk process again by repeating risk assessment steps and designing further studies. Examples of use of risk iteratively to select and prioritize factors to study in a systematic manner, usually in statistically-designed experiments are given.

How the understanding from these studies is used to establish control strategy options is explained and exemplified, particularly showing the links between CPPs and MAs, potentially from more than one unit operation to a CQA as shown in Table A. Examples of multi-variant design of experiments are given, leading to understanding of variability. How this understanding is represented in an algorithm and used to propose flexible processing is discussed. Additionally, use of this understanding to support real time release testing applying process analytical technology tools is exemplified.

Given control strategy options, selection of a control strategy for implementation into manufacturing is discussed.

Optionally, enhanced understanding could be presented as a design space and examples of design space are given with expanded discussion of how to derive a design space, options to represent a design space, role across the product lifecycle, and considerations of scale as a factor influencing design space.

Following introduction of commercial manufacture of the product, opportunities for appropriate improvements to process performance and/or product quality could be identified from, for example, development studies, the process performance and product quality monitoring system or the Corrective Action and Preventative Action (CAPA) system, and changes made using the change management system. This continual improvement process is iterative throughout the lifecycle of the product. The PQLI Guide Series discusses introduction of a product into manufacturing and introduces considerations for a company quality system, particularly

when a science- and risk-based approach has been used for development and transfer to manufacturing. It also introduces and discusses opportunities for continual improvement of process performance and product quality.

Continual Improvement of Process Performance and Product Quality is further described in Section 3 of ICH Q10. Section 3 is split into two parts, 1. Lifecycle Stage Goals, which is a summary of the product lifecycle stages and 2. Pharmaceutical Quality System Elements (PQSE), which has more detail of the PQS to support manufacturing operations. There are four sub parts to the PQSE and they are the following:

1. Process Performance and Product Quality Monitoring System
2. Corrective Action and Preventive Actions (CAPA) System
3. Change Management System
4. Management Review of Process Performance and Product Quality

Control strategy is discussed as part of the Process Performance and Product Quality Monitoring System section.

Technical and business processes that companies could consider to effect continual improvement of process performance and product quality, whether the product was originally developed using science applicable at that time or a science- and risk-based approach, are given in the *Journal of Pharmaceutical Innovation* paper, "Application of Science- and Risk-based Approaches (ICH Q8, Q9, and Q10) to Existing Products"[7] and will be included as a separate Guide in the PQLI Guide Series.

Activity by PQLI is planned to extend the learning and understanding relating to implementation and operation of important elements of a company's pharmaceutical quality system, for example, at the forthcoming ISPE Conference in Washington on 9 and 10 June, co-sponsored by the FDA. PQLI output from this activity may be the basis of further PQLI Good Practice Guides.

The PQLI Guide Series provides detail and considerations on "how to" implement Q8 (R2) and Q9 under a pharmaceutical quality system for achieving product realization. These suggestions must not be considered the only way to apply science- and risk-based approaches, nor should they be considered as regulatory guidance. As an example, companies have options to develop product and process understanding in many different manners and use this understanding to propose control strategies without describing a design space, as indicated in Appendix 1 of Q8 (R2).

Benefits of Using a QbD Approach

Benefits to companies of moving toward the enhanced approach are suggested in the PQLI Roadmap and examples are given, where possible.

Some examples of benefits that have already been achieved by companies applying the science- and risk-based approach to existing products are given in the case studies in reference 7.

Get Involved with Upcoming PQLI Events

You can learn and contribute with industry colleagues and regulators by attending the following ISPE meetings, seminars, and workshops:

- 20 to 22 March 2010
  Milan Congress: Science and Risk Assessment for Business Success
- 22 to 23 April 2010
  Japan Affiliate Annual Meeting 2010, including PQLI with A-Mab
- 7 to 10 June 2010
  Washington Conference: Applying Risk-Based Approaches, featuring an FDA co-sponsored two day interactive program on Pharmaceutical Quality Systems, and a separate two day program on application of QbD to product realization

  The A-Mab case study will promote discussion on the latest thinking in the application of QbD to biotechnology. A small molecule case study developed by a PQLI team, which is a core component of a forthcoming PQLI Good Practice Guide will explain some approaches to apply QbD for product realization
- 20 to 23 September 2010
  Brussels Conference, featuring discussion of A-Mab and explanation of the ISPE small molecule case study

If you want to be more involved in PQLI or to contribute to any of the current or future PQLI activities, please send an email to pqli@ispe.org.

References

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Pharmaceutical Development, Q8 (R2), August 2009.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Quality Risk Management, Q9 Step 4, 9 November 2005.

3. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Q10, Pharmaceutical Quality System, Step 4, 4 June 2008.

4. Nosal, R. and Schultz, T., PQLI Definition of Criticality, *J Pharm Innov*, (2008) 3:69-78.

5. Lepore, J. and Spavins, J., PQLI Design Space, *J Pharm Innov*, (2008) 3:79-87.

6. Davis, B., Lundsberg, L. and Cook, G., PQLI Control Strategy Model and Concepts, *J Pharm Innov,* (2008) 3:95-104.

7. Potter, C. J., PQLI Application of Science- and Risk-Based Approaches (ICH Q8, Q9, and Q10) to Existing Products, *J Pham Innov*, (2009) 1:4-23.

8. European Federation of Pharmaceutical Industries and Associations, www.efpia.org/Publications/Science and Technical Affairs.

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Improving the Facility Design Engineering Process for Major Capital Projects

by Joseph R. Hettenbach, PE

This article discusses design tools for the design of pharmaceutical facilities, management of the design engineering process, and ways to potentially improve the design process, including the application of a "strong front-end design approach."

An article was published in the July/August 2001 issue of *Pharmaceutical Engineering* entitled, "*The Changing Face of Engineering for Major Capital Projects*," which was nominated as a finalist for "Article of the Year." There was a very positive response to this article in the US and from some readership in Europe. As a follow-up to that article, a number of presentations were given on the subject of developments in process facility design. The presentations were well received throughout the US and in Ireland at the respective facilities of a number of Architectural and Design (A&E) companies, Engineering Design and Construction (ED&C) companies, and Construction Management (CM) companies; as well as at an AIChE Local Chapter Meeting in New York City.

This article explores some of the issues and concerns in the design of process facilities and suggests ways to improve performance and quality and potentially reduce costs based on experiences derived in a number of major process facility design projects.

3-D vs. 2-D Design Approaches

Computer 3-D design has been utilized for a number of years for selected projects. Although the 3-D mode offers a number of potential advantages over 2-D computer design, the 3-D mode is still limited in its application. There are a number of factors involved in the choice of 3-D vs. 2-D as the design mode:

1. The size, estimated cost, and schedule of the project to be done have to be considered. There is a significant effort involved to set up and manage a 3-D model, and it clearly may not be indicated for a smaller project.
2. The experience levels of the company doing the design and the client's staff who will be assigned to the project in executing a 3-D design has to be evaluated.
3. The experience levels of the prospective Construction Management Company and the construction team (trades people, supervision, etc.) working with 3-D generated designs, and utilizing the model in the field (to get the full benefits of the tool) has to be established.
4. Although 3-D is more descriptive, 2-D floor plans and elevations with a careful eye to potential interference situations with equipment, piping, etc. (one of the selling points for 3-D, i.e., "clash detection") can adequately cover those effects.
5. The initial costs and document updating costs for renovations in the facility would be lower for 2-D compared to 3-D. In addition, maintenance and updating 3-D documents to the extent that is required, would be more costly for the 3-D alternative.

3-D computer design has been used for some 18 years with mixed results. This powerful tool has not always been properly applied, and it is fair to say that performance in design execution leading to construction is variable with some of the same recurring issues (as previously reported), including:

- lack of a well defined scope and appreciation of the project costs involved
- starting the 3-D model work too soon
- not going far enough with the scope of the model
- clients not paying enough attention on a real time basis
- all design disciplines not fully applying the modeling tools; poor coordination among the disciplines

- going out too soon with the construction bid packages
- little or no participation by contractors and construction management in the design

The better projects, in our experience, are those in which the designers and their clients pay heed to these common mistakes.

Issues with 3-D Model Reviews

There are a number of problems which have occurred for 3-D projects, due to the inappropriate management of 3-D model reviews. Starting the modeling process too soon, i.e., before the design concept is reasonably fully developed, is an invitation to significant problems. Assuming that the concepts/tenets prescribed have been utilized in the development of the model, reviews should be conducted to verify that these concepts have been implemented. Sorting out minute details during the model review – after a significant unit of work has been done on the model – can be counterproductive in effect.

In addition, the ripple effects of changes cannot always be fully appreciated at the time of the review by a group of reviewers comprised of people with different backgrounds and perspectives. Any major repairs or changes to the model should be done "one on one" with a responsible party on the client side outside of group model reviews. Practically, these changes should not be done by committee (especially groups from different locations, who are not "face to face" for the exercise, i.e., via teleconferencing). If the up-front planning and design concept development is performed adequately, the model reviews should be relatively straight forward with the expectation that there should not be too many significant changes to consider. Conducting a few well structured and properly scheduled reviews is much better than having (too) many reviews, and following that course will result in fewer significant changes to deal with. Mismanagement of the model review process is a catalyst for confusion, and an invitation to rework, errors, and inefficiencies.

We must not lose sight of the fact that the 3-D model is a design tool which must be applied properly. Concepts must be built into the design-established prior to modeling - not applied on the fly, worse yet during a model review. Sometimes decision makers are not fully aware of the design rationale, and/or not sufficiently qualified (with all due respect) to make the changes. Environmental, Health and Safety (EH&S) and operational intents could be compromised (or even nullified) by some of these changes– and possibly could require repeating of Hazardous Operations (HAZOP) analyses. There must be a team effort to minimize (if not eliminate) "11th hour" type significant changes.

Managing the Design Process

At a time when a number of pharmaceutical companies are downsizing with the concurrent loss of valuable experienced people, the E&C companies could benefit from the following considerations, recognizing that they are dealing with reduced project loads. These potential changes could benefit the clients who utilize their services with the side benefit of improvement of morale of their staffs:

- fine tuning and strengthening their process engineering function
- bolstering their conceptual design capabilities through selective re-assignment within their ranks
- stabilizing their rosters by doing more sub-contracting to meet periods of higher workload
- streamlining and improving any training programs they have in place, concentrating on a select group of key designers
- maintaining a dialogue with the designers and the clients regarding potential changes in approach, as well as the needs of all of the parties involved

It is suggested that it is highly beneficial to have experienced staff from the customer's side in regular attendance at the design facility to closely follow things throughout the course of the design – particularly for larger projects – to the extent that is practicable. The alternative practice of customers performing periodic reviews (weekly or bi-weekly) at the designer's facility has often led to significant design issues, schedule delays, and increased costs, and can have significant adverse impact on the overall quality of the design (deliverables).

It was observed, while working on the design floor, that it is quite beneficial for both the company doing the design and the client's staff working on the project to maintain closer working relationships with the designers (the key players), which could include the following interactions:

- enlisting their valuable input
- nurturing their talents
- enabling them to learn and grow
- recognizing their limitations
- guiding them sensitively through upsets and changes
- yielding to their experience (posing challenges to management, at times)

Analysis of the variable performance of a number of major design projects indicates that a number of factors contribute to the success of the project. Although these elements are generally understood as being important, it is suggested that not enough attention and time is paid to them in actual practice and deficiencies in one or more of the following areas, elaborated on below, have adversely affected the outcome:

- leadership/teamwork
- importance of ownership
- "finishing" the design
- efficiency vs. quality
- customer expectations from process engineering

Leadership/Teamwork

At a time when "teams" are in vogue, there still is a basic need to have one (strong) leader of a project. With regard to the make-up of the team, the following considerations would be beneficial:

- Who's available?

- experience factors
- complementary skills
- team balance
- team chemistry

We should keep in mind that, as it is in competitive sports, "the best team doesn't always win… oftentimes, it's the team that plays the best."

Who's in Charge of the Design?

There have been increasing numbers of players on the project teams in many cases. All of the players must be managed. Again, the customers need to be satisfied. Construction management and building contractors have their needs, recognizing that A&E firms have somewhat different approaches compared to E&C firms.

Ownership

There should be single point(s) of contact and there is a need for "owners" of areas and systems. Keep in mind that at times, complex organizations can thwart communication. Care must be taken to accommodate the "user" (customers). It is vital to get "buy-in" from the designers, and the design should be built up from concepts agreed upon by the team.

Finishing the Job

The ultimate challenge is to maintain quality and enthusiasm for the last 5% to 10% of the design (or any project or venture).

Issues to be contended with (as the design staff is being reduced in numbers in the latter stages of the detailed design phase of the schedule) include the following:

- keeping the key resources intact and available
- managing continuity
- staying focused on the deliverables
- supporting the construction effort out in the field, which typically is commenced, while the design is being completed back in the design office

Efficiency vs. Quality

There are some classic battles that pit efficiency versus quality in both the work efforts and in the design itself, as it is developed. To ensure that each of these competing effects get their due, it is beneficial to:

- Build concepts in the "front-end."
- Get all of the appropriate disciplines involved.
- "Freeze" the scope – to the extent that it is practicable, at the appropriate time to maximize focus. Careful use of a 95% type rule is helpful, i.e., strive to minimize any significant changes, unless there are significant safety or operational issues to contend with in the design at that point (i.e., approximately 95% completed).
- Recognize that there is compromise needed in design to ensure an equitable balance of Environmental Health and Safety (EH&S), quality, operational, ergonomic, and maintenance related activity needs. Disagreements among the various groups involved can potentially be difficult to manage.
- Be cautioned to the ultimate trap: for 3-D designs, don't rely on the 3-D model reviews to get it right.
- Use modular concepts (building blocks), to the extent practicable.
- Make sure that areas involving unique equipment or novel systems and approaches get the special attention they require.

With regard to cost control, the following tenets should be integrated into the design management, based on observations:

- Cutting man hours on selected elements of the design doesn't always save money in the long run.
- The incremental costs of changes/reworks/additions aren't always fully appreciated at the time they are contemplated and then implemented.

The Process Engineering "Predicament"

Many operating companies no longer view process engineering as the viable function it was considered to be in the past, with the consequential erosion of the experience base. At the same time, process engineering experience has declined in E&C companies. Some E&C companies have been looking to partner with smaller companies (stronger in the process area) to offset this effect – resulting in situations where more players have to be managed. In any case, operating companies (customers) still need good process engineers to "talk" to the E&C companies in a real time manner.

Beyond the Process and Instrumentation Diagrams (P&IDs), hydraulic calculations, line sizing, equipment specifications, etc., process engineering needs vary with the customer and the project at hand. The best mode to follow, based on our experience, is co-development of concepts with a focus on modules, unit operations based, and "interconnectivity" of the components. Selected "specialty" skills can be covered by others to the extent that those particular skills are lacking "in-house." Some examples of these are: pressure relief venting, hydrogenation, cryogenics, and other special chemistries, emerging Process Analytical Technologies (PAT) which involve advanced instrumentation and process monitoring devices, and on new/novel technologies (e.g., microwave drying, end-of line treatment systems, etc.)

Process engineers are good agents for 'Right the First Time' type considerations in companies that have pursued this concept, relative to process facility design. The following considerations could be beneficial to the design process:

- firmly establishing the scope with associated costs – to avoid big surprises
- building the design on agreed upon concepts – to minimize significant changes
- minimizing re-iterations – to maintain the focus of the resources available
- maintaining accuracy and clarity of design documents –

which is the basis for appreciable savings in construction (fewer upsets, reworks, etc.)

There also is a need to stay abreast with new emerging trends involving novel equipment and systems, and new technologies and approaches. One example of this is the modular construction concept. Applications of modular construction are somewhat sensitive to scale, and there are many in the biotech area (the extension of the use of skids), a few in large scale, and some potential for the intermediate and pilot scales. Overall savings are not necessarily great, but selected use of modular units can improve the construction schedule and reduce density of field workers, in addition to getting all of the benefits of shop fabrication, in a controlled environment (compared to doing the same work out in the field).

Improving the Design Process

The prospect to reduce costs, without sacrifice to quality, is a challenge that can only be met by full cooperation between the customers and the E&C companies. The lack of process engineering expertise available to be intricately involved in the design is often encountered on the customer's side. The onus would then be on the E&C companies to face a number of challenges and entertain changes in their organizations with the goal of improving overall performance:

- to reduce and stabilize staffing to the extent that this is reasonably, comfortably achievable
- to improve consistency in focus (overall)
- to decrease the turnaround time on proposal development
- to maintain acceptable profitability
- to establish more, regular customers to the extent practicable
- to perform a serious review of overall staffing vs. the needs for a different approach - reducing levels of management and unnecessary overheads
- assemble the best talent pool available that will fit into their program, securing good team players willing to learn, teach, and grow
- establish a "strong front-end design approach" mode (defined below)
- aggressively master the use of the "intelligent P&ID" tools that can be integrated with 2-D and a 3-D software design programs
- improve and streamline the systems and databases utilized to decrease administrative paperwork which is, in the limit, very much counterproductive
- develop useful libraries to take advantage of repeatable elements

One of the fruits of these potential changes would be to free up resources for some engineering work that often cannot be done and to allow companies to follow trends more closely (conducive to a more invigorating and challenging work environment).

At the same time, customers (to the extent necessary) need to establish alliances with smaller, good, process-based companies preferably fluent with 3-D design (when it is utilized) to provide coverage for specialty process areas, validation, and commissioning support, etc.

A "Strong Front-End Design Approach" for Facility Design

The traditional project design schedule consists of conceptual, preliminary, and detailed phases. In our experience, the ability to bring fairly advanced P&IDs to the E&C company has provided a great head start for the design; the development of modules, i.e., standard approaches and set-ups, which can be basically reproducible also was very beneficial. It is understood that many customers are not able, due to resource constraints, to develop P&IDs, and don't have the luxury of having a number of previous projects/designs to bank on (and better yet, the same people who worked on the earlier projects being available).

In any case, it is proposed that there is significant potential in following a course starting with a "strong front-end" design with decent quality P&IDs in hand. (Details of this approach are described below). This alternative approach requires a strong team focused on a much more comprehensive level of definition, earlier on in the design development than in the traditional approach. In essence, the conceptual and preliminary phases are combined and extended in duration with the advantages of utilizing fewer numbers of design people to manage, and a shorter overall design schedule with a consequential reduction in design cost.

There are, of course, a number of variables which would affect the actual performance of the "strong front-end design" executed project. The figures depict a qualitative performance comparison of the relative man-power schedules for the traditional approach (Figure 1) and the "strong front-end design" approach (Figure 2) for a hypothetical facility design, which

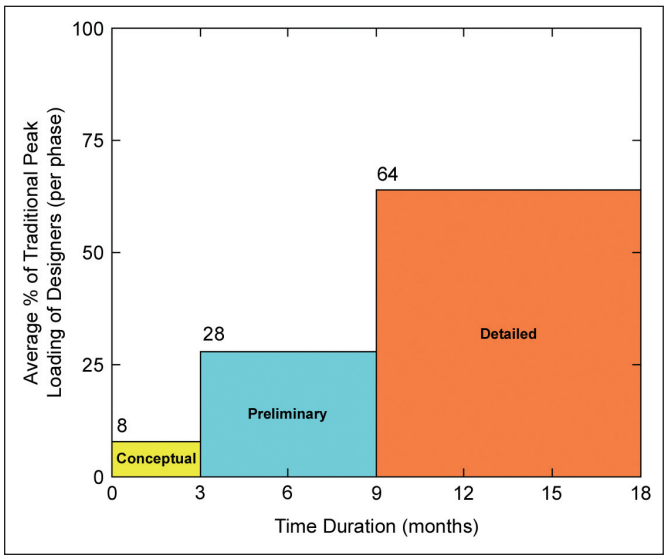

Figure 1. Traditional design approach. Consists of the "conceptual," "preliminary," and "detailed" phases with build-up of design staff to meet the demands of the design effort, which involves more designers and takes longer to complete the design when compared to the "strong front-end approach." Peak manpower in this example is assumed to be 100 designers.

in practice might involve a peak design loading (100%) of 100 designers and take 18 months to complete, using the traditional approach. Of course, there is a typical build-up and reduction of the numbers of designers during each phase. The details in these figures illustrate what we would expect based on some of our experiences and some guardedly optimistic projections.

In this hypothetical example, the "strong front-end design approach" predicts significant improvement compared to the traditional approach, assuming of course one has the appropriate resources in place and basic information in hand as delineated below. The average peak manpower loading in the detailed design phase is predicted to be lower for the "strong front-end" approach than for the traditional approach (50 designers on average during the detailed phase with a maximum of 75 designers versus 64 designers on average during the detailed phase with a maximum of 100 designers), and consequently, the overall design staff requirements (numbers of designers used for all phases) are predicted to be significantly lower for the "strong front-end design approach." In addition, the overall design schedule is predicted to be somewhat shorter in duration for the "strong front-end design approach" (16 months vs. 18 months in this hypothetical example).

The following describes the "strong front-end design approach" with enough detail included to allow a team interested in applying it to proceed with the "checklists" therein provided as ready references.

The attributes of a "strong front-end" team ideally would include the following:

- a small cohesive group
- good experienced people, willing and able to work together in this mode
- good communications within the group and outside of the group
- strong ability to interact with clients and project groups

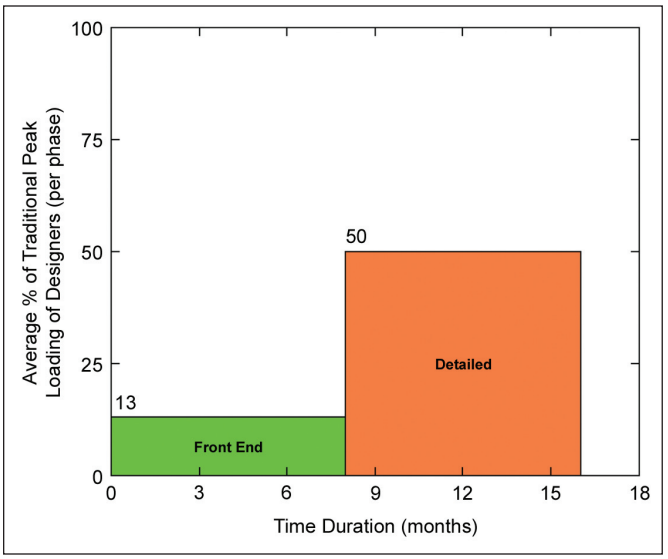

Figure 2. "Strong front-end design approach." Consists of a more concentrated effort in a "front-end" phase, and a reduced buildup in the "detailed "phase compared to the "traditional" approach; and a shorter overall time duration to completion. Peak manpower could be on the order of 75 designers.

The resources for the "strong front-end" effort ideally would include:

- a strong process design person (group) leader
- process engineers as required
- at least one strong process person from the client side, ideally with good process design experience, and fully able to represent the user and get all the necessary inputs in a timely manner
- one to three strong piping designers – depends on project size and timing, including at least one 3-D capable (if 3-D is to be utilized)
- an HVAC person
- a ready pool of a few civil/structural, electrical, instrumentation/controls people available to draw on
- ready access to a "codes" person
- ready access to a 3-D coordinator (if 3-D is to be used)
- ready access to a strong project person: to consult on design, handle cost estimation, preliminary schedule generation, and speak to constructability

The following are elements of a "strong front-end" approach (i.e., units of work to be completed, ideally). It is recognized that this list is extensive, and the areas listed should be covered to the extent practicable:

- P&IDs (approximately 95% quality) a collaborative effort with the client leading – utilizing modular type approaches
- GAs: general arrangement drawings – 2-D plans (layouts) and selected elevation studies of key systems
- conservative sizing (i.e., comfortably large enough) of columns and main beams (including dimensions and locations)
- major equipment list (down to pumps)
- instrument list and the definition, location, and rough (conservatively large enough) sizing of control panels, etc.
- identification and detailed definitions of a few "achievable" Process Analytical Technology (PAT) applications
- specifications for introduction to the 3-D model development (must lean on the client) – e.g., piping, instrumentation, equipment (if 3-D is to be used)
- a drainage plan
- sizing of emergency relief rupture discs
- sizing and routing of emergency relief venting headers and process vent headers
- sizing and routing of major utility headers and sub headers
- definition of the containment philosophy (for handling nasty/potent /toxic materials)
- designation of the number of air changes and conditioning (temperatures and relative humidity settings), and differential pressure profiles for the different room types/areas, corridors, etc.
- sizing (conservatively large enough) and routing of HVAC duct work (plans and elevations) and HVAC equipment
- major rack studies (for piping, electrical, and HVAC)
- definition of nozzle sizes/locations on vessel tops
- detailed definition of transfer stations (manifold rooms)

- routing of process piping (plans and elevations; some "3-D" work, if 3-D is used)
- electrical routing studies (e.g., cable tray), motor list, MCC room sizing (conservatively large enough), and location
- locations of eye wash stations and safety showers
- development of the specification for the 3-D design model, including equipment and numbering systems/color codes for lines and instrumentation, etc., (again in cooperation with the client) – if 3-D is to be used
- modeling (conservatively large enough sizing) of selected (sufficiently defined) major equipment (reactors, other vessels, filters, dryers, centrifuges, etc.)
- modeling (sizing – conservatively large enough) of the building shell
- a codes review and provisions made to satisfy them - e.g., emergency egress, etc.
- establishment of acceptable wall emergency relief areas
- materials flow study, including studies/plans for material movement
- establish solids charging (and discharging) and nasty liquids (and gases) charging modes and any peculiar containment requirements
- get agreement (in detail) on just how process cleaning is to be done (often overlooked in the early stages of design); and "approval" by manufacturing and quality assurance representatives
- definition of needs for "different" (new/unique) technologies
- definition of the needs for air and water pollution control and hazardous waste handling requirements; detailed plans to satisfy these needs
- definition of solvent storage and recovery needs, bulk chemical storage requirements, and systems for purified water (as required)
- development of specialty equipment items
- preliminary cost estimates
- evaluation of viable alternative schemes, where appropriate
- preliminary project schedules and manpower planning

The "strong front-end design approach" speaks to the quality of the design work derived and the efficacy of the overall project schedule to be achieved.

It has been observed that the quality of detail design work often suffers in a (sometimes, mad) rush to meet a deadline. A pitfall of the "fast-track" requirement often pushed for by the client management (for good business reasons) is that it can adversely affect quality and performance if not executed properly. We have found in a number of projects, that regardless of the schedule requirements, the best thing to do to approach getting things done more quickly is to do some really good planning (actually go at it very slowly in the beginning). Good planning, in our experience, is the key to success from the very start of any project, and on-going during the front-end development, and for the duration of the detailed design. It is a good thing to avoid unnecessarily large design groups which may be difficult to control (manage). Our experience has taught us that the best solution to a growing problem, along the way (i.e., during the course of the design) is not to just apply more resources (designers) to the project.

Good up-front planning helps to achieve an equitable balance between schedule, scope of work affected, and quality, which reduces stress levels for all concerned and makes the work more rewarding personally. Good planning allows for true continuous learning, prevents wasting time solving the "same old problems," and affords opportunities to improve the design process through positive experiences.

Case Study

The "strong front-end design approach" was utilized a number of years ago on the front-end of a project, which involved a major development facility project for the research division of a major pharmaceutical company. The scope (in the $300 million to $350 million range in cost) included support laboratories, a kilo lab, a 10 pool pilot plant (including two containment modules) of varying reactor size sets ranging from 50 to 750 gallons (three to four reactors per pool), and a separate hydrogenation building. We had decent quality P&IDs in hand (which we developed with key pilot plant operations personnel), and utilized a team of people with whom I had worked on several major projects (and had laid the groundwork together for the "strong front-end design approach"). This hand picked group for the 3-D design included: three piping designers/layout people, one process control person, and one HVAC person. We also had a process engineer and a few well experienced, senior operators from the existing pilot plant.

A major challenge in the design was to satisfy the requirement that the layout had to ensure that the 10 operating pools (30 reactors in total) of the pilot plant section be located in a manner to allow a more cohesive operation from a management perspective. A typical layout of a multi-reactor facility would be two rows of reactors located along outside walls to allow the appropriate pressure relief venting, required under National Fire Protection Association (NFPA) 68 stipulations. An illustration of this design is shown in Figure 3.

The issues with this standard layout/design are:

1. The operations would be spread out over a large area, making it more difficult to manage with a relatively small-sized staff.
2. The operators would tend to feel somewhat isolated in the

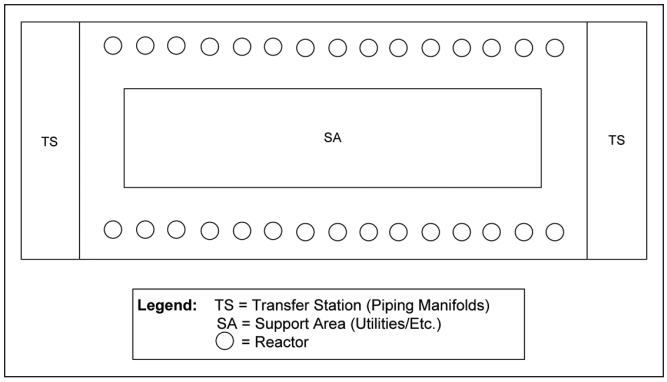

Figure 3. Schematic of a traditional pilot plant layout.

areas farthest from the offices/control room.

3. It would be very difficult to minimize potential cross contamination issues and to achieve some degree of containment (e.g., for nasty/toxic chemicals used) for the number of different processes manufactured at the same time in the different pools.

A novel design concept was developed, which would meet the client's requirements (as stated above) and address the issues posed by the standard layout/design. An illustration of this novel approach is shown in Figure 4.

This schematic illustrates the capability of managing eight pools from a centralized core area, while providing isolation of the pools, and two pools (on the right hand side of the schematic, which can be set up as higher "containment" type areas. In addition, the wall pressure relief venting requirements are met in this cross-shaped design. The symmetrical nature of the layout provides economies in the design in the form of "repeatable elements" with the added advantage that the size of the areas containing the groups of reactors and size of the transfer stations provides the opportunity for these "units" to be built as modules, off-site.

Things progressed smoothly according to our plans in this front-end study. The efficacy of the principles and performance of the "systems" predicted in the "strong front-end approach" defined above, were clearly, successfully demonstrated with a much stronger, better defined design package achieved, when compared to those we had done on a number of other projects, in which the more traditional approach was utilized (and using the same key designers). We also engaged the services of a Construction Management (CM) company (whom we were planning to use for the construction) in the very beginning of the study – which we had not done before. The CM group took an active part in the study. Unfortunately, management decided not to fully implement the project, due to some business developments. To be fair, having the key players available made that exercise somewhat ideal, but it is suggested that just working toward achieving the "strong front-end design" mode should reduce the number of designers needed, and enable completion of the design in a shorter time period, and improve the normally high-stressed work environment.

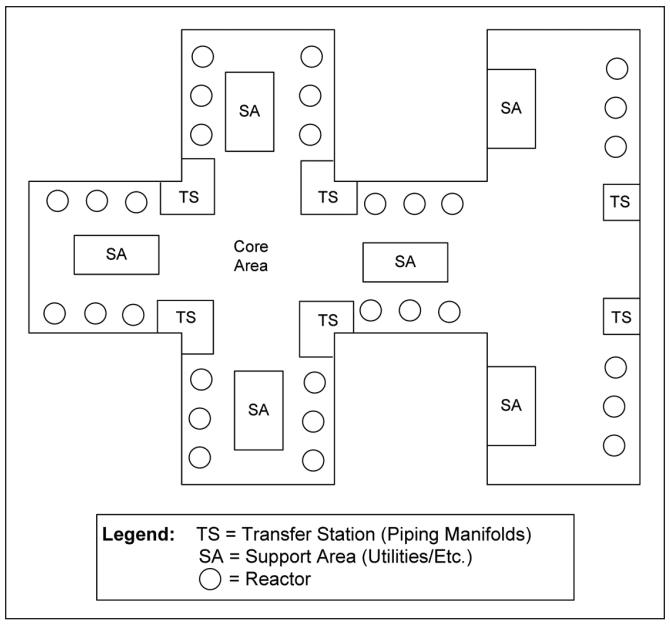

Figure 4. Schematic of a novel pilot plant layout.

Conclusions

For a number of years, we have observed a growing trend to satisfy the dictate of companies striving to do more with fewer people and lower capital outlays. This sentiment poses a significant challenge for those involved with the clear motive of reducing costs and being faster "to market" if new products are involved. One could assume optimistically, that somehow, the quality, schedule, and overall project cost goals can still be met by working in that mode. It is suggested that a "re-engineering" of sorts of the work processes that have been followed for many years for the design of facilities could facilitate meeting many of these goals. It is further suggested that application of the principles of a "strong front-end design approach" could help move the design process along a positive, rewarding path of "continuous" improvement, particularly when a 3-D design approach is utilized. In addition, since the utilization of a "strong front-end design approach" can potentially provide better design definition earlier in the design process, this would serve well the increased emphasis on the validation aspects and requirements for new facilities. In particular, the growing practices of Enhanced Design Reviews (EDR) and Design Qualification (DQ), more widely recognized as important precursors to validation, could be better supported by the "strong front-end design approach."

About the Author

Joseph R. Hettenbach has more than 35 years of process engineering and environmental engineering experience, including 20 years of process design related work. He spent 33 years at Pfizer Inc., working in their US manufacturing and research facilities and then out of their global engineering office and servicing facilities in many US locations, Puerto Rico, Ireland, England, and Singapore. He has a Bachelors and a Masters in chemical engineering and a Masters in environmental engineering from Manhattan College. He is a licensed Professional Engineer in New York State and the Principal of "Process Engineering Works P.C.," registered in New York State to provide professional engineering services. He has managed the detailed process design of a number of projects for laboratory development, kilo plant, pilot plant, and commercial scale manufacturing API facilities. He has made presentations on the subject of "Improving the Process Design of Facilities" to a number of E&C, A&E, and CM companies throughout the US and in Ireland; to the AIChE in New York, and to the new staff of a world class (Pfizer, Inc.) API facility in Singapore (as a training exercise). He can be contacted by email: tjchett@optonline.net.

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Life-Enhancing Biotherapeutics Company Nets Healthier Equipment

by Kevin Pait and Preston Ingalls

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

Introduction

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

The Company

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

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

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

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

Pre-Planning

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

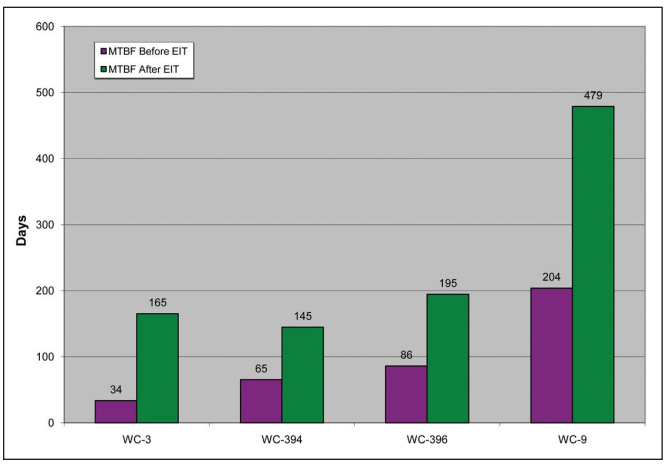

Figure 1. Westfalia centrifuge – MTBF.

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

on the Equipment Improvement Team (EIT).

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

Determining the Issue

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

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

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

The Process

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

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

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

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

Equipment-Focused Improvement Techniques

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

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

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

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

Employee-Focused Improvement Techniques

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

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

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

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

"Focusing on cosmetic and mechanical order helps establish an operational respect for the equipment and also creates a department-wide sense of ownership."

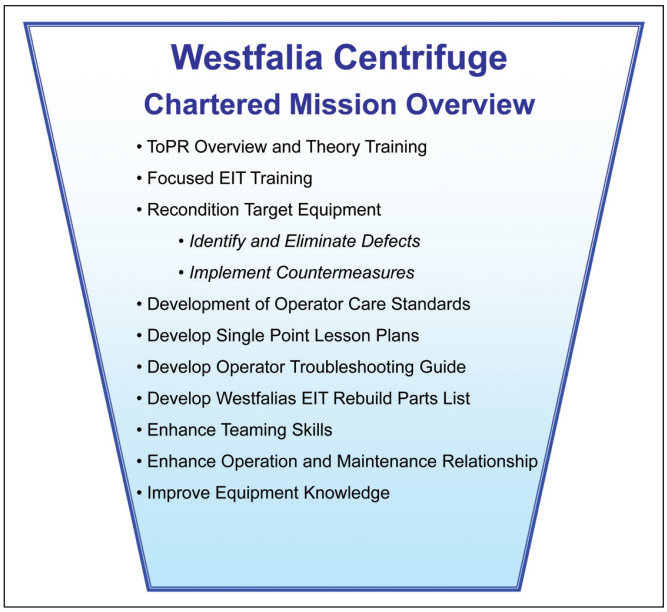

Figure 2. Westfalia centrifuge chartered mission overview.

Inspect What You Expect

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

Results

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

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

Summary and Conclusion

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

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

About the Authors

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

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

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

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

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

Introduction

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

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

Project Goals

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

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

Key Definitions and Regulations

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

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

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

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

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

Challenges for Clinical Manufacturing

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

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

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

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

Problem Definition and its High Level Causes

Key voice of the customer requirements were rated accord-

"Key voice of the customer requirements were rated according to their impact on the three measurable project goals of external release testing spend, internal release hours, and identification-to-release cycle time."

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

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

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

Process Demand Analysis

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

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

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

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

Selected Background Data

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

Numbers of Tests

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

Testing Turnaround Time

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

Repeated and New RM/CMs

About 100 to 150 different types of RMs/CMs were ordered each year with about 140 RMs types maintained in inventory for in-house CM preparation and other clinical manufacturing

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

The percentage of new RM/CM types was about 50% (range of 40 to 70%) over the past three years. Higher percentages of new RM/CM types occurred in years when new clinical manufacturing processes were introduced from novel processes being development to support new products entering the portfolio. About 15 to 25% of RM/CM types were excipients with an average of 3.8 (±1.5) per project (~20 excipients, ~2.5 containers/excipient). Thus, a significant number of RM/CM types were subject to the excipient requirement of 100% ID testing of containers.

Use at Risk

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

Out-Of-Specification (OOSs) Results

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

Types of RMs/CMs

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

Vendors

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

Areas of Identified Pain

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

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

ment personnel; meaning of approval signatures on release plans and CM preparation batch sheets); 6. mother nature – externally-located (e.g., different state) release testing laboratories; changing worldwide quality regulations.

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

Current States

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

The process for RM identification to release had up to four sequential key steps depending on whether the RM was new, the RM was compendial, the vendor was new, or the vendor was external, including: 1. RM identification by process development, 2. procurement, delivery, release plan authoring, release assay development, sampling and submission, solicitation of vendor questionnaires, 3. release plan approval, sample testing, release package assembly, quality questionnaire response evaluation (including obtaining missing TSE/BSE information and clarifying vendor responses), and 4. quality approval/release. The simplest case was an existing material from an internal vendor and the most complex case was a new RM from a new, external vendor. Based on associated

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

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

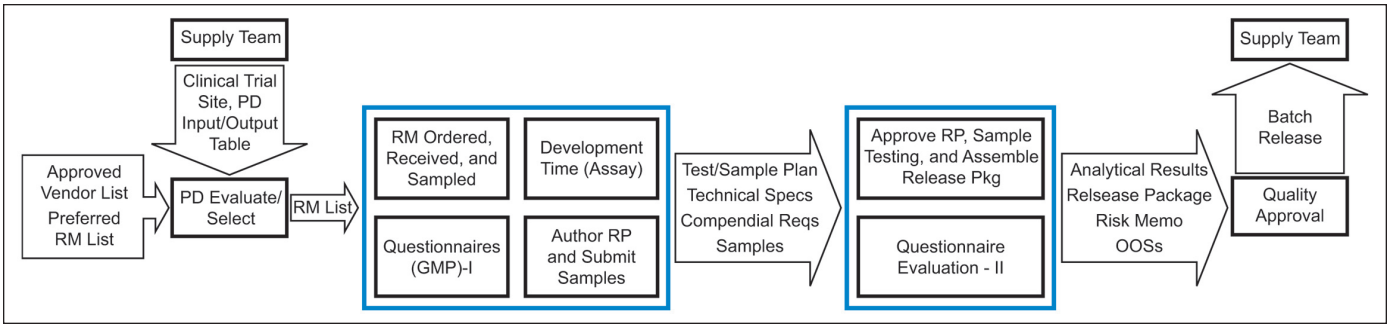

Figure 1. Current state RM value stream map (new RM from an existing or new external vendor).

requirements, five scenario groups were developed from 12 different scenarios and the most complex case was selected for rigorous evaluation - *Figure 1.*

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

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

Future States

Redesigning and Reorienting Workflow Solutions

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

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

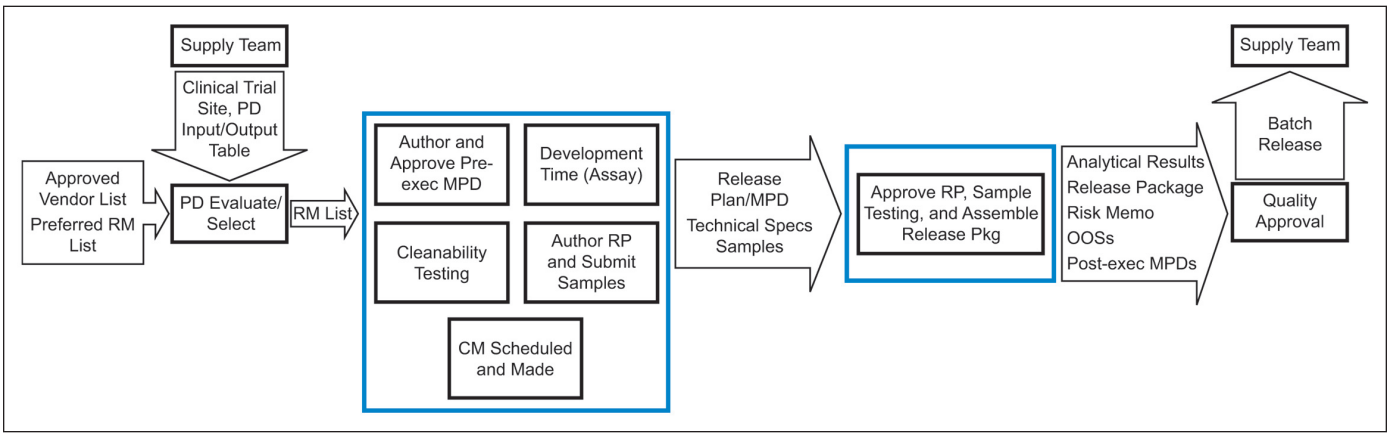

Figure 2. Current state CM value stream map (new CM constituted in-house).

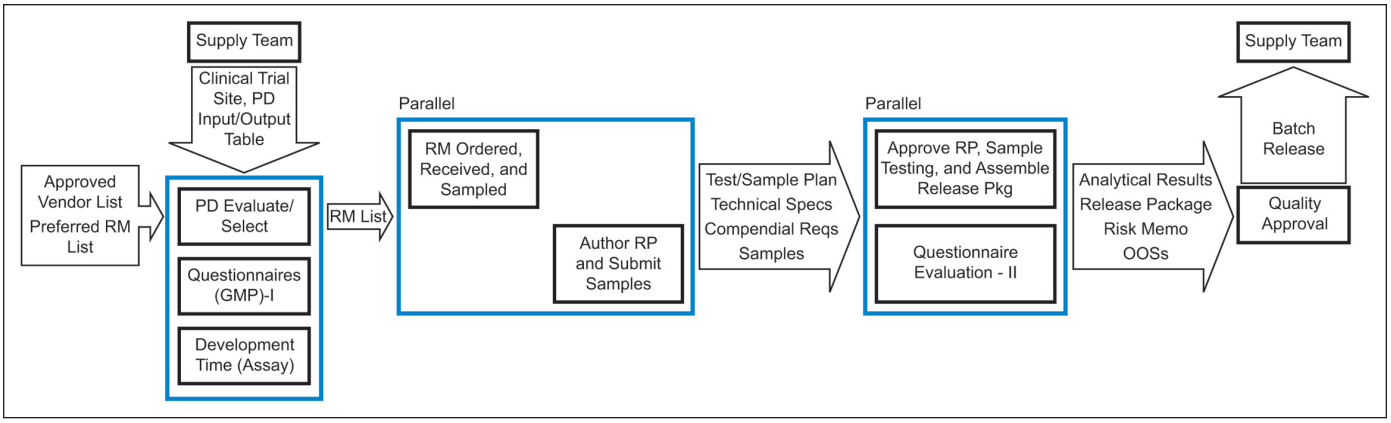

Figure 3. Future state RM value stream map (new RMs from an existing or new external vendor).

be executed for the top three leading candidates being tested for process performance. This pre-investment permitted identification of RMs/CMs substantially closer to the date of clinical manufacturing.

In addition, steps were rearranged to increase the amount of RM/CM testing and release activities conducted in parallel rather than in series, a key method to reduce overall cycle time - *Figure 3*. Specifically, the questionnaire solicitation and release assay development steps were to be conducted at risk. Thus, if a proposed new RM/CM material was tested by process development and not ultimately incorporated into the process, these completed tasks might be used to enhance the supermarket listing of desirable approved RMs/vendors. Key to avoid clogging the system with "at risk" activities was to ensure that (1) only a few (~3) proposed RM/CM candidates underwent "at risk" steps and (2) the "at risk" steps (i.e., quality questionnaires and release assay development) ran efficiently.

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

Alignment ("Out of the Box") Areas

Further efficiencies likely were possible **if quality risks were able to be sufficiently minimized** via current or improved controls. Since each of these ideas required substantial discussion to ensure acceptable quality risk levels, Pugh ratings were used to select the future states with greatest impact on

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

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

this particular efficiency project's goals. Next, an assessment of benefits, risks, and mitigations to achieve acceptable risk was conducted and Probability of implementation Success (POS) estimates assigned. Those ideas with acceptable risk/mitigation were evaluated using FMEA to generate workable solutions for implementation. Specifically, there was potential for the following: 1. using at-line methods (e.g., handheld Raman spectroscopy, laboratory osmometer) for conducting the required ID testing for RM solids as well as ID and potentially composition testing for CM liquids and 2. reducing compendial testing overlap. It was considered highly challenging at this time to mitigate risk 1. for extending RM expiry, 2. reducing the rigor of BSE/TSE questionnaires, 3. accepting RMs based solely based on the vendor's COA, or 4. releasing in-house constituted buffers based only on review of CM preparation batch sheets.

Solution Selection

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

New RM/CM Identification Workflow

A new RM/CM identification (ID) workflow was drafted, incorporating additional front-end structure around new RM/CM selection to permit front-loading longer cycle time steps to minimize overall cycle time - *Figure 4*, including: 1. process development (including upstream, downstream, or formulation) personnel identified the need for a new RM/CM, 2. approval was obtained from the ranking scientist or

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

Table D. FMEA of current and future states.

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

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

group manager according to pre-defined documented criteria (i.e., experimental due diligence to eliminate reasonable and timely alternative solutions, identification of potential collateral impacts to other parts of the process, generation of a comprehensive and ranked list of alternative RM/CM candidates along with pros and cons), 3. candidate RMs/CMs were researched, proposed, and checked for presence on approved, posted RMs/CMs clinical and manufacturing

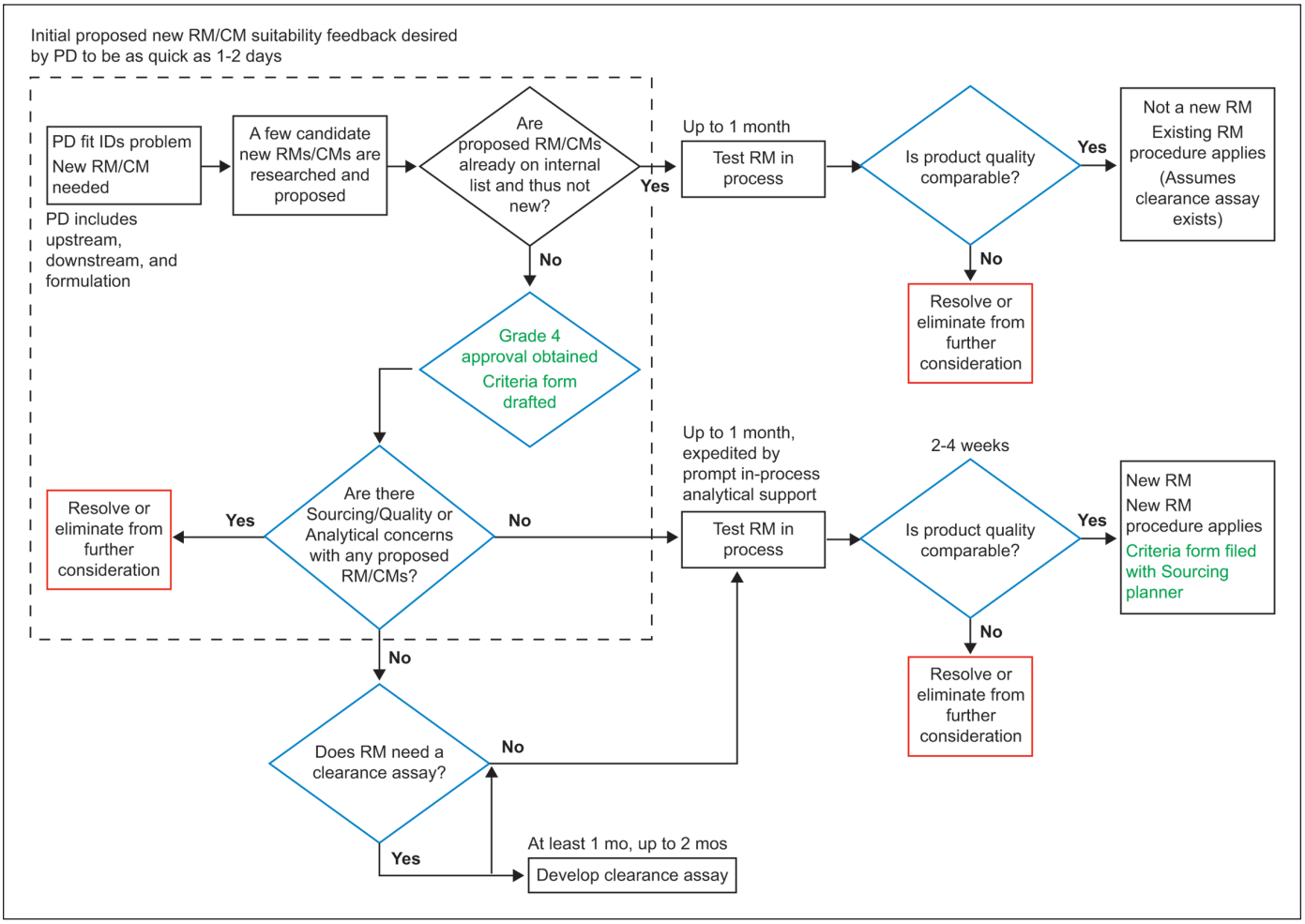

Figure 4. Proposed workflow for new RM/CM identification.

listings, 4. RMs/CMs not on approved listings were vetted for quality, analytical, or procurement concerns, 5. top-ranked, proposed RM/CMs (typically ~3) were use-tested in the process for improved performance with comparable product quality and simultaneously questionnaire solicitation and assay development commenced at-risk, 6. if needed, a clearance assay was developed, and 7. completed approval criteria charts were filed with the area's raw material planner for quarterly review by stakeholders.

It was desired by process development for steps one to four to occur within one to two days (Figure 4) so as not to delay further process development progress, typically on the critical path to clinical studies. There also was considerable benefit from this procedure controlling early process development efforts for a project, even during screening of future production strains to avoid altered strain performance when strains were subsequently transferred to process development. Thus, it was proposed to include an RM/CM evaluation within the developmentability assessment conducted for product candidates as a formal criteria for approval. In addition, line of sight sourcing for new and even existing RMs/CMs used for process development experiments was considered important: similar grades, but not necessarily vendors, were used for simple items, such as salts, while the same grade and vendor were used for complex items, such as proteins unless equivalence was shown via use or release testing.

Alternate ID, Compositional, and Color/ Appearance Testing

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

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

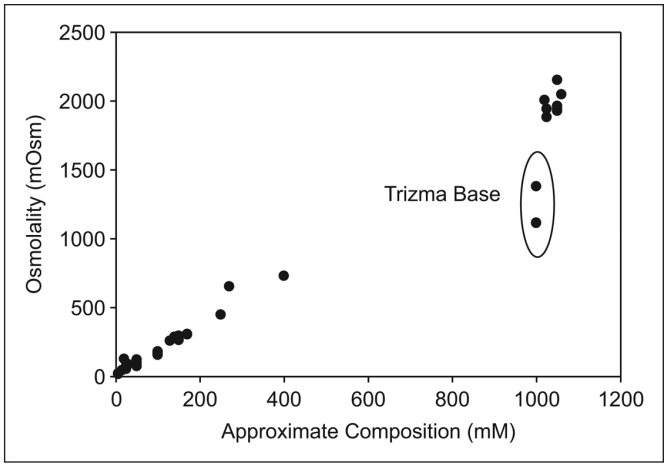

Figure 5. Increase of osmolality with composition.

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

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

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

"Past experience demonstrated that valid failures when repeating compendial tests already conducted by RM vendors were rare; typically failures were classified as invalid after investigation."

then can be correlated with the laboratory procedure and evaluated for suitability.

Compendial Overlap Reduction

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

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

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

Quality Questionnaire Workflow

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

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

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

Leverage RM/CM Expertise

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

A mapped list of issues/contacts facilitated deployment:

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

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

"Single points of contact were established to leverage expertise in both the laboratory technical support group within the manufacturing area and the analytical group within clinical manufacturing area."

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

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

Release Assay Development and Sample Testing Turnaround

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

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

Roles and Responsibilities

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

Projected Achievement of Benefits

Three areas of the workflow were selected to quantify improvements in RM/CM identification-to-release cycle time: questionnaire solicitation response time (first step), release assay development, and sample testing. Using current state estimates for average and standard deviation, the number

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

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

of data points, n_m or n_t (and thus, required time post-implementation) required to determine a significant minimum and target difference, δ_m and δ_t respectively, was estimated using a one-sample T-test (power = 0.8, $\alpha = 0.05$) - *Table G*. Based on forecasted work initiation timing, the time estimated to obtain the target number of data points for $\delta_t = 0.25$ months ranged from 1.5 to 12 months depending on the step.

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

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

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

Despite the clear projected benefits, major factors challenging implementation of these somewhat modest changes center around workload prioritization and management sponsorship. As RM/CM testing and release delays continue to increase, affected groups have begun requesting to speed up implementation. Until the majority of the changes have been implemented, it is difficult to demonstrate a significant overall performance improvement. However, the methodology presented, along with selected solutions, is applicable to other clinical and potentially even licensed manufacturing settings.

References

1. Kupp, G.D., Challenges, Considerations, and Benefits of Raw Material Testing, Pharmaceutical Technology, Analytical Chemistry and Testing, 1 February 2003, pp. 22-27.

2. US Pharmacopoeia 31, National Formulary 26, 2008.

3. Japanese Pharmacopoeia 15, 2006.

4. European Pharmacopoeia 6.0, 2008.

5. Wiggins, J., Compliance with Multi-Compendial Testing Requirements for Excipients: Challenges and Strategies, American Pharmaceutical Review 6(2): 10-14, 2003.

6. Wiggins, J., Skutnik, J.A., Shimek-Cox, J.L., Schwarzwalder, N.A., Compendial Issues: A Position Paper on the Ideal Pharmacopeia, Pharmaceutical Technology 32(11): 122-125, 2008.

7. Cundell, A.M., Managing Microbiological Quality of Pharmaceutical Excipients, PDA J Pharm Sci Technol, 59(6): 381-395, 2005.

8. Shadle, P.J., Qualification of Raw Materials for Biopharmaceutical Use, Biopharm 17(2): 28-41, 2004.

9. Mortellaro, S., Devine, M., Advances in Animal-Free Manufacturing of Biopharmaceuticals, Biopharm International Supplement, May, 2007, pp. 30-37.

10. Halsey, S., Ensuring Raw Material Quality, Pharmaceutical Technology Europe, 1 March 2009.

11. Junker, B.H., Hunsberger, K., Griffin, V., Hamaker, K., Holz, C., Caparoni, A., Kistler, K., Graczyk, J., Gayton, M., Clinical Manufacturing Efficiency, Pharmaceutical Engineering, 29(2): 48-58, 2009.

12. Committee for Medicinal Products for Human Use, "Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials," EMEA, London, 31 March 2006, www.emea.europa.eu/pdfs/human/qwp/18540104en.pdf, accessed 25 September 2008.

13. FDA Center for Drug Evaluation and Research (CDER), "Manual of Policies and Procedures: Acceptability of Standards from Alternative Compendia," (MAPP 5310.7), 3 November 2007, www.fda.gov/cder/mapp/5310.7R.pdf.

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From Seattle to San Diego—the Japan Affiliate's 2009 US Plant Tour

by Osamu Matsumoto and Michael Lucey

Following the successful 2008 tour of pharmaceutical plants in the eastern US through to participation in the Boca Raton Annual Meeting, the Japan Affiliate again organized a tour of US plants, but on this occasion traveling the West Coast and concluding the itinerary at the San Diego Annual Meeting. The tour, as an important annual event offered by the Affiliate, not only helps participants broaden their industry knowledge, but also allows for networking among one another as well as with peers in the US. Moreover, the tour and related events underscore for participants the benefits brought by ISPE, and in doing so contribute to increased membership.

The Affiliate's 2009 US Plant Tour Organizing Committee began its planning in June. The Committee led by Shigeru Nakamura and Osamu Matsumoto, together with Masayuki Akutagawa, studied the available options and narrowed down the candidate destinations to plants in Seattle, San Francisco/Fremont, and Los Angeles. In addition to valuable guidance and support from ISPE HQ in Tampa, plant selection for the tour was owed to the personal connections of Mason Waterbury and Michael Lucey, both of whom are Japan-based and served on the Committee. As a result, five plants were contacted for visits in the November 2 to 6 period, and approval received.

The sign-up phase for the tour began in August. The group proved to be a well-balanced total of 17 participants: seven from pharmaceutical companies, seven from engineering and construction companies, and three from equipment manufacturers. During the early preparation, a level of anxiety was expressed about the impact of the globally spreading swine influenza. Fortunately, the tour members were all able to participate, and importantly, destination plants remained unaffected and available to accept the scheduled visits. Sincere appreciation is expressed by the Japan Affiliate for the consideration extended by the hosts, all of whom warmly welcomed their visitors. Each of the plants visited is outlined below.

Amgen Helix (Seattle)

Advanced R&D facility for biotechnology comprising three R&D buildings connected by corridors, arranged with a view toward future expansion. The facility is characterized by an aseismic design and isolation techniques for stable R&D activities with redundancy considered in the utility facilities.

Amgen Fremont (San Francisco/Fremont)

Production plant for antibodies consisting of two trains of culture tanks with a maximum capacity of 10 m^3. Transparent partition walls are installed between the facility areas and the walkways for visitors so that all facilities can be viewed.

Bayer HealthCare (San Francisco/Berkeley)

Bio plant for blood products where stable production is maintained throughout in order to obtain just several hundred grams of products yearly. From a process perspective, the features of the plant are continuous fermentation and harvesting.

Genentech (South San Francisco)

A research facility for the identification of proteins, Building 42 has enabled research work to be accelerated by the introduction of robots and the customization of laboratory equipment.

With Kelly Keen at Genentech in South San Francisco.

Building 43 is a kilo-lab facility working with small molecules, again remarkable for its customized equipment aimed at efficient R&D work.

Baxter BioScience (Los Angeles)

World-leading plant for blood plasma fractionation products. The tour and explanations fully covered the chilled storage of raw materials, to thawing, fractionation, packaging, and sterilization.

A key element of the tour's overall program was the San Francisco/Bay Area Chapter-organized Commuter Conference hosted by Amgen Fremont. With a formal invitation received, the visitors from Japan attended the Conference's guest lectures and joined the plant tour and networking party, as well as a social dinner in the Fremont area. Organized by the San Francisco/Bay Area Chapter, the dinner together was an ideal opportunity for local Chapter and visiting Affiliate to get to know one another and to plan for the future with reciprocity in Japan as a topic also discussed!

In the evenings, having returned to the hotel, members attended daily wrap-up meetings with delegated persons compiling reports on the day spent. Leader Osamu Matsumoto was later to provide a total presentation on the tour to the Japan-based membership at the Affiliate's Winter Meeting held in December 2009 in Osaka.

But it was certainly not all work in the US as the travel itinerary happily included Safeco Stadium in Seattle, wine tasting in the Napa Valley, Universal City in Burbank, the Getty Center in Los Angeles, and of course a wonderful diversity of restaurants to close out each day of a memorable week. A reunion party is now planned in Japan to join the 2008 and 2009 tour members, further expanding the potential for networking. Benefiting from feedback and advice received, planning is already underway for another tour this year with Orlando as the final destination!

ISPE Co-sponsors Official ICH Quality Implementation Working Group (Q-IWG) "Integrated Implementation Training Workshops" for ICH Q8, Q9, and Q10

2-4 June 2010 | Tallinn, Estonia
6-8 October | Washington, DC, USA
25-27 October | Tokyo, Japan

Official International Conference on Harmonisation- (ICH-) endorsed training workshops on integrated implementation of the ICH Q8, Q9, and Q10 guidelines will kick off on 2 to 4 June in Tallinn, Estonia. The training, cosponsored by ISPE and PDA (in the USA and Europe), is presented by members of the ICH Quality Implementation Working Group (Q-IWG), which consists of industry and regulator experts from the three ICH regions — USA, Europe, and Japan — and observers from Canada and Switzerland (EFTA countries), and the World Health Organization (WHO).

The training will use a presentation and workshop format including a full day discussion with Q-IWG members. It is designed for all persons, regulator and industry, who have an interest in, or responsibility for, the integrated implementation of these guidelines. On the regulator side, the workshops should be valuable to assessors and GMP inspectors. The USA and Japan training workshops will be repeated in Washington, DC, USA on 6 to 8 October and in Tokyo, Japan on 25 to 27 October, respectively.

The workshops have been designed under the guidance of the ICH Q-IWG, and many of the faculty will be regulator and industry experts serving on the Q-IWG. Additional instructors will be industry and regulator experts involved in development of the actual ICH Q8, Q9, and Q10 guidances. Jean-Louis Robert, Rapporteur/Chairman for ICH Q-IWG, is serving as the Chairman of the Faculty for the workshops.

Attendees will receive training on the integrated implementation of Q8, Q9, and Q10 and how they apply along the product lifecycle. In addition to technical development and manufacturing details, the workshops will provide comprehensive information on regulatory aspects, including regulator expectations, dossier preparation, assessment and GMP-inspections. Workshop features include:

- How Q8, Q9, and Q10 can benefit pharmaceutical development, manufacturing, regulatory assessment, scale up to commercial operations, and GMP-inspection.
- A case study on opportunities for combined implementation of Q8, Q9, and Q10 in specific quality systems and operations.
- Discussions among industry and regulators on solutions to implementation challenges.
- Smaller breakout sessions for industry people in development and manufacturing as well as for regulators in assessment and inspections to explore possibilities over the product lifecycle

Feedback from the workshops will be used by the Q-IWG to further facilitate the harmonized implementation of ICH Q8, Q9, and Q10 and included in the official Q&A (www.ich.org/LOB/media/MEDIA5783.pdf). The final workshop materials and outcomes will be summarized by regulators and industry from the ICH regions and made available to other regions as well. The workshop materials will be suitable for further internal training by industry and regulators.

For more information on the ICH workshops in Europe and the USA, please visit www.ISPE.org/2010ICHworkshops. Information on the ICH guidances on Pharmaceutical Development (Q8), Quality Risk Management, including the Q9 briefing pack (Q9) and Pharmaceutical Quality System (Q10) is available at www.ICH.org.

"We Get It"

2009 was a challenging year for the industry and for many of our Members with mega-mergers, industry shifts, and a global economic crisis that affected almost everyone. We know that many of us will continue to feel the effects well beyond 2010. There is no question that the industry is changing…and ISPE is changing too. Our Members need help, and we understand that. ISPE is here to serve your needs and solve your problems.

What is ISPE doing to help? We're rolling out a series of powerful resources for Members in job transition or insecure in their current employment, including:

- "Career Solutions," a new Members only area of the ISPE Web site geared specifically to your needs with articles, job postings, upcoming events for networking opportunities and job fairs, and links to additional resources that can help. The "Career Solutions" center will continue to grow, as we develop strategies to get more job postings and locate additional resources from expert providers to add to the site.
- A series of live webinars geared toward Members who are insecure in their jobs or job-seeking. These sessions also will be recorded and made available on demand at no cost to Members.
- A new discussion group for Members to interact, share ideas for job hunting, and to garner support among your peers in the industry.
- A broader Hardship Program that enables Members in good standing the ability to extend your membership at no charge while unemployed. The program also allows Hardship Program Members free access to networking events at international conferences, such as the Milan Congress, Washington D.C. Conference, Brussels Conference, and Annual Meeting.
- Active outreach to Members in companies where layoffs have been announced with a viral component so others within the company also can benefit from joining ISPE

And, There's More Value for Your Membership Coming Soon!

Every month, we will notify ISPE Members about a package of timely, free benefits, including webinars, Knowledge Briefs, Web site features, and some new resources as well. These free benefits packages will be available to Members only although non-members may be able to access a few of the items on an al a carte pricing basis.

So, coming in June, look for new monthly e-communications giving you access to these Members-only benefits packages.

If you are not receiving ISPE email, be sure to visit www.ISPE.org or read *Pharmaceutical Engineering* magazine, where you will find notices about the greater benefits available to ISPE Members.

If you don't see something that will help you, please let us know. We'll listen to your feedback, and with the counsel of ISPE's Volunteers, make ongoing adjustments so that the benefits we offer meet the changing needs of our Members.

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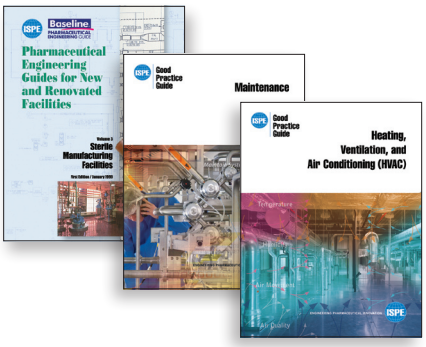
ISPE Launches Electronic Document Delivery System



ISPE has released its first three technical documents in electronic format. ISPE will release one to three technical documents per month in this new format throughout 2010.

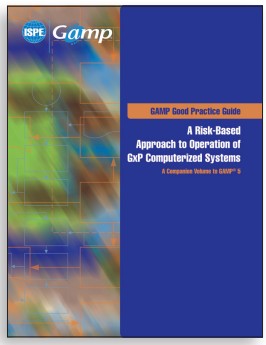
Sterile Manufacturing Facilities Baseline Guide, ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning (HVAC), and ISPE Good Practice Guide: Maintenance are now available for sale as individual PDF downloads from the ISPE Web site. Professionals who are familiar with ISPE's indispensable industry technical resources can now download these guides, cut and paste, search, print, and include TOC bookmarks and links in the PDF file. Each document is customized with individual watermarks, identifying the user who downloaded the document.

The next five documents slated for electronic download will be:

- GAMP® 5
- Oral Solid Dosage Forms Baseline Guide, 2nd Edition
- GAMP® Good Practice Guide: A Risk-Based Approach to Operation of GxP Computerized Systems
- GAMP® Good Practice Guide: Manufacturing Execution Systems (MES)
- GAMP® Good Practice Guide: Validation of Process Control Systems (VPCS)

Now Available: New ISPE GAMP® Good Practice Guides

ISPE GAMP® Good Practice Guide: A Risk-Based Approach to Operation of GxP Computerized Systems



Regulated computerized systems should be maintained in a demonstrable state of control and in accordance with regulatory requirements. Recovery from a failure to maintain control of a regulated system during the Operation Phase can be both time-consuming and expensive, and increase the risk to data integrity, product quality, and patient safety.

During the operational life of a GxP system, regulators usually focus on the integrity, consistency, and completeness of controls required to maintain compliance.

This Good Practice Guide, a companion volume to GAMP 5, aims to increase the awareness of the importance of the Operation Phase of the system life cycle, when the return on investment for the significant time and resource expended in implementing new computerized systems can be achieved.

This Guide aims to help regulated organizations to achieve regulated computerized systems that are fit for intended use and compliant with applicable regulations and provides comprehensive guidance for maintaining control of regulated systems throughout their operational life, including:

- provide a better understanding of both the individual operational processes and the interrelationships between them
- help organizations to assign clear roles and responsibilities to required activities throughout the Operation Phase
- embed scalable risk-based approaches into the definition and management of those internal and external operational processes

When applied as intended, this Guide can provide detailed direction on the required control processes which form a substantial part of an appropriate Quality Management System (QMS).

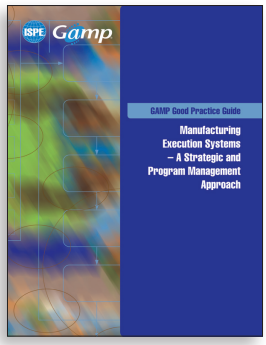
This Guide addresses the operational and support processes that need to be established to receive regulated computerized systems into the Operation Phase of their life cycle and to maintain them in a state of compliance throughout their operational life, through to system retirement. Guidance provided is scalable and can be applied to a range of systems, including:

- laboratory systems
- process control systems
- IT applications

This Guide contains comprehensive information, including:

- a detailed consideration of process scope
- risk-based scalability considerations
- the appropriate assignment of roles and responsibilities
- identification of associated records
- example procedures

ISPE GAMP® Good Practice Guide: Manufacturing Execution Systems – A Strategic and Program Management Approach



The true potential of Manufacturing Execution Systems (MES) lies in the integration of capabilities and functionality of systems through a well designed 'MES Domain,' which can provide benefits, such as reduced cost, faster turnaround, and improved quality, through elimination of redundant data entry, transcription errors, etc.

The Guide uses the framework of GAMP 5, as a complete life cycle approach to the development and use of MES for regulated manufacturing. It does so, not as a system or application, but as a collection or domain of manufacturing related functions that integrates business and process controls, information flow, and human interaction to facilitate the operation of an organization. The potential benefits of integrated manufacturing systems for recipe-driven operations include:

- improved scheduling and resource utilization
- improved manufacturing flexibility and process changeover
- reduced Work In Progress (WIP) and improved material tracking
- shorter production cycles
- enforced sequence of operations
- reduced production record errors, electronic or hybrid
- improved visibility, accuracy, and consistency of manufacturing data, enhancing decision support, Process Analytical Technology (PAT), and investigations capabilities
- minimized product recalls
- increased plant reliability
- realize paperless manufacturing
- automated Key Performance Indicator (KPI) generation and reporting, such as an Overall Equipment Efficiency (OEE) calculation
- support knowledge management and PAT
- reduce quality unit resources required for day to day operations by providing functionality, such as Electronic Production Records (EPR) and Review By Exception (RBE)

This Guide is intended to help to facilitate the planning,

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

New Member Benefit: Final ISPE/PDA endorsed White Paper: Use of Interactive Voice Response or Web Systems to Manage IMP Retest Dates

Now available and free to Members is the final ISPE/PDA endorsed White Paper: Use of Interactive Voice Response or Web Systems to manage IMP Retest Dates. This White Paper provides guidance on how to employ this technology for use in removing use by dates from CTM labels.

It is current practice within the pharmaceutical industry to manage dating of Investigational Medicinal Products (IMPs) by placing "expiration" and/or "retest" dates on IMP labels when used in EU/EEA studies. Most IMP supplies are research materials in various stages of development and are intended for eventual commercialization. In the development lifecycle for these compounds, stability programs run concurrently with Clinical Trials. It is common for the retest dates to be extended beyond the initial assigned date based on evolving data. In general, expiration dates cannot be extended. Managing retest date updates for IMPs that are in use at study sites is costly, labor intensive, and based on the specific process used to update existing IMP labels, can introduce some risk.

In accordance with Annex 13, Rules Governing Medicinal Products in the European Community, Volume IV, the period of use (use-by-date, expiry date, or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity must be provided on the IMP label "unless its absence can be justified, e.g., use of a centralized electronic randomization system."

The objective of this paper is to provide guidance on how one might employ Interactive Voice Response (IVR) and/or Interactive Web Response (IWR) technology to support retest date management of IMPs, remain in compliance with the EU Directives, and help ensure patient safety.

This report does not imply that permission has been granted by EU/EEA Competent Authorities to eliminate expiration and retest on IMP labels for trials in all EU countries. The ability to take this approach must be confirmed for each trial via the registration process.

The White Paper is available under the "Other Publications" section of the ISPE Web site.

New GAMP® Good Practice Guides

Continued.

development, testing, and operation of MES by:

- providing an understanding of MES
- providing a practical framework for applying the principles and concepts of GAMP 5 to MES
- identifying regulatory and compliance aspects of MES
- providing guidance for MES suppliers
- addressing MES technical considerations

It aims to enable organizations to:

- shorten development and implementation times by leveraging industry experience
- implement design and testing methods that improve life cycle activities
- build compliance into the process
- provide improved understanding and coordination of the complete manufacturing environment
- reduce the risk of project failure
- better balance costs of implementation and operation
- clarify Quality Unit resources required for ongoing system operational support

Knowledge Briefs Free to Members

Knowledge Briefs are concise, summary documents that provide general information on issues, processes, and technologies impacting the contemporary pharmaceutical industry. Although it may contain technical content, *Knowledge Briefs* are written in terms a non-technical reader can understand and are intended to help industry professionals get up-to-speed quickly on a particular topic. Each brief includes links to additional ISPE resources, such as technical documents, *Pharmaceutical Engineering* articles, webinars, Communities of Practice, and educational seminars and training courses to provide more specific and detailed information on the subject.

The following recently published *Knowledge Briefs* are free to ISPE Members and available for immediate download:

Applied Risk Management in Commissioning and Qualification

by David D. Dolgin and Jörg Block Level: Intermediate

This *Knowledge Brief* describes the general concepts of an ISPE Good Practice Guide under development intended to "bridge" the differences between traditional C&Q, as discussed in the ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification, and the risk-based ASTM verification practices.

Best Practices in the Sponsor-Provider Partnership to Optimize the Clinical Trials Development Process

by Timothy S. Brewer Level: Fundamental

This *Knowledge Brief* explains seven best practices that can be adopted and adapted to drive improvements in the sponsor-provider relationship to optimize the development process and timeline.

Clinical Supply Chain Logistics of Small Molecules vs. Biologics – A Provider's Perspective

by Timothy S. Brewer Level: Fundamental

This *Knowledge Brief* gives a provider's perspective overview of and considerations in the differences between clinical supply chain logistics of small molecules versus biologics; a comprehensive project management approach to supply chain planning; managing appropriate import licenses; and ensuring stability through continuous monitoring.

Containment Hierarchy of Controls

by Beth Brock Level: Fundamental

This *Knowledge Brief* explains the basics of the Containment Hierarchy of Controls, as also described in ISPE's Baseline® Guide: Volume 1 – Active Pharmaceutical Ingredients. Information beyond the hierarchy described in the Baseline Guide has been added to illustrate alternative considerations typically contained in other versions of hierarchies, such as those used in Industrial Hygiene or Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP).

Forecasting for Clinical Trials

by Marisa Ehinger Level: Fundamental

This *Knowledge Brief* provides a high level overview and clarification of the basic concepts, terminology, methodologies, and benefits of forecasting for clinical trials.

Packaging Material Selection: Things to Consider

by David Williams Level: Fundamental

This *Knowledge Brief* looks at the major types of packaging materials, how they are manufactured, and some issues for consideration to achieve stability of the product with the immediate container, closure system – the most important feature of a packaging material.

Recent Evolution of Clinical Trial-Related Regulatory Environment in Belgium

by Nicolas Butz Level: Intermediate

This *Knowledge Brief* provides information on the recent regulatory changes and clarifications that occurred in Belgium concerning the requirements related to the CTA and the declaration of Investigational Medicinal Products (IMPs). It also provides an overview of expectations to meet in order to run a clinical trial in Belgium, with references to the appropriate required documents.

Technology Solutions for Challenges in Cold Chain Supply Management

by Timothy S. Brewer Level: Fundamental

This *Knowledge Brief* gives an overview of the newest technologies that offer solutions for the growing challenges in cold chain supply management, specifically: phase change materials, global positioning systems, RFID, and USB drives.

Chinese Version of GAMP® 5 Now Available

ISPE has released the Chinese version of GAMP 5. The Chinese GAMP 5 helps facilitate a better understanding of the English version without having to worry about the contrast between both versions. A dedicated team of pharmaceutical industry experts went through several rounds of review and translation. Please contact China@ispe.org for more details and to order this new version.

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March/April 2010, Vol. 30 No. 2

Design, Validation, and Control of Sterile Manufacturing Facilities: A Brief Overview from the Perspective of Risk Management and Existing Regulations

This article presents the design, validation, and control of sterile manufacturing facilities; discusses the implementation of risk management, and provides an overview of existing regulations.

by Ana Quinto and José C. Menezes

Introduction

One of the most critical operations in pharmaceutical manufacturing is the processing of sterile products. The production of sterile products, specifically the ones that cannot be terminally sterilized, involve complex and demanding processes to prevent the products' contamination and require a great amount of resources.

The inherent risk of microbiological contamination associated with aseptic operations is critical because it has a direct relation with human health. The difficulty in detecting contamination makes the outcome of these processes less predictable, naturally having higher risk, and being more difficult to control and manage:

"Aseptic manufacturing processes are unique since the severity of harm is always going to be high and detection of loss of sterility is always going to be low."[1,2]

To enter this business successfully, it is important to have a deep knowledge of what underlies this type of manufacturing, such as the strict and extended regulations applicable and the cost of what is necessary to start and maintain these

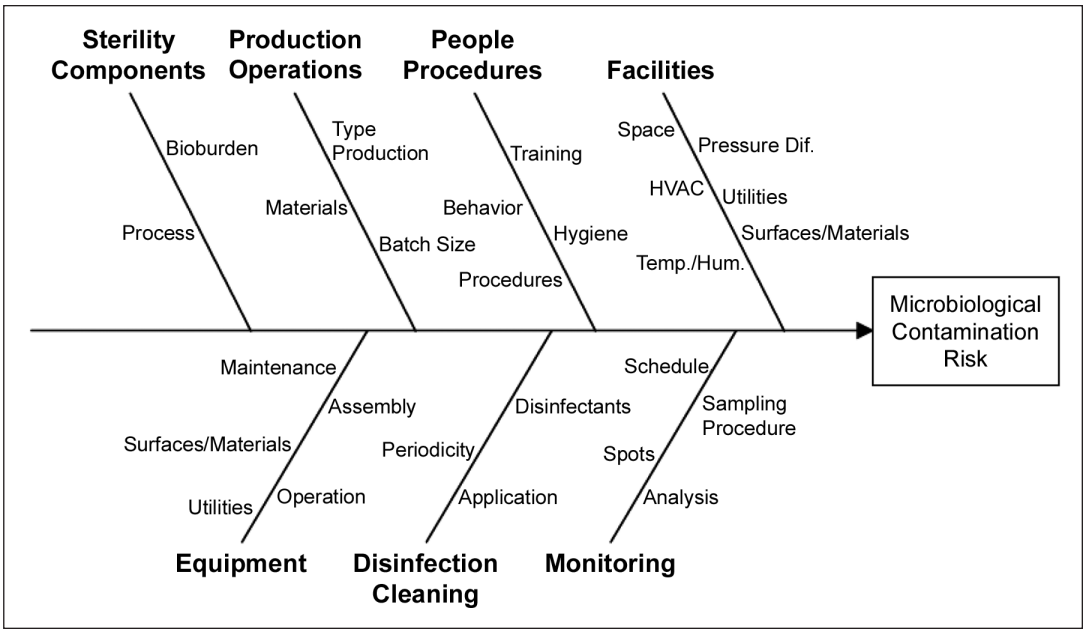

Figure 1. Cause and effect diagram with microbiological contamination parameters from an aseptic process.

types of processes. Adequate facilities, equipment, materials, procedures, operators, and a strong and robust sterility assurance policy are examples of these requirements. The EU GMP Annex 1 reinforces this idea referring that:

"Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test."[1,2]

Sterile products can be processed by aseptic manufacturing or can be terminally sterilized. These two types of processes have different characteristics and involve specific conditions. The regulatory guidelines describe specific conditions expected for each one regarding every step of the process.[2,3]

Terminally sterilized products involve manufacturing processes, where microbiological contamination can happen within highly controlled conditions. Sterility is obtained through a final sterilization step, where the product is already in its final container.[2,3]

Aseptic manufacturing is more demanding as there is no final sterilization step.

Freeze-drying is a specific type of production process that involves products that are unstable as solutions. In these situations, the process involves the filtering of the solutions before a filling step, adding the freeze-dry step that happens with the containers opened. The final closure of the containers only occurs much later in the process, which represents a great contamination risk.[4]

Sterility of products, particularly the ones produced by aseptic processing, is obtained guaranteeing the conformity of the processes' different factors - *Figure 1*. To obtain sterile products, it is essential that all the processing is done in a way that minimizes the risk of contamination hazards.[1,2]

A contamination event in any of the referred factors in the previous diagram is considered critical for the sterility of the process. The concept of Quality by Design is discussed in the FDA's Guidance for Industry: PAT:

"Quality cannot be tested into products; it should be built-in or should be by design."[5]

The changes in the industry in the last 10 years helped define a strong and growing set of regulations and guidance documents related to this subject. These regulatory documents define requirements supported by standards and industry guidance published by groups, including ISPE and PDA.

Risk Management

Although for many years, the concept of risk management also has been applied in the pharmaceutical industry in an informal manner, formal applications are more recent and still considered limited. The FDA's initiative in 2002, "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach" was extremely important in promoting risk management since it presented the first structured approach in this area.[1] The main purpose of the use of risk management is to support decisions using rational methodology although it is important to underline that compliance with regulatory aspects continues to be a requirement.[1,6]

Quality risk management was defined in the guideline ICH Q9 as a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product throughout its lifecycle.[6,7]

An adequate use of quality risk management tools provides better and more informed decisions, enabling, for example, regulators to assert a company's capability to deal with risk problems and positively affect the thoroughness of direct regulatory supervision. The main purpose of the use of risk management is to support decisions using rational methodology although it is important to underline that compliance with regulatory aspects continues to be a requirement.[1,6]

Facilities

Most sterile manufacturing processes are performed in cleanrooms. A cleanroom can be defined as a room in which the concentration of airborne particles and other environmental conditions, such as temperature, humidity, and pressure, are controlled.[9]

This type of environment is a requirement for the manufacturing of sterile products in order to minimize the risk of microbiological, particle, and pyrogen contamination.[2,3] The air handling and the type of surface materials are examples of important issues to be dealt with in the construction of a cleanroom. The necessary space must be available in cleanrooms so all the operations and procedures can be performed properly. Equipment and other items introduced in cleanrooms should be considered since they can influence the cleanroom's performance.[4]

The air that enters the cleanroom has to be filtered by an adequate High Efficiency Particulate Air (HEPA) filter, in order to prevent contaminations from the outside. The number of air changes has to be adequate to dilute contamination generated from the process; equipment and personnel and airflow patterns inside the clean areas must prevent the contamination of the critical areas, where sterile products and other important items are manipulated. The pressure differentials inside the aseptic facility must prevent airflows from less clean areas to cleaner areas. When dealing with potent parenteral products, the pressurization scheme also must address containment issues.[4]

Cleanrooms can be divided in four types, according to the airflow pattern:

- Conventional
- Unidirectional Flow
- Mixed Flow
- Isolators, RABS, or Microenvironments[11]

Isolators, RABS (open or closed), or microenvironments are the ones that offer better processing conditions since access to the critical area is very limited. These critical areas, where sterile materials are exposed, are completely segregated and protected by unidirectional flow.[11]

Mixed flow is considered the basic design concept for a cleanroom with a unidirectional flow inside a conventional

room with turbulent flow. In this case, the critical areas are not as protected as the previous situations.[11]

Unidirectional flow cleanrooms are completely covered by unidirectional flow. In this case, the critical areas are not segregated from other areas.[11]

Conventional cleanrooms are the ones that present less protection for the product, as the critical areas also are not segregated from other areas and the flow inside the room is turbulent.[11]

In situations where the product is less protected, very well defined procedures are required to prevent contamination.[11]

Cleanroom Classification

Regulatory documents and norms define tests and specifications to demonstrate the compliance of the cleanroom to certain cleanliness classes. EU and FDA GMPs refer to ISO Standards in what concerns detailed methods for classification of cleanrooms.[2,3,4]

Parameters that must be evaluated when testing a cleanroom involve:

- leak tests to the HEPA filters
- number of particles
- air change rates
- recovery times of the cleanroom after a contamination event
- airflow patterns
- pressure differentials

Nevertheless, the number of total particles is one of the main issues when classifying a cleanroom. ISO and FDA particle limits for classification purposes are determined from the following Equation 1.[9]

$$Cn = 10^N \times \left(\frac{0.1}{D} \right)^{2.08}$$

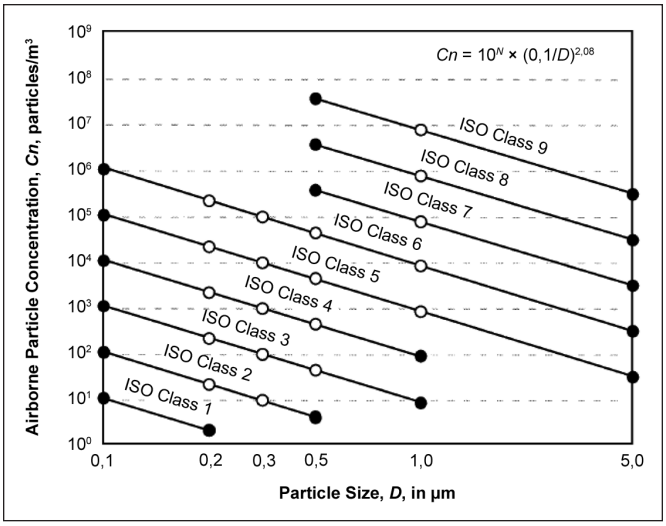

Figure 2. Graphical illustration of the airborne particulate cleanliness classes.[9]

where, Cn is the maximum permitted concentration (particles per m^3) of particles, equal to or larger than the considered particle size, N is the ISO classification number, D is the considered particle size in micrometers, 0.1 is a constant with a dimension of micrometers.[9]

Figure 2 has a graphical representation of airborne particulate classes obtained using Equation 1.[9]

The last version of the EU GMPs still presents some differences in these specifications compared to the ISO and the FDA. Table A has the concentration limits of airborne particles for each grade of cleanliness, according to the latest version of Annex 1 EU GMP,[1,2] ISO 14644-1,[9] and FDA guidance,[3] where it is possible to observe the differences and similarities between their specifications.

Regarding these limits, the major controversy happened with the 5 µm limits, as the EU limit in the 2003 version of the guideline, was 1/m^3 – a number not achievable given the measuring limitations.[7,12] In the 2005 GMP Annex 1 propos-

Guideline	Grade	At Rest		In Operation	
		0.5 μm	5.0 μm	0.5 μm	5.0 μm
EU	A / B**	3 520	20 / 29	3 520	20
ISO*	5	3 520	29	3 520	29
FDA	100	---	---	3 520	---
EU	---	---	---	---	---
ISO*	6	35 200	293	35 200	293
FDA	1000	---	---	35 200	---
EU	B***	---	---	352 000	2 900
ISO*	7	352 000	2 930	352 000	2 930
FDA	10 000	---	---	352 000	---
EU	C	352 000	2 900	3 520 000	29 000
ISO*	8	3 520 000	29 300	3 520 000	29 300
FDA	100 000	---	---	3 520 000	---
EU	D	3 520 000	29 000	Not defined	Not defined
ISO*	9	35 200 000	293 000	35 200 000	293 000
FDA	---	---	---	---	---

*ISO designation should include the classification number and the occupancy state to which the classification applies – "as-built," "at rest," and "operational," as there is no other discrimination in the limits.[8] **Refers to grade B at rest. ***Refers to grade B in operation.

Table A. EU, ISO, and FDA maximum permitted number of particles per m^3 for each grade.[2,3,9]

als of amendment, a limit of 20/m^3 was suggested for reasons related to false counts associated to electronic noise.[13] This limit of 20/m^3 for the 5 µm particles was officially adopted in the latest version of 2008. The other EU limits also were slightly different from those of the ISO.[1,2,3,9]

Although smaller, the differences in the limits presented by the current EU guidelines and the ISO/FDA still exist, but there is a strong international pressure to end the differences, and obtain a global harmonization.[7,14] The major differences between the current EU particle limits, the ISO, and the FDA are:

- FDA only considers 0.5 µm particle limits
- EU 5 µm limits (20/m^3) are more rigorous regarding the ISO limits (29/m^3)
- FDA only considers limits for operation conditions, EU has limits for "at rest" and "in operation," and ISO has only one type of limits, meaning that ISO designation should include the classification number and the occupancy state to which the classification applies – "as-built," "at rest," and "operational"
- FDA/ISO consider an intermediate classification level between 100/ISO 5 (EU grade A) and 10 000/ISO 7 (EU grade B), which is Class 1000/ISO 6. This level can be used, for example, for areas surrounding Class 100.
- FDA does not consider the cleanliness level corresponding to EU grade D.[1,2,3,9]

Another controversial issue concerned the minimum sample volume of 1 m^3 for cleanrooms' classification purposes referred to in the EU guideline, which is a much higher value compared to the ISO values (view Equation 2).[1,2,15]

$$Vs = \frac{20}{Cn,m} \times 1000$$

where, *Vs* is the minimum single sample volume per location, expressed in liters, *Cn,m* is the Class limit (number of particles per cubic meter) for the largest considered particle size specified for relevant class, 20 is the defined number of particles that could be counted if the particle concentration were at the class limit.[15]

Nevertheless, the ISO document is currently going through its periodic review with some sections being modified. The number of sampling points proposed in ISO 14644-1 for classification purposes was adopted both by EU and FDA, which is the number corresponding to the area's square root.[1,2,15]

Microbiological limits also are a critical issue when evaluating pharmaceutical production cleanrooms.[1,2,3] The manufacturers are expected to have standards based on their processes' historic values. The characterization of the microorganisms also is an expectation.

Table B presents the microbiological limits in Colonies Forming Units (CFU) for each grade of cleanliness, according to the latest version of Annex 1 EU GMP (2008) and the FDA.[1,2,3] Microbiological limits in both guidelines are similar, the following are the major differences between the EU and the FDA guideline:

- EU allows average numbers, which is a controversial topic between the two agencies, since it is much less restrictive than the individual limits presented by the FDA. This issue is particularly relevant in Grade A/Class100.
- FDA has limits for Class 1000.
- FDA does not present limits for contact plates or gloves although referring that operators' gloves and gowns involved in aseptic operations, should be contamination-free.
- FDA considers settling plates as an optional type of monitoring.[1,2,3]

Regarding microbiological limits, there were no changes introduced by the 2008 version of the EU Annex 1.[1,2,12,13]

The ISO documents were not referred as they do not present any microbiological limits, only referring tools and methodologies for biocontamination control.[16,17]

The regulatory guidelines define expected minimum classification conditions for each step of sterile production processes, which must be considered when designing a manufacturing process.

Ventilation and Cleanroom Design

Guideline	Grade**	Air Sample (CFU/m^3)	Settle Plates diameter 90 mm (CFU/4 hours)	Contact Plates diameter 55 mm (CFU/plate)	Glove Point 5 fingers (CFU/glove)
EU	**A**	< 1	< 1	< 1	< 1
FDA	**100**	1*	1*	---	---
EU	---	---	---	---	---
FDA	**1000**	7	3	---	---
EU	**B****	10	5	5	5
FDA	**10 000**	10	5	---	---
EU	**C**	100	50	25	---
FDA	**100 000**	100	50	---	---
EU	**D**	200	100	50	---
FDA	---	---	---	---	---

*No microbial contamination is expected on samples from Class 100.
**The association between EU and FDA grades was performed assuming in operation values (view Table A).

Table B. EU and FDA recommended limits for microbial contamination.[2,3]

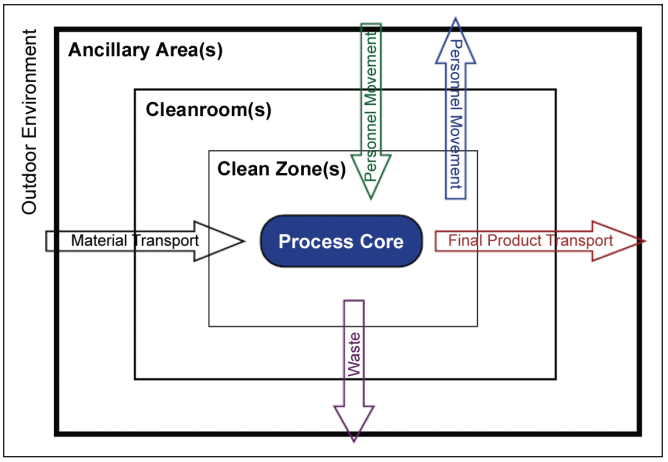

Figure 3. Shell-like contamination control concept.[19]

necessary to install the capacity for the necessary airflow rate, considering each cleanroom's particle generation rate. Entries and exits of air should be installed according to the room characteristics, equipment's layout, and the production processes that will be performed.[18]

The airflow between different areas must prevent contamination of cleaner areas. Figure 3 presents a shell-like contamination control concept with a progressive protection of the process core at which the most critical operations occur.[19] Like referred earlier, when dealing with potent products, the pressurization scheme is different and more complex, as containment issues also must be addressed.

Material transport inside the clean zone is accomplished through sterilization/depyrogenation/sanitization processes. Personnel movement regarding the clean zone is usually done using gowning zones with several steps, and separated entrance and exit areas.[19] The final steps of the gowning zones must be of the same grade as the areas where people are going to enter.[1,2,3]

In the most critical areas, where sterile items are exposed, Grade A/Class 100 environment is a requirement. Unidirectional flow is a condition referred to in the guidelines for Grade A/Class 100.[1,2,3] The aim of this unidirectional flow is to prevent any contamination entering the clean space and also to remove any contamination from the critical areas as fast as possible.

The regulatory documents refer minimum pressure differentials that must be met between areas with different classification. Pressure differentials of 10 to 15 Pa can be considered guidance values for both EU and FDA guidelines.[1,2,3]

The number of change rates and locations of entries and exits of air are very critical issues that deeply influence the performance of a clean process, which must be established for each particular situation. The location of Grade A/Class 100 areas also must be considered. Regarding these issues, the FDA only refers 20 air changes per hour as an acceptable number for Class 100000 – number being challenged by many people in the industry, and higher change rates for superior cleanliness Classes.[3] The EU GMPs refer that "at rest" limits should be achieved after a short recovery period of 15 to 20 minutes after operations occur.[1,2]

Practical study of the airflow patterns with smoke and determining recovery times using real simulation models can be extremely useful when establishing the necessary conditions of a clean area.[18,21] Another option to determine these cleanroom parameters is the use of computer simulation models, such as, airflow design methods that allow incorporating the referred performance variables. The Dilution Model and Computational Fluid Dynamics are examples of methods for airflow design.[20,22]

The accurate determination of air supply also concerns energy savings, as these areas are highly energy consuming.[23] In this context, ISO 14644-4 also refers the possibility of reducing air supply on cleanrooms during non-operating periods to reduce costs.[19]

Equipment

Equipment and all other items used in aseptic processing areas have specific requirements to allow the compliance with the necessary environmental classifications. Characteristics like the type of materials that must be non-shedding and shape of surfaces are crucial in order to comply with the necessary conditions and to enable an adequate cleaning and disinfection. Appropriate equipment design can prevent turbulence and stagnant air in the critical areas. Equipment's layout inside the aseptic processing areas also should be addressed. The components that are going to be in direct contact with the sterile product must be sterilizable.[1,2,3]

The equipment and manufacturing process must be designed and operated in a way that prevents contamination.[1,2,3] All the required characteristics deemed important when designing a process or choosing equipment should be clearly defined and documented regarding the processes' needs and regulatory requirements.

Utilities

All utilities supplied to sterile processes, like any other item entering the processes, must guarantee that the required conditions for each step of the process are not disturbed.[1,2,3]

Validation and monitoring of utilities is a critical issue.[24] Examples of such utilities, besides the air introduced into the cleanrooms, are water, steam, and gases (e.g., compressed air or nitrogen). The quality required is increasingly demanding when closer to the critical areas.

Water to be used in the critical steps of sterile manufacturing must comply with the requirements of Water for Injection (WFI). Examples of such use are injectable product preparations, preparation of injections, final rinse after cleaning equipment and components that come into contact with injectable products, and final rinse of a washing process in which no subsequent thermal or chemical depyrogenization process is applied.[26] The European Pharmacopoeia is more demanding in what concerns production of WFI, as it only considers acceptable distillation as a production process.[27] The USP allows other type of production processes.[28] The most critical issues in the production and distribution of water for pharmaceutical use, and particularly WFI, are related to microbiological and endotoxin contamination control, involving

special requirements.[25]

Specifications of steam to contact a sterile product or component should comply with the specifications for WFI when condensed.[26]

The production of medicinal gases is usually a specialized industrial process, which is not normally undertaken by pharmaceutical companies.[29,30]

Validation of Sterile Processes

Process validation is defined in the Annex 15 of the EU Guide to GMP as the documented evidence that a process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.[31]

Classic process validation concepts are being replaced by a new validation strategy based on process and product understanding throughout the entire product's lifecycle, particularly after the FDA initiatives "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach."[32] Science-based methodologies and modern technology, such as, PAT[5] and risk-based approaches,[7] were strongly encouraged for process validation, monitoring, and control. The release of products without having to perform all the tests in the specifications, based on the information collected from the manufacturing process and on the compliance with other specific GMP compliance related to parametric release,[33] is only considered in this context of sterile manufacturing for terminally sterilized products, based on the compliance of the critical parameters of sterilization.[34]

A multi-disciplinary team is essential when dealing with validations of sterile processes. Engineering, production, quality assurance, microbiology, validation, and product development are examples of people who must be involved.

The planned validation steps should be formally concluded before moving to the next step. Process validation must be completed prior to the distribution and sale of the medicinal product. Revalidation of the processes should be addressed regarding each specific situation to guarantee that the processes remain valid, considering the situation when process modifications occur.[31]

Qualification

Qualification can be defined as a documented scientific process, used by pharmaceutical manufacturers, to assure the reliability and capability of equipment and/or processes before approval for use in manufacturing. Examples of processing equipment that should be qualified in this aseptic processing context are sterilizers, washing equipment, filters, fillers, closure placement equipment, sealing machinery, and freeze-dryers.[35]

A risk-based approach should be considered throughout all the qualification phases. The establishment of monitoring programs also should be based on a risk-based approach considering the data collected during the qualification. Smoke studies, showing air flow distribution and particle data, are valuable information to be considered, particularly when determining the monitoring locations.[3] The determination of the time for monitoring should consider critical activity timings and production contingencies.

Process Simulation Testing

The most challenging issue, when validating a sterile production process, is the microbiological contamination control, as this type of process is expected to guarantee zero contamination. Other quality parameters specific of this type of product, such as total particle counts and pyrogens, also are important, but their limits and the experience indicates that they are much easier to comply with.

To demonstrate that a certain manufacturing process can consistently produce a sterile product, it is necessary to assess the production system throughout the simulating of the manufacturing process using a nutrient medium. This simulation process using a nutrient medium, instead of the real product, is usually called media fill.[35]

The latest version of the EU GMP Annex 11,[2] and the FDA guideline regarding sterile production,[3] present similar guidance regarding the number of containers that should be filled to simulate the processes, frequency of tests, and also acceptance criteria - *Table C*. Both documents refer that the contamination goal of media fills should be zero.

Initial validation involves three consecutive satisfactory simulation tests per shift. Media fills should be repeated at defined intervals (e.g., twice a year) and when significant process modifications occur.[1,2,3]

When designing the simulation test, it is necessary to select worst-case scenarios (e.g., maximum number of operators, potential interventions in critical areas, and time of production process).[35] Risk assessment tools are useful to help determine the validation process. All operations must be included, such as, compounding or filling. When simulating a powder filling production line, the simulation test must be performed allowing the same type of evaluation, for example, using a powder placebo and adding a step in the filling process where media is inserted into the container.[35]

The protocol should include all the information describing the process simulation test and supporting the choices made. Identification of the process and operators, number of containers being filled, type of containers, speed of the filling line, interventions, type and amount of media and placebo,

Production Batch Size (Containers)	Minimum Containers Tested Per Run	Results and Required Actions
< 5000	Size of production batch	No contaminated units should be detected. One (1) contaminated unit – investigation and revalidation.
≥ 5000	5000 – 10 000	One (1) contaminated unit – investigation and consideration of a repeated media fill. Two (2) contaminated units – investigation and revalidation.
	≥ 10 000	One (1) contaminated unit – investigation. Two (2) contaminated units – investigation and revalidation.

Table C. Media fill number of containers and acceptance criteria.[2,3]

duration of filling, environmental monitoring, acceptance criteria, incubation conditions, rejected units, and results are examples of information that should be included in such protocols.[35]

This test is an important tool to have an idea of the aseptic process capability, including environment, equipment, procedures, and personnel. It does not assure the sterility of all products produced in the tested manufacturing process, but in combination with proper control of the processes (e.g., routine monitoring program, validation, and personnel qualification), it is possible to have an acceptable level of sterility assurance regarding the aseptic processes.[35]

Maintaining Compliance

Control of the implemented processes is critical to assure the maintenance of the installed conditions. A Routine Monitoring Program (RMP) of an aseptic process intends to evaluate the aseptic processes' performance; therefore, the parameters tested and the information acquired in the performance qualification phase should be considered in the risk assessment when developing this program.[24,35]

Regarding the referred parameters being monitored, a RMP should include:

- monitoring spots
- frequency of monitoring
- duration of sampling
- when to sample
- monitoring methods
- alert and action levels
- actions to be taken when limits are exceeded[3,35]

It is important to develop a proper management system to help deal with the collected data and ease the evaluation process.[35]

Conclusions

The design, validation, and control of sterile manufacturing facilities were reviewed considering the most relevant regulatory guidelines, applicable ISO documents, and other significant references. A reference regarding implementation of risk management in the context of sterile manufacturing was presented. The most important issues that must be considered in this type of facilities were discussed, including the types of cleanrooms, cleanroom classification, ventilation and design, equipment, utilities, validation, qualification, and maintenance. Although it is clear that the trend throughout the world is to harmonize regulations, the main differences concerning the EU and the FDA GMPs were highlighted.

References

1. PDA Technical Report No. 44, "Quality Risk Management for Aseptic Processes," PDA Journal of Pharmaceutical Science and Technology, 62(S-1) Supplement, 2008.
2. EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Revision to Annex 1: Manufacture of Sterile Medicinal Products, European Commission, Brussels, February 2008. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/2008_02_12_gmp_annex1.pdf.
3. Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, FDA, Rockville, September 2004, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070342.pdf.
4. Möller, A., Chapter 2 – International Standards for the Design of Cleanrooms, in Whyte W., Cleanroom Design, 2nd Edition, John Wiley and Sons Ltd, England, 1999, pp. 21-50.
5. Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, FDA, Rockville, September 2004. http://www.fda.gov/CDER/guidance/6419fnl.pdf.
6. EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 20: Quality Risk Management, European Commission, Brussels, February 2008. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/2008_02_12_gmp_annex20.pdf.
7. ICH Q9 - Risk Management, Technical Report, International Conference on Harmonization, November 2005. http://www.ich.org/LOB/media/MEDIA1957.pdf, 2008.
8. Farquharson, G., "Using New Cleanroom Standards with Sterile GMPs," *Pharmaceutical Engineering*, November/December 2002, Vol. 22, No. 6, pp. 72-77, www.ispe.org.
9. ISO 14644-1, Cleanroom and Associated Controlled Environments – Part 1: Classification of Air Cleanliness, ISO 1999.
10. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 3 – Sterile Manufacturing Facilities*, International Society for Pharmaceutical Engineering (ISPE), First Edition, January 1999, www.ispe.org.
11. Whyte, W., Chapter 1 – An Introduction to the Design of Clean and Containment Areas, in Whyte, W., **Cleanroom Design**, 2nd Edition, John Wiley and Sons Ltd, England, 1999, pp. 9-20.
12. EC Guide to Good Manufacturing Practice Revision to Annex 1: Manufacture of Sterile Medicinal Products, European Commission, Brussels, May 2003, http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/revan1vol4_3.pdf.
13. GMP Annex 1: Proposals for amendment to the environmental classification table for particles and associated text, amendment to section 42 concerning acceptance criteria for media simulations, amendment to section 52 concerning bio-burden monitoring, and additional guidance in section 88 on the sealing of vials, (EMEA/INS/GMP/318222/2005/Correction), EMEA Inspections, September 2005, http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2005/11_05/annex_1_amended_09-2005.pdf.
14. Valle, M., "USA/EC/ISO Regulatory Considerations for Designing Aseptic Processing Facilities," *Pharmaceutical Engineering*, July/August 2004, Vol. 24, No. 4, pp. 36-46, www.ispe.org.

15. ISO 14644-2, Cleanroom and Associated Controlled Environments – Part 2: Specifications for Testing and Monitoring to Prove Continued Compliance with ISO 14644-1, ISO 2000.
16. ISO 14698-1, Cleanrooms and Associated Controlled Environments – Biocontamination Control – Part 1: General Principals and Methods, ISO 2003.
17. ISO 14698-2, Cleanrooms and Associated Controlled Environments – Biocontamination Control – Part 2: Evaluation and Interpretation of Biocontamination Data, ISO 2003.
18. Farquharson, G., Whyte, W., Chapter 4 – The Design of Cleanrooms for the Pharmaceutical Industry, in Whyte W., **Cleanroom Design**, 2nd Edition, John Wiley and Sons Ltd, England, 1999, pp. 78-113.
19. ISO 14644-4, Cleanroom and Associated Controlled Environments – Part 4: Design, Construction, and Start-Up, ISO 2001.
20. Jaisinghani, R., "Analytical Methods for Cleanroom Airflow Design," *Journal of GXP Compliance*, 9(1): 80-92, October 2004.
21. Ljungqvist, B., Reinmuller, B., **Practical Safety Ventilation in Pharmaceutical and Biotech Cleanrooms**, PDA, DHI Publishing LLC, USA, 2006.
22. Jaisinghani, R., "Energy Efficient Low Operating Cost Cleanroom Airflow Design," Paper presented at IEST's ESTECH Conference, Phoenix, May 2003. http://www.cleanroomsys.com/downloads/docs/Energy_Efficient_%20IEST_03.pdf 92009].
23. Schicht, H., Chapter 7 – Cost-Efficiency and Energy-Saving Concepts for Cleanrooms, in Whyte, W., **Cleanroom Design**, 2nd Edition, John Wiley and Sons Ltd., England, 1999, pp. 141-155.
24. Vincent, D., "Validating, Establishing, and Maintaining a Routine Environmental Monitoring Program for Cleanroom Environments: Part II," *Journal of Validation Technology*, 9 (1): 33-50, November 2002.
25. EMEA, "Note for Guidance on Quality of Water for Pharmaceutical Use" [online], May 2002, http://www.emea.europa.eu/pdfs/human/qwp/015801en.pdf [2009].
26. WHO, Chapter 1 – WHO Good Manufacturing Practices: Main Principals for Pharmaceutical Products (Water for Pharmaceutical Use), in WHO, Quality Assurance of Pharmaceuticals [online], Vol. 2, 2nd updated version, 2007, pp. 170-186, http://www.who.int/medicines/areas/quality_safety/quality_assurance/QualityAssurancePharmVol2.pdf [2009].
27. Water for Injections, European Pharmacopoeia, 6th Edition, Vol.2, EDQM, Strasbourg, 2008, pp. 3209-3215.
28. <1231> Water for Pharmaceutical Purposes, USP 31-NF 26 S2, United States Pharmacopoeia Convention Inc., 2008, pp. 691-710.
29. EC Guide to Good Manufacturing Practice, Final Version of Annex 6: Manufacture of Medicinal Gases, European Commission, Brussels, 2001, http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/v4an6.pdf.
30. Nilsson, C., Åkerlindh, K., Ernblad, A, "Regulations Governing Gas Used in Pharmaceutical Production," *Pharmaceutical Engineering*, November/December 2004, Vol. 24, No. 6, pp. 88-98.
31. Final version of Annex 15 to the EU Guide to Good Manufacturing Practice: Qualification and Validation, Brussels, July 2001, http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/v4an15.pdf.
32. FDA, 30/04/2009, "Pharmaceutical CGMPs for the 21st Century – A Risk-Based Approach" [online], Food and Drug Administration, September 2004, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm137175.htm [2009].
33. EMEA, "Note for Guidance on Parametric Release" [online], March 2001, http://www.emea.europa.eu/pdfs/human/qwp/301599en.pdf [2009].
34. <1222> Terminally Sterilized Pharmaceutical Products – Parametric Release, USP 31-NF 26 S2, United States Pharmacopoeia Convention Inc., 2008, pp. 678-681.
35. ISO 13408-1, Aseptic Processing of Healthcare Products, Part 1: General Requirements, ISO 1998.
36. PDA Technical Report No. 22, "Process Simulation Testing for Aseptically Filled Products," *PDA Journal of Pharmaceutical Science and Technology*, 50(6) Supplement, November-December 1996.

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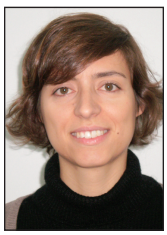

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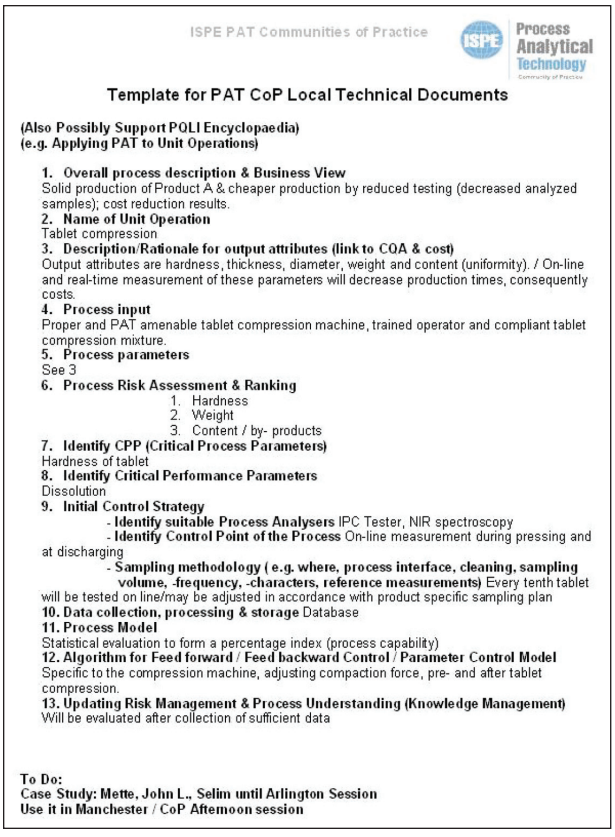
A Simplified Statistical Model to Assess Product Capability

by Selim Seyhan, Tolga Özcan, and Merve Öktem

This article presents a simplified model that can be used after future refinements to identify the specific process capability in pharmaceutical manufacturing. Data for a concrete production stage of a solid product is presented. Technologies, present and future, are identified.

Introduction

There is a distinct trend today with regard to validating manufacturing processes, which is different than from the long accepted notion that validated processes remain constant. We now know that starting materials and equipment undergo difficult to detect changes over time, which necessitates subsequent modifications in the "classical" sense of validation processes. The latter had been "frozen" according to the currently accepted validation concept. Product quality had been related solely to specifications, resulting in process understanding assuming a secondary role. As a result, the FDA published important guidance addressing this issue.[1] Much publicized in the ensuing four years, many companies around the globe accepted the ideas promulgated in this document, such as Process Analytical Technology, Quality by Design, and Parametric Release as a way of understanding their processes; however, there has been little progress in obtaining concrete results. This also is evident by the relatively few number of products, which have been approved to be released parametrically. This article presents a simple model that was developed at a manufacturing facility, PharmaVision, Istanbul, Turkey, which is currently being tested for a number of products manufactured by various member companies of the ISPE Turkey PAT COP.



ISPE PAT Communities of Practice

Process Analytical Technology

Template for PAT CoP Local Technical Documents

(Also Possibly Support POLI Encyclopaedia)
(e.g. Applying PAT to Unit Operations)

1. **Overall process description & Business View**
Solid production of Product A & cheaper production by reduced testing (decreased analyzed samples); cost reduction results.
2. **Name of Unit Operation**
Tablet compression
3. **Description/Rationale for output attributes (link to CQA & cost)**
Output attributes are hardness, thickness, diameter, weight and content (uniformity). / On-line and real-time measurement of these parameters will decrease production times, consequently costs.
4. **Process input**
Proper and PAT amenable tablet compression machine, trained operator and compliant tablet compression mixture.
5. **Process parameters**
See 3
6. **Process Risk Assessment & Ranking**
   1. Hardness
   2. Weight
   3. Content / by- products
7. **Identify CPP (Critical Process Parameters)**
Hardness of tablet
8. **Identify Critical Performance Parameters**
Dissolution
9. **Initial Control Strategy**
   - **Identify suitable Process Analysers** IPC Tester, NIR spectroscopy
   - **Identify Control Point of the Process** On-line measurement during pressing and at discharging
   - **Sampling methodology (e.g. where, process interface, cleaning, sampling volume, -frequency, -characters, reference measurements)** Every tenth tablet will be tested on line/may be adjusted in accordance with product specific sampling plan
10. **Data collection, processing & storage** Database
11. **Process Model**
Statistical evaluation to form a percentage index (process capability)
12. **Algorithm for Feed forward / Feed backward Control / Parameter Control Model**
Specific to the compression machine, adjusting compaction force, pre- and after tablet compression.
13. **Updating Risk Management & Process Understanding (Knowledge Management)**
Will be evaluated after collection of sufficient data

To Do:
Case Study: Mette, John L., Selim until Arlington Session
Use it in Manchester / CoP Afternoon session

Figure 1. Filled for Tablet A, compression stage.

The Model

In line with the PAT Template (Figure 1) developed by the ISPE Turkey PAT COP, manufacturing processes were dissected into distinct unit operations, such as compression, coating, and packaging in order to monitor the process and establish a standard to compare production processes.

The process for tablet compression was selected for the model, because of its simplicity. Almost every In-Process Control (IPC) laboratory takes samples to test various parameters, usually every hour or half an hour from this process; therefore, enough data is accumulated to analyze this process.

Critical Quality Attributes (CQA) for the particular product demonstrated in Figure 1 are hardness, thickness, diameter, weight, and content (uniformity) for the tablet compression process.

Critical Process Parameters (CPP) influencing such attributes, on the other hand, are compression force, homogeneity

Factor for Control Limits			
n	X Chart	n	X Chart
	A_2		A_2
2	1.880	8	0.373
3	1.023	9	0.337
4	0.729	10	0.308
5	0.577	11	0.285
6	0.483	12	0.266
7	0.419		

Table A. Factors for constructing variables control charts.

and flow rate of the powder, and speed of the compression machine.

In the current actual situation, the IPC laboratory takes samples at regular intervals, per specifications of the particular product, from the tablet compression process and measures their hardness, weight, diameter, and thickness.

There are warning (alert) and action limits for the weight. For manual operations, when the warning limits are exceeded, IPC warns the compression operator and the operator makes the necessary adjustments.

However, when the action limits are exceeded, the machine is stopped and the collected product further examined. This standard in-process procedure applies in all tablet compression operations. With automated systems employing feed-forward capabilities, such adjustments can be done without stopping the equipment. Yet, the basic principle remains the same, i.e., from accumulating live data, a meaningful and simple to comprehend number should emerge, which will give the operator an indication of process robustness and control. Following is the statistical background and justification for arriving at such an index, which will be referred to as "robustness index."

Statistical Justification

In order to find an index for a product (Tablet A), the weight, hardness, and disintegration and assay data for a minimum of 30 batches was collected. The first step required was to check whether the process was in control or not.

$\bar{X}$ Control Charts

In any work environment, no matter how well a process is designed or maintained, there will be a certain amount of inherent or natural differences in the parts, services, or process settings. This natural variation is the cumulative effect of many small and sometimes uncontrollable causes, for instance, the floor shaking, the air circulating, air pressure changing, and so on. As long as these differences remain small, they are considered acceptable for the process. In fact, from a process control point of view, this variation is often called a "stable system of chance causes" or "common variation." A process that is operating with only this common variation present is said to be in statistical control.[2]

Control charts also may be used to estimate the parameters of a production process and through this information, to determine the capability of meeting process specifications. The control chart also can provide information that is useful in improving the process. Finally, remember that the eventual goal of statistical process control is the elimination of variability in the process. Although it may not be possible to eliminate variability completely, the control chart helps reduce it as much as possible.[3]

In order to draw $\bar{X}$ control chart, the following calculations must be performed: mean of every sample ($\bar{X}$), average of the sample means ($\bar{\bar{X}}$), mean range of the samples ($\bar{R}$), Upper Control Limit (UCL), and Lower Control Limit (LCL).

$$\bar{X} = \frac{x_1 + x_2 + \ldots + x_n}{n} = \frac{\sum_{i=1}^{n} x_i}{n} \quad \text{(sample mean formula)}$$

i is the number of samples (i = 1, 2, 3, ... n)

$$\bar{\bar{X}} = \frac{1}{m} \sum_{j=1}^{m} \bar{X}_j$$

$$\bar{R} = \frac{1}{m} \sum_{j=1}^{m} R_j$$

j is the number of batches (j = 1, 2, 3, ... m)

Upper Action Line = $\bar{\bar{X}} + A_2\bar{R}$ (for $\bar{X}$ chart)
Lower Action Line = $\bar{\bar{X}} - A_2\bar{R}$ (for $\bar{X}$ chart)
Upper Warning Line = $\bar{\bar{X}} + 2/3\ A_2\bar{R}$ (for $\bar{X}$ chart)
Lower Warning Line = $\bar{\bar{X}} - 2/3\ A_2\bar{R}$ (for $\bar{X}$ chart)

Equation 1

where n is the sample size, m is the number of samples, and A_2 is constant that is tabulated for various sample sizes in Table A.

Upper Action Lines (UAL) and Lower Action Lines (LAL) are known as action lines, because beyond this point, an action should be taken. There also are warning lines, which are two thirds of the distance between the control limit and action lines. These lines are illustrated in Figure 2.

From this data, $\bar{X}$ control chart can be established. The observations of weight are in Table B.

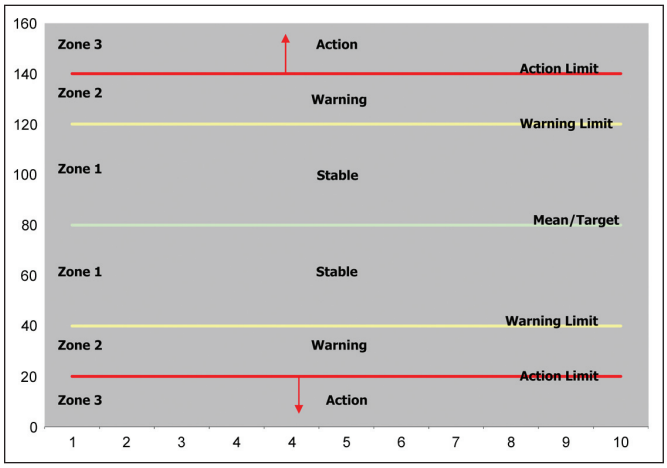


Figure 2. Zones on the control charts.

No.	1	2	3	4	5	6	7	8	9	10	$\bar{X}$	R
1	641.6	644.0	658.7	649.7	632.4	641.1	664.2	661.3	671.1	653.9	651.8	38.7
2	663.4	651.7	652.2	634.7	653.7	624.2	648.4	646.5	647.6	646.3	646.9	39.2
3	654.7	655.7	651.4	648.3	649.6	642.4	646.8	629.5	649.0	644.5	647.2	26.2
...	...	...	...	...	...	...	...	...	...	...	...	...
28	657.2	649.2	651.5	659.0	658.5	629.4	653.6	643.4	645.8	648.7	649.6	29.6
29	651.6	635.0	655.4	622.2	665.7	659.8	668.5	667.3	656.6	666.5	654.9	46.3
30	654.4	658.1	659.5	662.9	654.2	653.2	646.1	652.6	659.4	653.7	655.4	16.8

Table B. The observations of weight attribute.

The parameters for weight attribute are calculated according to the formulas in Equation 1.

$$\bar{\bar{X}} = \frac{651.8 + 646.9 + ... + 654.9 + 655.4}{30} = 651.6$$

$$\bar{R} = \frac{38.7 + 39.2 + ... + 46.3 + 16.8}{30} = 28.3$$

UAL = 651.6 + 0.308 X 28.3 = 660.3 (Upper action line for $\bar{X}$ chart)

UWL = 651.6 + 0308 X 28.3 X (2/3) = 657.4 (Upper warning line for $\bar{X}$ chart)

LAL = 651.6 – 0.308 X 28.3 = 642.9 (Lower action line for $\bar{X}$ chart)

LWL = 651.6 – 0.308 X 28.3 X (2/3) = 645.8 (Lower warning line for $\bar{X}$ chart)

The resulting chart is as follows - *Figure 3*.

Before the control charts are used or the process capability is assessed, it is important to confirm that when the samples were taken, the process was indeed 'in statistical control,' i.e., the distribution of individual items was reasonably stable.

If the process from which the data was collected is in statistical control, there will be:

- no mean or range values, which lie outside the action limits (Figure 2, Zone 3)
- no more than about one in 40 values between the warning and action limits (Figure 2, Zone 2)

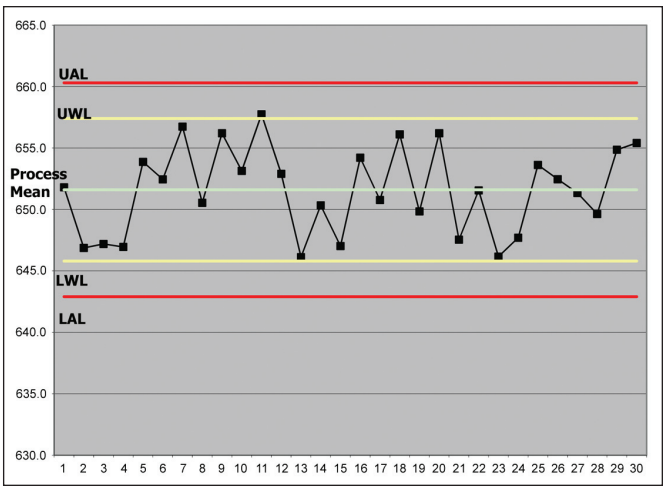


Figure 3. Chart for weight attribute.

- no incidence of two consecutive mean or range values, which lie outside the same warning limit on either the mean or the range chart (Figure 2, Zone 2)
- no run or trend of five or more, which also infringes a warning or action limit (Figure 2, Zone 2 or 3)
- no runs of more than six sample means, which lie either above or below the grand mean (Figure 2, Zone 1)
- no trends of more than six values of the sample means that are either rising or falling (Figure 2, Zone 1).[4]

Process Capability

After assessing the state of the control, the process capability can be calculated. Lower Specification Limits (LSL) and Upper Specification Limits (USL) of critical attributes are taken - *Table C*.

For each batch, sample mean and standard deviation of each attribute is calculated ($\bar{X}$, s) according to the following formulas.

$$\bar{X} = \frac{x_1 + x_2 + ... + x_n}{n} = \frac{\sum_{i=1}^{n} x_i}{n} \quad \text{(sample mean formula)}$$

$$S = \sqrt{\frac{\sum_{i=1}^{n} (x_i - \bar{x})^2}{n - 1}} \quad \text{(sample standard deviation formula)}$$

where n is the sample size and x_is are the readings of attributes.

Equation 2

There are some assumptions made for some of the calculations. For example, in the case of assay, this parameter is only measured once in every batch and it is assumed that this measured value is taken as sample mean of this batch. Similarly, the standard deviation for 30 batches is assumed constant for that parameter.

The mean of the batches are listed in Table D. The standard deviations of the batches are listed in Table E.

A process capability index is a measure relating the actual performance of a process to its specified performance, where processes are considered to be a combination of the plant or

Attribute Name	LSL	Target	USL	Unit
Weight	617.50	650.00	682.50	Mg.
Hardness		Min. 70		N
Assay	475.00	500.00	525.00	Mg.

Table C. Specification limits of Tablet A.

Batch No.	Weight	Hardness	Assay
1	651.8	99.5	503.4
2	646.9	97.6	511.0
3	647.2	91.7	496.0
...	...	...	...
28	649.6	87.8	508.5
29	654.9	91.9	503.5
30	655.4	89.1	502.7

Table D. Mean of the batches.

Batch No.	Weight	Hardness	Assay
1	12.15	8.97	4.32
2	10.73	9.20	4.32
3	7.45	9.19	4.32
...	...	...	...
28	8.86	10.44	4.32
29	15.25	12.08	4.32
30	4.72	9.44	4.32

Table E. Standard deviations of the batches.

equipment, the method itself, the people, the materials, and the environment.

In order to manufacture within a specification, the difference between the USL and the LSL must be less than the total process variation. So a comparison of 6σ with (USL - LSL) gives an obvious process capability index, known as the C_p of the process:

$$C_p = \frac{USL - LSL}{6\sigma}$$

where σ is the short-term process standard deviation, USL is the Upper Specification Limit, and LSL is the Lower Specification Limit.

Clearly, any value of C_p below 1 means that the process variation is greater than the specified tolerance band so the process is incapable. For increasing values of C_p, the process becomes increasingly capable.

The process width denominator is chosen as 6 standard deviations, because this is deemed to be a reasonable representation of the width of the process (99.73% of data points lie between ±3 standard deviations in any normally distributed data).[5]

C_p index gives no indication as to process centering, but it is a simple comparison between the variation and specification limits.

C_{pK} represents the distance of the center of the process to the nearest specification limit in units of process width. Therefore, it shows the amount of variation and the centering of the process. C_{pK} is calculated according to the Equation 3.

$$C_{pL} = \frac{\bar{X} - LSL}{3\sigma} \qquad C_{pU} = \frac{USL - \bar{X}}{3\sigma} \qquad C_{pK} = \min\{C_{pL}, C_{pU}\}$$

Equation 3 – Capability Index

In the model, for each batch, process capability (C_{pK}) of each attribute is calculated.

Batch No.	Weight	Hardness	Assay
1	0.8	1.1	1.7
2	0.9	1.0	1.1
3	1.3	0.8	1.6
...	...	...	...
28	1.2	0.6	1.3
29	0.6	0.6	1.7
30	1.9	0.7	1.7

Table F. C_{pK} values.

CpK Range	Score Range
$0 < C_{pK} \leq 1$	0 – 25
$1 < C_{pK} \leq 1.33$	25 – 50
$1.33 < C_{pK} \leq 1.67$	50 – 75
$C_{pK} > 1{,}67$	75 – 100

Table G. C_{pK} vs. model index.

The C_{pK} values of each attribute for every batch is listed in Table F.

We would like to simplify the above detailed theoretical background to a less sophisticated model and numerical value, which the operator will understand as the process takes place and can react upon. The latter will actually happen in the future, when relevant PAT technology is available and is implemented, such that measurements will be made on-line and adjustments (within design space) completed as the manufacturing progresses. C_{pK}, we thought, is a statistical term, too specific for an operator to react to; what would a number of 1.33 mean to direct line operator?

A 0 to 100 scale index, we thought would be more practical and easier to understand. Also, to assign a C_{pK} value to a process (or even a unit operation) is extremely difficult and very susceptible to manipulation. Obviously, QA personnel and engineers also will benefit from the model, even in the shorter term, as they are the ones to design the system and technology for process understanding before handing over to the operator level. C_{pK} and robustness Index conversion is shown in Table G.

A C_{pK} value of less than 1.0 means that the result is out of specification and unacceptable accordingly. Since the process has to prove capable of producing aimed results directly related to pharmaceutical product quality, C_{pK}=1.33 and higher is the desired state. The values in 1.0 to 1.33 range indicate the need for improvement. Commonly, $C_{pK} > 1.67$ is needed for running critical processes or setting targets during design stage. C_{pK} equal or higher than 2 reminds us of six sigma studies and according to the model's calculation method, such values are given the highest score.

Table H shows the model index values after the conversion of C_{pK} to Model index values.

In order to compare the batches and the other products tablet compression process, a percentage was assigned to each attribute.

We don't want to overstate the score of products; therefore, we give low percentages to attributes, which have relatively high scores. Percentage determination procedure is given as follows:

Batch No.	Weight	Hardness	Assay
1	21	32	75
2	23	25	31
3	50	20	72
...	...	...	...
28	41	14	45
29	15	15	74
30	93	17	79
Score Mean	41	20	73

Table H. Model index values.

$$\text{Score Mean of the k}^{\text{th}}\text{ attribute} = \overline{SM}_k = \frac{\sum_{j=1}^{m} Z_{jk}}{m}$$

(m is the total number of batches, Z_{jk} is the score of k^{th} attribute in the j^{th} batch)

$$\text{Percentage of k}^{\text{th}}\text{ attribute} = yk = \frac{1/\overline{SM}_k}{\sum_{k=1}^{p} 1/\overline{SM}_k}$$

(p is the total number of attributes, $\overline{SM}_k$ is the score mean of k^{th} attribute)

Equation 4 – Attribute Percentage Calculation

Using the formulas in Equation 4, the percentages of the attributes are calculated.

$$\text{Percentage of weight attribute} = \frac{1/41}{1/41 + 1/20 + 1/73} = 32\%$$

The other percentages are calculated and listed in Table I.

After determination of percentages, batch total scores and product scores can be calculated.

$$\text{Batch Score} = \sum_{k=1}^{l} Z_{jk} y_k$$

(Z_{jk} is the score of k^{th} attribute in j^{th} batch, y_k is the percentage of k^{th} attribute)

$$\text{Product Score} = \frac{\sum_{j=1}^{m}\sum_{k=1}^{l} Z_{jk} y_k}{m}$$

For the Tablet A example, batch and product score are shown in Table J.

$$\text{Tablet A score} = \frac{35 + 25 + \ldots + 23 + 50}{30} = 34$$

Conclusion and Future Work

The methodology listed above is admittedly in its development stage and will need further refinement. Yet, the preliminary scores received for various products indicate a fairly good correlation between this score, the robustness index, and the retrospective assessment of the product, such as Annual Product Review (APR) results, complaint history, deviation data, etc. This is certainly an improvement over the present state, where 'validated' processes do not necessarily deliver compliant products, as evidenced by huge expenditures associated with not right-first-time productions.

We anticipate that in the current year, together with other member companies of ISPE Turkey PAT COP, we will be testing this model with selected products from our manufacturing lines as a comparative backup to our ongoing regular release procedures. At that stage, we plan to reassess the correlation between the robustness index predicted by the model described in this article with the current specification based release parameters. It is neither practical, nor intended in the short term to replace release criteria for established processes, where testing methods are already well defined and implemented. This exercise is rather to contribute to the ongoing culture change emphasizing process understanding in lieu of off-line testing. It will take time, data from various manufacturing sites, and more sophisticated data processing and statistical evaluation, as well as regulatory permissions, before such a model to replace or supplement the current specification based lot release criteria.

Weight	Hardness	Assay
32 %	54 %	14 %

Table I. Percentages of attributes.

Batch No.	Batch Score
1	35
2	25
3	36
...	...
28	27
29	23
30	50

Table J. Tablet A, batch and product score.

References

1. FDA, "Guidance for Industry: PAT-A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance," 2004.
2. Stamatis, D.H., **Six Sigma and Beyond – Statistical Process Control, Volume IV**, St. Lucie Press – A CRC Press Company, First Edition, 2003.
3. Montgomery, D.C., and Runger, G.C., **Applied Statistics and Probability for Engineers**, John Wiley & Sons, Inc., Third Edition, 2003.
4. Oakland, J.S., **Statistical Process Control**, Butterworth-Heinemann, Fifth Edition, 2003.
5. Wedgwood, Dr. Ian, **Lean Sigma: A Practitioner's Guide**, Prentice Hall, First Edition, 2006.

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Systems Turnover Coordination: Effective Application and Integration of the Supplier-Provided Engineering Turnover Package (ETOP)

by Carol Susla

This article presents the process for leveraging supplier knowledge and documentation in the context of applying a risk-based approach to compliant commissioning and qualification programs.

Introduction – Leveraging Vendor/ Supplier Involvement

The recurring theme of leveraging supplier knowledge and documentation continues to surface through the discussion of current pharmaceutical industry trends in the context of applying a risk-based approach to compliant commissioning and qualification programs. GAMP® 5 dedicates a full section of the Guide to Supplier Activities, Section 7, in which good practice activities are described as applicable to product and application development and support for GxP computerized systems.[1] The decision to leverage supplier knowledge, documentation, and testing is driven by the objective of eliminating the duplication of effort and time such that the defined programs and contributions of the supplier are directly applied to the end-user commissioning and qualification programs.

As a precursor to capitalizing on the involvement of the supplier and leveraging supplier provided documentation, a formalized supplier assessment program must be established. This prerequisite assessment is detailed in GAMP 5 and reinforced in a broader manner through Sub-Practice 2: Supplier Audit Plan of the ISPE Good Practice Guide: Good Engineering Practice, in which the need for a Supplier Audit Plan is reiterated.[2] The ASTM Standard E2500-07 expands on supplier management systems, under the Quality Risk Management discussion in which "the risks pertaining to delivery including supplier or construction risk,…should be considered relative to their ultimate impact on product quality and patient safety."[3] Once supplier capability has been fully determined, and the documented assessment provides sufficient evidence of supplier accreditation, capability, and adequacy of quality management systems, the opportunity exists to truly capitalize on maximizing supplier involvement through the lifecycle of the equipment or system.

This discussion specifically details the steps to effectively apply supplier involvement and leverage the supplier role on the project team to support the Engineering Turnover Package. There are two primary objectives in transforming from a traditionally based equipment/system delivery and turnover process to a supplier leveraged process:

- Reduce efforts, cost, and scheduling overruns caused by the duplicity of testing, documentation generation, and compilation.
- Increase resource capacity for the project lifecycle by applying supplier knowledge, in-house expertise, and experience. Establish capable suppliers as direct contributors to the project deliverables and documentation systems.

The Role of the Systems Turnover Coordinator

The concept and necessity of the Engineering Turnover Package (ETOP) has been widely accepted in support of the overall commissioning and qualification program within the pharmaceutical manufacturing arena. In a brief sojourn into the history of the ETOP, the *Pharmaceutical Engineering* article published in March/April 1996, authored by Mr. Daniel Dunbar, presented

a "Systems Approach to Mechanical Construction." In the referenced article, turnover packages are described to "contain all the documentation required to show the facility has been built per the construction documents in a high quality manner."[4] This concept has since been applied beyond the historical context of facility construction, extending to the full scope of pharmaceutical systems. Two definitions of "system" serve to define the broader perspective, including:

System – an organization of engineering components which have a defined operational function, e.g., piping, instrumentation, equipment, facilities, computer hardware, computer software.[5]

Manufacturing Systems – elements of pharmaceutical and biopharmaceutical manufacturing capability, including manufacturing systems, facility equipment, process equipment, supporting utilities, associated process monitoring and control systems, and automation systems that have the potential to affect product quality and patient safety.[3]

In the contemporary context, the requirements of the Systems Turnover Coordinator are established with the following functions:

- Provide start-up/commissioning/turnover package management.
- Maintain the Commissioning and Qualification program standards to ensure the effective compilation of all system related engineering documentation.
- Ensure construction to commissioning turnover documentation integrity.
- Develop and extend the interfaces between the owner and all responsible parties (supplier and sub-contractors) to ensure that all construction and equipment design/fabrication/assembly/testing documentation is reviewed, retained, and consistent with pre-determined documentation practices and site-specific Good Engineering Practices.
- Implement effective communication channels between the owner representatives, supplier, and (sub)-contractors to monitor progress of the generation of the ETOP.
- Define the ETOP infrastructure to ensure that all compliance requirements for the system turnover process are met.
- Deliver the enhanced turnover package without incurring delays or rework (due to incomplete or missed documentation).

This listing of accountabilities mirrors a job description, because it is intended to capture the key accountabilities that can be transferred to the supplier. With effective planning, defined requirements, and a formal assessment of capabilities, this role may be effectively held, entirely or in part by an accredited pharmaceutical supplier. This article further serves to delineate the steps to transfer partial or complete accountability of the ETOP from the in-house Engineering staff at the pharmaceutical manufacturing facility to a supplier-coordinated initiative. Table A summarizes the six essential steps needed to facilitate the application and integration of the supplier-provided turnover package.

A Six Step Process for the Supplier-Coordinated ETOP

Step 1: Formally Assess Supplier Competence and Quality Capability

The criticality of the supplier assessment process is underscored as the evaluation of supplier capability serves to support the basis and extent of involvement of each key supplier through the specification, design, and verification process. The structure of the supplier assessment program and strategy thereof is best detailed in a high level procedure or policy document. Alternatively, the supplier assessment strategy can be presented within the context of the Validation Master Plan.

The key prerequisites are reinforced:

Step	Process Step	Rationale
1	Formally assess supplier competence and quality capability.	Supplier assessment is a prerequisite to the application of the supplier-provided turnover package.
2	Develop the ETOP requirements as an input to the Requirements Phase of the Specification, Design, and Verification Process.	Provides for consistency in the delivery of the Engineering Turnover Package. Requirements are provided as an input to the specification and design phases.
3	Build the ETOP infrastructure: procedures/work instructions, checklists, and the ETOP matrix.	The overall strategy is identified in Step 2; the development of the ETOP is facilitated in this step. Provides for the supporting documentation to facilitate the process.
4	Integrate the ETOP matrix requirements with the system/equipment specification. Leverage the procurement process.	Through the issuance of the equipment specification (purchase specification) to the supplier, the ETOP documentation requirements, and timelines are clarified.
5	Define and standardize good documentation practices for engineering documentation; download to supplier quality representatives.	Communication of the documentation requirements early in the process will reinforce expectations and mitigate delays at the later stages of the project.
6	Establish the turnover schedule, communication channels, and issue resolution process.	By ensuring that conformance to the turnover schedule is monitored and communicated, visibility to the timeline is maintained through the duration of the project.

Table A. Six steps toward integration of a supplier-generated turnover package.

- Define the supplier assessment process.
- Establish a project specific approach.
- Communicate the approach and expectations to the key suppliers supporting the project as soon as practically possible, such that potential gaps are addressed prior to the procurement phase of the project.

It is critical that the assessment process incorporate the quality requirements defined by the supplier management program. As such, the sub-team responsible for the implementation of the supplier assessment strategy typically includes membership from quality assurance, engineering, and site procurement/purchasing, at a minimum. It is recommended that the supplier assessment sub-team members be provided directly from the project execution team, as the overall project plan, commissioning and qualification objectives are best represented by the cross-functional members involved in the execution of the project.

The Good Engineering Practice Guide provides both a supplier audit template and supplier quality questionnaire as reference documents which serve as good starting points to support the development of the supplier assessment process. From an OEM perspective, supplier quality questionnaires to gather baseline data are becoming increasingly accepted as the basis for the evaluation. In addition to the questions provided with the sample quality questionnaire areas outlined in the Guide, we've recently seen the following questions posed as an OEM serving the pharmaceutical and biotechnology sectors:

- Company Details:
  - Company history, cumulative projects completed in healthcare/pharmaceutical applications; participation/revenue by industry sector and by application (custom build/automation system/system type).
- Quality Management System:
  - Request for a summary of the professional development and training programs in place, training hours/employee per annum.
  - Request for breakdown of staffing utilizing a recognized professional job classification/coding system.
  - Number of professional societies represented and number of members.
  - Summary skill matrix, including staff members with cleanroom application; microbiology, pharmaceutical formulation/filling/inspection/packaging experience. Detailed skill matrix for control, automation system, and MES expertise.
- Listing of all calibrated equipment and instrument available onsite; summary of all associated calibration procedures.
- Deliverables:
  - Along with providing a listing of standard documentation, include a listing of all standard protocol templates/forms and document templates.
  - Request for additional details regarding drawing standards and in-house standards library.

The collection of the baseline data through the Supplier Quality Questionnaire provides the basis for the audit process conducted at the vendor's site and provides added insight into the level of direct supplier involvement anticipated through the execution of the project.

In addition to the seven audit areas presented in the Good Engineering Practice Guide, end-user review of the supplier change control system and non-conformance/deviation management system is considered essential. From the perspective of the supplier, the review of these two key quality systems ensures that there is an alignment of expectations on the reporting requirements, and a process for addressing system changes or deviations incurred during fabrication and assembly of equipment. The supplier audit visit provides the ideal opportunity to establish the guidelines and expectations regarding change control and deviation handling, while formalizing the communication and escalation processes from both the supplier and end-user perspective.

Step 2: Develop the ETOP Requirements as an Input to the Requirements Phase of the Specification, Design, and Verification Process

As defined in the ISPE Baseline® Guide, Volume 5, Commissioning and Qualification, First Edition, the project turnover strategy is "a plan for hand-over or transfer of responsibility of the project."[6] The Engineering Turnover Package serves as a compilation and collection of all engineering documentation generated through the design, procurement, construction, and installation phases of the project. The ETOP compilation is the repository for all associated engineering documentation. The ETOP compilation furnishes, in part, the technical document package for commissioning and qualification of the manufacturing system.

By defining the process of developing and compiling the ETOP through a formalized procedure, and providing reference thereof in the system/project specific Commissioning Plan and Validation Plans, the requirements of the ETOP and overall responsibilities for the documentation across the life cycle of the manufacturing system are clearly delineated. In a 2008/2009 pharmaceutical capital expansion project for which the concept and design phases have been recently completed, the engineering and quality team members developed Commissioning Standards, re-defined local Good Engineering Practices, and formalized the requirements for the Engineering Turnover Package, through the issuance of updated and enhanced Commissioning Procedures.

The Commissioning Program, as defined in the associated site standard operating procedures, includes the following provisions:

- Definition of the ETOP and ETOP matrix. Specifically, the matrix provides a summary of the document types provided as part of the overall turnover package. The matrix serves as a guideline and is customized based on the manufacturing system impacted, constructed, or modified within the scope of the project. A sample ETOP matrix is provided in Table B.

- Outlined responsibilities for the development and compilation of the ETOP. More specifically, the responsibilities of the Commissioning Team are detailed to ensure that ownership and maintenance of the ETOP are clearly defined.
- Recommendation that the intended level of supplier/contractor documentation support and ETOP coordination be reviewed at the early phases of the project, namely the requirements and design phases to ensure alignment of engineering and quality.
- Reference to the supplier assessment process and prerequisites to implementing a supplier coordinated turnover package.

As a project specific document, the Commissioning Plan references the ETOP requirements prescribed by the site specific SOPs, while further establishing the ETOP matrix for the specific manufacturing systems and presenting detailed turnover schedules.

Document Type	Responsibility	Approval Sign-off	Approval Sign-off
System General Information:			
System Description			
Engineering Calculations Examples: Pressure relief, pump and tank sizing, performance curves; system capacity calculations			
Purchase Order Specification History including Addenda, Change Orders			
Change Documentation			
Drawings:			
Vendor's List of Drawings, Catalogues, and Documents			
General Arrangement, Outline Drawings			
P&ID's			
Assembly Drawings			
Fabrication Drawings			
Motor Drawings			
Certified Drawings			
Name Plate Details			
Major Components List			
Detailed Parts List, Bill of Materials, Fabrication Documentation			
Warranty			
All related material certification documents: - Mill Certificates - Material Certificates			
Code Certificates: - ASME - Seismic - NEC			

Table B. Example ETOP matrix.

Step 3: Build the Documentation Infrastructure: Procedures/Work Instructions, Checklists, and Define the ETOP Matrix

In the 2001 Baseline Guide for Commissioning and Qualification, the Guide states that "strategies for turnover should be determined early in the planning stages of the project Commissioning Plan." Within the last eight year period, the infrastructure has evolved from a description of intent and strategy in the Commissioning Plan document to the development of the following procedures and related controlled documents:

- Commissioning Program Procedure – a high level procedure under the ownership of engineering detailing the key elements of the end-user program, prerequisites for supplier involvement, overview for the development and compilation of the ETOP.
- Turnover Procedure – detailing the steps required to develop and compile the ETOP, including two primary engineering responsibilities: identification of the documentation deliverables required to support the turnover process; definition and communication of the requirements related to document scope and content, timing, format, layout, numbering, and identification. Document maintenance and specific storage/retention requirements through the system/equipment lifecycle may be specified.
- ETOP Matrix – serves to record all required contents of the Engineering Turnover Package, presented in Table B. The ETOP matrix provides a summary of the document types provided as part of the overall turnover package. This matrix serves as a guideline and is customized based on the manufacturing systems impacted, constructed, or modified within the scope of the project. A master ETOP matrix is used to tabulate all documentation deliverables for projects involving multiple manufacturing systems.
- The Turnover Checklist is project specific and provides for review by the contractor/supplier designee with end-user Engineering final approval.
- The ETOP Manual table of contents identifies the order and sequencing of the turnover package documentation set for ease of reference

Step 4: Integrate the ETOP Matrix Requirements with the System/Equipment Specification. Leverage the Procurement Process.

Through effective navigation of the procurement process and with a skillful oversight of the contractors and companies supplying the manufacturing systems and engineering services, greater economic value can be achieved. By integrating the engineering documentation deliverables into the overall purchasing specification, the procurement process:

- captures the needs of the ETOP implementation strategy

- allows for the opportunity of leveraging supplier capability for documentation
- provides for a contracting/procurement model, which adapts to the project specific economies
- builds a provision to extend engineering resource capacity, by capitalizing and leveraging the capabilities of the supplier based engineering personnel

By defining the ETOP requirements at the onset of the procurement phase, there is a greater transparency in the procurement process, which ensures a "level playing field" in the bid review process. Additionally, the potential for incremental hidden costs associated with the generation of compliant engineering documentation is minimized. An example of the Equipment Specification Document Deliverables matrix is presented in Table C.

This tool serves to identify each document deliverable, the prescribed format/style/identifiers, number of copies (hard/soft), and target delivery date. Utilizing a pharmaceutical filling system as an example, the detailed mechanical drawings are identified as deliverables; the drawing format is specified to be either AutoCAD or SolidWorks, the sheet format for the mechanical drawings is based on the ASME Y14.100 title block and drawing numbering is based on the customer provided format. Similarly, detailed electrical drawings are also identified as a document deliverable with the same drawing format, same title block and numbering requirements, symbology identified as IEEE 315 (ANSI Y32.2), and a drawing layout on D-size (plotted, A – size landscape).

In both cases, the document deliverables matrix identifies the number of soft and hard copies. It is essential that the purchasing specification identifies the soft copy requirement prior to finalization of the purchasing agreement, in order to secure electronic versions of the drawings, essential for ease of documenting future changes at the manufacturing facility without reliance on supplier-sourced drawing updates, necessitated to support change control.

For both deliverables, the delivery time frame has been specified to ensure issuance of the initial P&ID following the issuance of the purchase order, drawing approval during the design phase with final versions available at a defined time point prior to the Factory Acceptance Testing (FAT), supplemented with drawing verification at FAT in order to support commissioning and qualification.

With the first steps toward a complete and compliant ETOP taken in the early phases of the project, the pharmaceutical supplier is better equipped to collaborate through the execution phases of the project.

Prior to engaging formally in the quality partnership and as a prerequisite to the integration of supplier-coordinated turnover packages, the supplier must be assessed to establish ability to handle the requirements and scale of the project.

Step 5: Define and Standardize Good Documentation Practices for Engineering Documentation; Download to Supplier Quality Representatives

Establishing the documentation standards and formally communicating the expectations regarding good documentation practices are value-added activities, which serve to prevent documentation delays in the latter stages of project execution. It is essential that the documentation requirements be presented to the supplier prior to the development of the engineering documentation. Suppliers are often prepared to supplement in-house training programs for documentation practices for their key engineering staff to underscore the needs of a pharmaceutical client and to further customize practices to the pharmaceutical customer's standards. The

	Deliverable	Format		Copies		Target Delivery Timeframe		
				Soft	Hard	For Approval	Pre-FAT Requirement	For C&Q
1	Detailed Electrical Drawings	Drawing Format to be provided	AutoCAD/Solid Works	2	3	Design Phase	6 weeks prior to FAT	Verify at FAT
		Symbology	IEEE 315 (ANSI Y32.2)*					
		Title Block	Vendor provided format					
		Drawing Layout	D-size (plotted - A-size landscape)					
		Numbering	Vendor provided format					
2	Detailed Mechanical Drawings	Drawing Format to be provided	AutoCAD/Solid Works	2	3	Design Phase Initial P&ID Submitted 1 week after P.O.	6 weeks prior to FAT	Verify at FAT
		Sheet Format	Based on ASME Y14.100** (B, D, and E sheet sizes)					
		Title Block	Vendor provided format					
		Numbering	Specified by end-use SOP - #####					

* IEEE 315 (ANSI Y32.2), Graphic Symbols for Electrical and Electronics Diagrams (Including Reference Designation Class Designation Letters), The Institute of Electrical and Electronics Engineers, Inc., September 1975, Reaffirmed 1993.
** ASME Y14.100-2004, Engineering Drawing Practices, American Society of Mechanical Engineers, September 2005.

Table C. Equipment specification document deliverables matrix.

End-User Benefits	Supplier Benefits
• Fully defined expectations; formalized process for generating the ETOP. • A detailed ETOP timeline with clear deliverables, leveraging the procurement process. • An efficiency gain by utilizing the engineering resource pool at the OEM. • The elimination of duplicity of efforts in document generation and testing by capitalizing on supplier capabilities and contributions.	• Fully defined expectations from the end-user customer. • A detailed ETOP timeline with clear deliverables. • A competitive advantage to those suppliers equipped with the infrastructure, resources and systems to satisfy the needs of the pharmaceutical industry. • The ability to leverage in-house expertise and provide a value added service to the end-user customer.

Table D. The advantages of supplier-leveraged turnover packages.

key to ensuring that engineering documentation is clear, concise, consistent, and compliant is early expectation sharing combined with on-going reinforcement of the standards.

Step 6: Establish the Turnover Schedule, Communication Channels, and Issue Resolution Process

A turnover schedule ensures that all deliverables are tracked through completion and that adherence to the turnover timelines is measured. The point at which to define and align to requirements for supplier and contractor turnover packages is the procurement stage (Step 4) concurrent with the negotiation of terms of the agreement and equipment/system delivery schedules.

By having defined responsibilities and timelines incorporated into the contract documents, the end-user is provided with added leverage, and the supplier is provided with clearly delineated expectations in the early stages of the project plan. In addition to the document deliverables identified in the ETOP matrix, timing for the final punch lists, system walkdowns, as built drawings, and system turnover are specified in the turnover schedule.

Defined communication channels facilitate the management of the turnover plan/schedule, and for larger scale projects, it has been recommended that ETOP meetings be scheduled on a weekly basis through design and fabrication phases to ensure continuity in the review of deliverables and to address any potential issues related to testing/verification as they occur. Near real-time review of any potential changes during the early stages of the project execution plan limits the impact to the schedule rather than resolution at the formal factory acceptance testing stage.

Conclusions

The six step process supports the overall objective of effective application and integration of the supplier provided ETOP. There are four key benefits - *Table D.*

It is important to note that the supplier-leveraged turnover package reduces, but does not fully eliminate effort and coordination needed by the engineering team. More specifically, engineering is responsible for identifying the documentation deliverables required from the supplier, along with communicating the expectations and standards related to document requirements, content, timing, format, layout, nomenclature, and identification. With a well-defined process, the supplier can assume the responsibilities of coordinating the document generation process, and ensuring a "real-time" adherence to documentation standards. This additional support by the supplier reduces the potential of rework once the ETOP is reviewed by the engineering project team as part of the documentation verification phase of the installation.

The upfront planning effort lays the groundwork for the transition from the more traditional approach of ETOP generation. With the development of a formal process, which serves to leverage supplier involvement, the supplier-provided turnover package can be fully integrated as part of the overall project plan.

References

1. *GAMP® 5: A Risk-Based Approach to Compliant GXP Computerized Systems,* International Society for Pharmaceutical Engineering (ISPE), Fifth Edition, February 2008, www.ispe.org.
2. *ISPE Good Practice Guide: Good Engineering Practice,* International Society for Pharmaceutical Engineering (ISPE), First Edition, December 2008, www.ispe.org.
3. ASTM E2500-07: Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment, July 2007.
4. Dunbar, D.B., "A Systems Approach to Mechanical Construction," *Pharmaceutical Engineering*, March/April 1996, Vol. 16, No. 2. www.ispe.org.
5. ISPE Glossary of Pharmaceutical and Biotechnology Terminology, August 2007.
6. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 5 - Commissioning and Qualification*, International Society for Pharmaceutical Engineering (ISPE), First Edition, March 2001, www.ispe.org.
7. IEEE 315 (ANSI Y32.2), Graphic Symbols for Electrical and Electronics Diagrams (Including Reference Designation Class Designation Letters), The Institute of Electrical and Electronics Engineers, Inc., September 1975, Reaffirmed 1993.
8. ASME Y14.100-2004, Engineering Drawing Practices, American Society of Mechanical Engineers, September 2005.

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Europe

Denmark

Guideline on Variations to Marketing Authorizations for Medicinal Products[1]

This guideline covers variations to marketing authorizations granted by the Danish Medicines Agency, cf. section 8(1) of the Danish Medicines Act, including marketing authorizations for natural remedies, vitamin and mineral preparations, as well as radiopharmaceuticals. The guideline covers authorizations granted under the Decentralized Procedure, the Mutual Recognition Procedure, and the purely National Procedure.

This guideline does not cover variations to marketing authorizations granted under the Centralized Procedure, cf. regulation 726/2004.

This guideline replaces the Danish Medicines Agency's guideline no. 47 of 16 July 2007 concerning applications for variations to marketing authorizations submitted under the National Procedure and Mutual Recognition Procedure (MRP).

European Medicines Agency

European Medicines Agency Outlines 2010 to 2015 Priorities[2]

Building on the achievements made by the previous Road Map initiative between 2005 to 2010, the focus of the new Road Map to 2015 is on continuous high-quality delivery of the Agency's core business in an increasingly complex regulatory and scientific environment. In addition, the document 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. These include:

- **Addressing Public Health** needs by stimulating research and medicines development in areas of unmet medical needs or for neglected and rare diseases; facilitating new and innovative approaches to the development of medicines; implementing effective preparedness plans to deal with public health threats.

- **Facilitating Access to Medicines** by addressing the high attrition rate during the development process of medicines; improving the Agency's model for the assessment of benefits and risks of medicines; improving the quality and scientific and regulatory consistency of the medicines review process.

- **Optimizing the Safe use of Medicines** by strengthening the evidence base on the benefits and risks of a medicine following its authorization; applying novel pharmacovigilance methodologies and risk minimization tools; by taking patient experience into account for improved decision-making; becoming a reference point on information about medicines evaluated by the Agency.

Comments should be sent using the Agency's comment form by 30 April 2010 to: roadmap@ema.europa.eu.

European Medicines Agency gives First Opinion on Compassionate Use[3]

The Agency's Committee for Medicinal Products for Human Use (CHMP) has given its first opinion on the compassionate use of a medicine. Compassionate use programs are intended to give patients with a life-threatening, long-lasting, or seriously disabling disease, who have no available treatment options, access to treatments that are still under development, and that have not yet been authorized.

A CHMP opinion on a medicine intended for compassionate use provides recommendations to all European Union (EU) Member States. It describes which patients may benefit from the medicine, explains how to distribute and use the medicine, and gives information on safety.

This first CHMP opinion on compassionate use was based on a request from Finland. It relates to an intravenous formulation of oseltamivir, Tamiflu IV, to treat critically ill patients with a life-threatening condition, due to suspected or confirmed pandemic or seasonal flu, who cannot take authorized antivirals by mouth or as an inhalation.

European Medicines Agency Launches New Organizational Structure and New Visual Identity[4]

The European Medicines Agency officially unveiled a package of changes on 8 December 2009 with the launch of a new organizational structure and new visual identity.

Among the highlights of the new organizational structure is the integration of human pre- and post-authorization activities into one unit to guarantee seamless lifecycle-management of medicines. The creation of a new unit for patient health protection further strengthens the Agency's focus on safety-monitoring of medicines. In addition, a dedicated group for the management of product data and documentation will improve the efficiency of data management processes throughout the Agency.

The new visual identity will help to promote public recognition of the Agency and its contribution to public and animal health.

A new public Web site for the Agency is nearing the end of development and will be launched in the coming months. With the current Web site being visited more than 700,000 times each month, the new site is being designed with the needs of the public in mind, offering improved navigation and search functionality, providing better access to information on public-health issues.

Also the Agency's Web site has a new address, www.ema.europa.eu, and Agency e-mail addresses take the extension '@ema.europa.eu.'

Malta

Malta's Medicines Authority Awarded the Foundation for Human Resources Development - HR Award[5]

The Medicines Authority was awarded the Foundation for Human Resources Development – HR Award for Excellent Training and Development Initiative. The Initiative is a Twinning Light Project entitled 'Further Capacity Building at the Medicines Authority,' which was organized in a partnership with the Netherlands Ministry of Health, Welfare, and Sport – National Institute for Public Health and the Environ-

ment (RIVM) in collaboration with the Medicines Evaluation Board (MEB) of the Netherlands and the Healthcare Inspectorate. The project was aimed to train technical staff of the Medicines Authority to carry out advanced assessment work and inspections to enable Malta to act as a Reference Member State for the Mutual Recognition and Decentralized procedures.

The award acknowledged the standard of good practice of the initiative, which went beyond the overall purpose of the project. The project has led to the involvement of people from different departments within the organization, further motivated and empowered the staff of the Medicines Authority, and has led to an increase in performance and quality of the operations.

Netherlands

Dutch Medicines Evaluation Board Announces Growth in Authorization of Medicinal Products in 2009[6]

The Medicines Evaluation Board has approved more than 1,600 new medicinal products for humans in 2009 and entered them into the register. This is an increase of 30% in comparison to 2008. This is particularly due to a larger number of medicinal products being entered through the decentralized procedure. The MEB has refused marketing authorizations for 23 medicines and suspended 65 medicinal products. The number of authorized medicinal products as of 31 December 2009 is more than 12,500, a slight increase in comparison to 1 January 2009.

Sweden

Guideline to the Medical Products Agency's Regulation (2005:11) on Labeling and Package Leaflets for Medicinal Products[7]

This guideline is intended to promote a consistent application of the Medical Products Agency's regulation on labeling and package leaflets for medicinal products. The guideline is aimed at the companies that will be producing labeling and package leaflets. The intention of the guideline is to describe and interpret the contents of current legislation. A guideline may contain additional information compared with the legislation, in order to improve understanding of the requirements of the legislation.

United Kingdom

New Appointments to the British Pharmacopoeia Commission[8]

The British Pharmacopoeia (BP) Commission and the Appointments Commission announced the appointment and re-appointment of members to the BP Commission. The BP Commission is responsible for preparing new editions of the BP and the BP (Veterinary) and for keeping them up to date. It also provides advice to the United Kingdom delegation to the European Pharmacopoeia Commission and devises British Approved Names. Beginning 1 January 2010, two new appointments were made for a period of four years. The new members are Dr. Graham Cook and Dr. Brian Matthews. Professor David Woolfson has been re-appointed for a further four-year term as Chairman beginning 1 January 2010 as well. The following members also have been re-appointed from 1 January 2010 for periods of two or four years: Professor G. Buckton; Professor D. Cairns; Mr. B. Capon; Professor A.G. Davidson; Dr. T.D. Duffy; Mr. C.T. Goddard; Dr. R L. Horder; Dr. L. Tsang; Mrs. J. Turnbull; and Professor E. Williamson.

Earlier Access to New Medicines in the UK[9]

The Ministerial Industry Strategy Group (MISG), an initiative that brings together relevant UK government ministers and pharmaceutical industry chief executives, asked the Medicines and Healthcare products Regulatory Agency (MHRA) and the Association of the British Pharmaceutical Industry (ABPI) to explore the feasibility and desirability of introducing a scheme in the UK to make certain new and promising medicines available to patients before they are formally licensed.

A working group co-chaired by the MHRA and ABPI – which also sought views from the public and healthcare professionals – developed a framework for an earlier access scheme to operate within the existing regulatory regime and this was reviewed and approved by MISG in early December 2009. The report describing the key elements of the scheme, the reports of the work undertaken to gauge the views of the public and healthcare professionals, and the minutes of the working group that developed it have now been published on the MHRA's Web site.

The MHRA will undertake a 12-week public consultation on the scheme and how it will operate in the New Year with a view to finalizing the scheme for introduction in the UK later in 2010.

Asia/Pacific

Australia

Australia's TGA Updates Increased Transparency of the Prescription Medicine Regulatory Process[10]

Australia's TGA has released several documents providing information on Australian Public Assessment Records (AusPARs) to increase the transparency of the prescription medicine regulatory process. AusPAR provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. AusPARs are prepared and published by the TGA. An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications. Prior to publishing the AusPAR, the TGA provides the sponsor with an opportunity to review the AusPAR (allowing 14 calendar days) with the purpose of ensuring the document does not contain commercially confidential information.

New documents available include an overview document with information about the structure and processes for the compilation, review and publishing of an AusPAR, including guidance on the principles for determining what information is commercially confidential; Key Questions and Answers About AusPARs; Consultation Summary of the responses to the AusPAR documents released in August 2009; and a sample AusPAR.

Fourth Bill to Enhance the Therapeutic Goods Act 1989[11]

On Wednesday 25 November 2009, the fourth Bill, the Therapeutic Goods Amendment (2009 Measures No 3) Bill 2009, was introduced to the House of Representatives by the Parliamentary Secretary for Health, the Hon. Mark Butler MP. The Bill can be located on the Australian Parliament House Web site. The Bill makes a number of key amendments, principally to: implement a new framework for the regulation of biologicals (human cellular and tissue based therapy products); provide more flexible arrangements to recall batches of goods; enable information to be sought from past sponsors of medicines and therapeutic devices, but only for the five year period before the request is made, and improve the operation of the Act through a range of minor technical amendments.

China

SFDA Issues Quality Management System Regulations for Medical Devices (Interim) and Requirements for Medical Device Quality Management System Inspection (Interim)[12]

In order to intensify supervision on medical device manufacturing, standardize quality management systems for medical device manufacturing, strengthen the management of medical device quality management system inspection in accordance with Regulations for Supervision and Administration of Medical Devices and other related regulations, the State Food and Drug Administration formulated Quality Management System Regulations for Medical Devices (interim) and Requirements for Medical Device Quality Management System Inspection (interim). Quality Management System Regulations for Medical Devices (interim) comprises 13 chapters, 69 articles, and will take effect as of 1 January 2011.

SFDA to Crack Down on Illegal Ads with Four Measures[13]

In order to protect health and safety of the public, the State Food and Drug Administration recently issued a notice targeting illegal drug advertisements, requiring food and drug regulatory departments at all levels to enforce administration and crack down on illegal drug, medical devices, and health food advertisements on four aspects: First, rigorously enforce advertisement review and approval; secondly, intensify monitoring of the illegal drug advertisement; thirdly, strictly punish the enterprises releasing the illegal advertisement; and finally, earnestly fulfill the responsibility of advertisement examination and supervision.

North/South America

Canada

Validation Guidelines for Pharmaceutical Dosage Forms (GUIDE-0029)[14]

This document provides guidance on issues and topics related to systems, equipment qualification, and product and process validation for sterile and non-sterile dosage forms. These topics reflect an area in pharmaceutical, biological, and radiopharmaceuticals manufacture that is noted as being important by both the Inspectorate and the pharmaceutical industry. These guidelines have been prepared to provide guidance to inspectors, evaluators, and the industry in dealing with issues related to validation. Utilization of this information should facilitate compliance with Division 2, Part C of the Regulations to the Food and Drugs Act.

United States

FDA Unveils First Phase of Transparency Initiative[15]

The US Food and Drug Administration unveiled the first phase of its Transparency Initiative, which is designed to explain agency operations, how it makes decisions, and the drug approval process. During an online presentation, the Chair of the FDA's Transparency Task Force, Principal Deputy FDA Commissioner Joshua Sharfstein, described a Web-based curriculum called "FDA Basics," aimed at helping the public better understand what the Agency does. The curriculum is accessible via a link on the FDA Web site.

The curriculum includes: questions and answers about the Agency and the products it regulates; short videos that explain various Agency activities; and conversations with Agency personnel about the work of their office. In addition, senior officials from the FDA product centers and offices will answer questions on various topics during future online sessions. Each of these sessions will be announced on the FDA Web site.

US FDA Announces New GMP Regulations for PET Drug[16]

The US Food and Drug Administration issued regulations on current Good Manufacturing Practice (cGMP) for Positron Emission Tomography (PET) drugs. The regulations are intended to ensure that PET drugs meet the requirements of the Federal Food, Drug, and Cosmetic Act regarding safety, identity, strength, quality, and purity. In this final rule, they establish cGMP regulations for approved PET drugs. For investigational and research PET drugs, the final rule states that the requirement to follow cGMP may be met by complying with these regulations or by producing PET drugs in accordance with the United States Pharmacopeia (USP) general chapter on compounding PET radiopharmaceuticals. This regulation is effective 12 December 2011.

US FDA Expands Presence Outside US with Opening of Mexico City Post[17]

As part of its continuing effort to buttress food and medical product safety in this country by working with its regulatory partners overseas, the US Food and Drug Administration announced the opening of its Mexico City post. This is the Agency's third post in Latin America and its tenth international post in the past 13 months.

International

ICH Quality Implementation Group on Q8-Q9-Q10 has Released a New Set of Q&As[18]

This Questions and Answers document (Q&A) refers to the current working procedure of the ICH Q-IWG on implementing the guidelines of Q8, Q9, and Q10, which have been approved by the ICH Steering Committee. It addresses

topics including: design space, real time release testing, control strategy, pharmaceutical quality system, impact on GMP inspection practices, knowledge management, and software solutions.

References

1. Danish Medicines Agency, http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=16066.
2. European Medicines Agency Press Release 26 January 2010, http://www.ema.europa.eu/pdfs/general/direct/pr/5405010en.pdf.
3. European Medicines Agency Press Release 21 January 2010, http://www.ema.europa.eu/pdfs/human/compassionate_use/4243810en.pdf.
4. European Medicines Agency Press Release 8 December 2009, http://www.ema.europa.eu/pdfs/general/direct/pr/70491809en.pdf.
5. Malta Medicines Authority Press Release, http://www.medicinesauthority.gov.mt/pub/Press%20Release_02-2009%20HR%20Awards.pdf.
6. Dutch Medicines Evaluation Board, http://www.cbg-meb.nl/CBG/en/human-medicines/actueel/2010-01-20-annual-notice/default.htm.
7. Sweden's Medical Products Agency, http://www.lakemedelsverket.se/upload/eng-mpase/v%c3%a4gledningar%20eng/V%c3%a4gledningen_LVFS_2005-11%20engelsk.pdf.
8. Medicines and Healthcare Agency, Press Release 21 January 2010, http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON068467.
9. Medicines and Healthcare Agency, http://www.mhra.gov.uk/NewsCentre/CON065755.
10. Australia's TGA, http://www.tga.gov.au/pmeds/pmbpi-transparency.htm.
11. Australia's TGA, http://www.tga.gov.au/regreform/regreform4.htm.
12. State Food and Drug Administration, http://eng.sfda.gov.cn/cmsweb/webportal/W43879541/A64031363.html.
13. State Food and Drug Administration, http://eng.sfda.gov.cn/cmsweb/webportal/W43879541/A64031427.html.
14. Health Canada, http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/gui_29-eng.php.
15. US Food and Drug Administration, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm197222.htm.
16. US Food and Drug Administration, http://edocket.access.gpo.gov/2009/pdf/E9-29285.pdf.
17. US Food and Drug Administration, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm194165.htm.
18. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, http://www.ich.org/LOB/media/MEDIA5783.pdf.