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Increased Process Understanding Through Monitoring and Scale-Down Models: Case Study of a Cell Culture Harvest Fluid Titration and Filtration Process

by Kurt Yanagimachi, Corey Dodge, and Marisa Hewitt

This article presents a case study demonstrating the use of detailed process monitoring and scale-down modeling in determining the root causes of yield losses in the manufacture of a therapeutic enzyme and identifying alternative technologies to improve the manufacturing process.

Introduction

The identification of ways to improve a manufacturing process often require understanding of the process beyond the "black-box" treatment, in which only the basic metrics such as step yield and product quality are determined. A higher level of process understanding can be accomplished by closely monitoring key process attributes, ideally in real-time, and performing an in-depth study of the process using scale-down models. The combination of these two approaches also

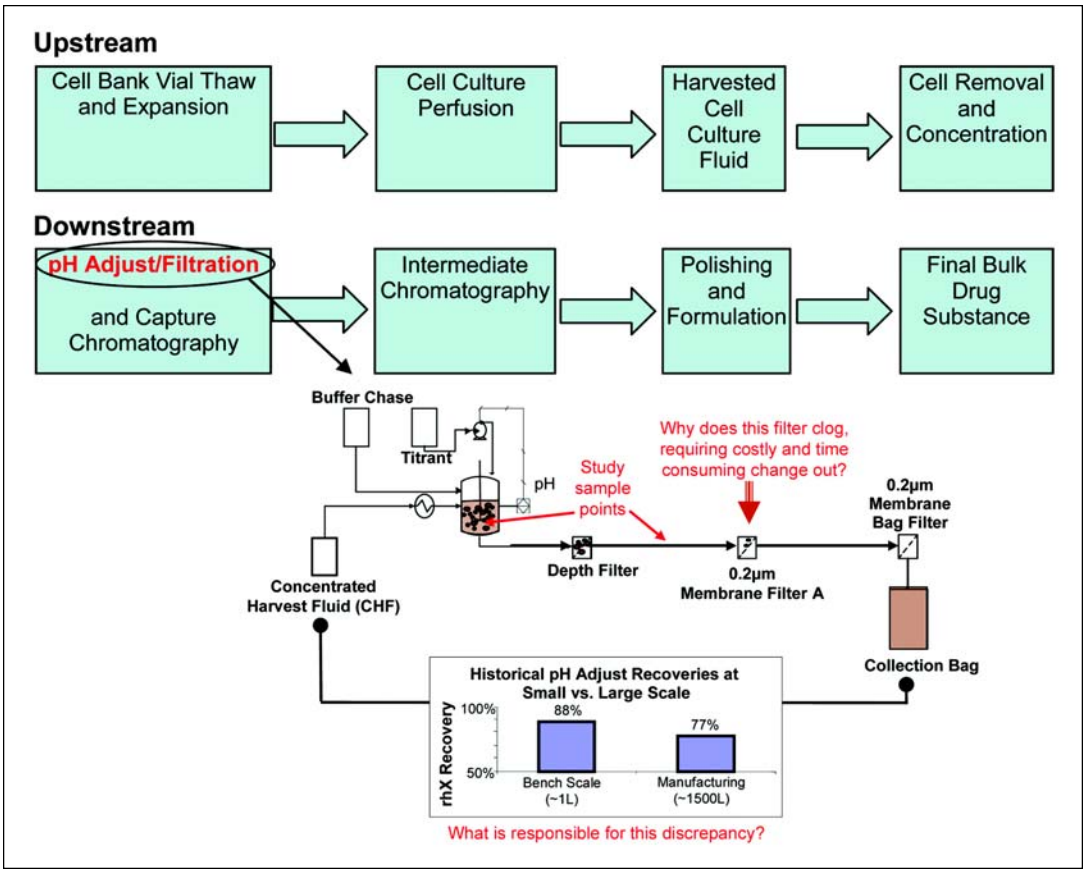

Figure 1. rhX manufacturing process and pH-Adjust process flow diagram.

can allow the identification of discrepancies between scales and can potentially highlight process improvements that may not be obvious with study at only one particular scale. The following case study is an example of how this combination approach lead to the identification of the root cause for process-scale yield loss and highlighted alternative technologies that would allow for the recovery of this product upon implementation.

An important step in the manufacture of a recombinant enzyme biopharmaceutical "X" (rhX) is the titration and subsequent filtration of cell culture Concentrated Harvested Fluid (CHF) prior to the first chromatographic step. This titration results in significant precipitation of Host Cell Proteins (HCP) and the loss of a small, but significant amount of rhX that becomes entrained in the precipitate. Figure 1 shows the position of the pH adjust unit operation within the production process of rhX, as well as a flow diagram of that particular step. The process is summarized as follows:

- A pool of concentrated harvest fluid is pumped into the pH adjust tank by way of a heat exchanger.
- Low pH titrant is added via a pH controller until the CHF pool reaches the target pH. During titration, isoelectric precipitate consisting mainly of HCP is formed and must be filtered.
- Titrated CHF is pumped through the filter train to remove precipitate. The filter train consists of a lenticular depth filter, followed by a 0.2 µm (5.1 mil) membrane filter, followed by a second 0.2 µm sterile bag filter. The filtered product is stored in a sterile collection bag until ready to load onto the chromatography column.
- Chase buffer is added to the pH adjust tank and is pumped through the filter train into the collection bag. The filter housings are then purged with air to collect as much of the residual product as possible.

The yield of this unit operation at the bench scale during process development was in the range of 85-90%. However, upon scale-up to the cGMP manufacturing facility, the yield had been considerably lower, averaging 77%. Also, filtration clogging occasionally occurred with one of the filters (labeled "Membrane Filter A" in Figure 1) at manufacturing scale which was not observed during process development and which continues to elude reproduction at the bench scale. Some possible reasons for these discrepancies could include:

- Differences in mixing or mass transfer characteristics at small and large scale that lead to differences in yield on the titration step.
- Differences in filtration due to filter geometry or filter design impact. The manufacturing filters are of a lens-shaped lenticular cell design, allowing more filter surface area to be condensed into a smaller volume. Conversely, the filters available for small-scale studies are flat, circular discs contained in a small capsule or housing.
- Differences in filtration due to filterability of the titrated CHF. If mixing characteristics are different at small vs. large scale, this could lead to differences in the size distribution of the precipitate particles formed.

Objectives

The primary objective for this work was to increase the fundamental process understanding, and if possible, to formulate a plan of action for increasing yield and/or reducing/eliminating the occurrence of filter clogging. The plan for this study was to:

1. Follow two batches of the pH-adjust process in the manufacturing plant and conduct extensive sampling and real-time monitoring to quantify each source of yield loss.
2. Develop a representative scale-down model of the pH adjust operation.
3. Utilize the scale-down model to determine the root causes of the drop in yield and occasional membrane filter clogging incidents.
4. Evaluate process alternatives that could possibly alleviate the aforementioned problems.

Monitoring of Manufacturing Batches and Scale-Down Modeling

Before evaluating any potential process alternatives with the hopes of improving yield and filtration performance, understanding of the process in its current state was enhanced. According to current standard operating procedure, samples are taken only of the starting material (CHF) and of the final sterile-filtered column load. In order to determine exactly where in the process rhX is being lost, two batches of the pH-adjust process in the manufacturing plant were followed. Samples of each pool of CHF were taken before titration, during titration at regular pH intervals, and after the final pH setpoint was reached (refer to Figure 1 for sample locations). Samples also were taken from several points in the filtration train throughout the filtration of each pool of pH-adjusted CHF and during the buffer chase. Each sample was assayed for rhX activity, total protein, turbidity, and in some cases, particle size. In addition to the detailed sampling, an on-line back-scattering turbidity probe was installed in the pH adjust tank to monitor turbidity during titration and an in-line forward-scattering turbidity probe was installed in between the depth filter and the first 0.2 µm membrane filter in order to monitor depth filter breakthrough in real time.

Titration	Power input/unit volume
	Impeller type (A310 hydrofoil)
	Turbulence (as determined by the Reynolds Number)
	Acid addition site
	Acid titrant addition rate per volume CHF
	Final pH
	Temperature
Filtration	Flux (CHF flow rate/unit filter area)
	Load (Total volume CHF/unit filter area)
	Volume chase buffer/unit filter area
	Filter media types

Table A. Summary of scaling variables and conditions maintained for titration and filtration.

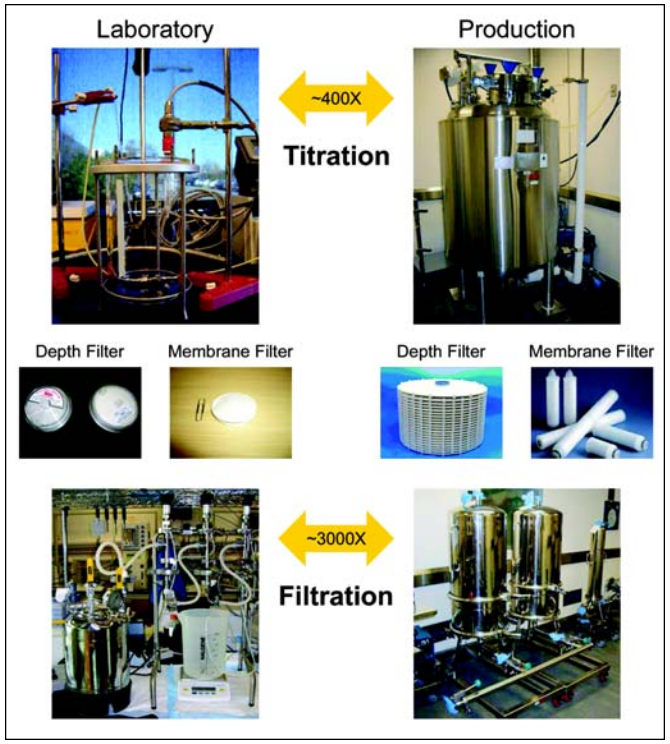

Figure 2. Small-scale and manufacturing equipment used for titration and filtration.

Scale-Down Experiments

Small-scale pH adjustments and filtrations were conducted with the goal of reproducing the performance of the manufacturing-scale pH adjustments and filtrations that were previously followed. Samples of each CHF pool prior to titration were taken to use as starting material for the small-scale pH adjustments in order to rule out lot-to-lot variability of CHF as source of discrepancy between small and large-scale data. Table A details the scaling variables used to scale down the titration and filtration steps.

Literature references were consulted that highlighted the importance of mixing in processes involving reaction, aggregation, and precipitation.[1,2] In the majority of these cases, the most important variable in scaling down a mixing step is the power input per unit volume (P/V), which determines the average shear rate and micromixing time scale. P/V is calculated as follows:[3,4]

$$\frac{P}{V} = \frac{P_o N^3 D^5 \rho}{V}$$

Where:
N = Impeller rotation rate
D = Impeller diameter
ρ = Liquid density
V = Liquid volume
P_o = Dimensionless power number.

The P/V was matched as close as possible to the process-scale P/V calculated for each individual batch, while maintaining geometric similarity if possible (see Figure 2 for photos of small and large scale titration equipment). The titrant addition rate per volume of concentrated harvest fluid and the position of the acid addition site relative to the impeller also were kept the same between the small and large scale. Turbidity was monitored on-line using the same back-scattering turbidity probe used with the full-scale system. Samples were taken at prescribed pH values and later assayed for total protein, rhX activity, and in some cases, particle size.

For filtration scale-down, the filter surface area ratio between the depth filter and downstream membrane filter was maintained.[5] A small-scale filterability system (see Figure 2 for photos of small and large scale filtration equipment) was used to measure the in-line system pressures, volume of filtrate recovered, and instantaneous flow rate. The forward-scattering in-line turbidity meter was installed in between

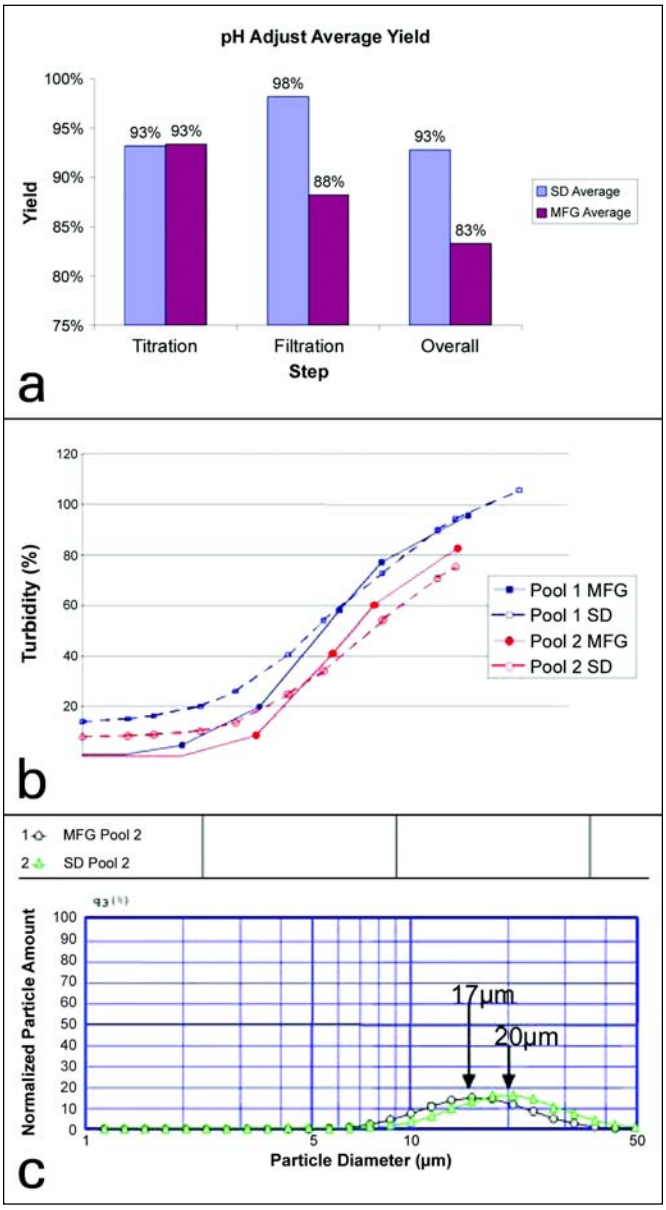

Figure 3. Comparison of the pH adjustment at different scales, (a) Averaged titration and filtration yields for each step at Scale-down (SD) and Manufacturing scale (MFG), (b) Turbidity profile of two titrations at both scales, and (c) Particle size distribution of precipitates formed at each scale.

the depth filter capsules and membrane filter disk housing. The amount of each pool to be filtered was determined by using throughput/unit depth filter area as a scaling factor. Flow rate/unit area also was conserved between large and small scale. Samples were taken in between the depth filter and first 0.2 µm membrane filter, as well as between the 0.2 µm filters. Following filtration of the appropriate amount of each titrated pool, the scaled-down amount of chase buffer was pumped through the filtration train.

Scale-Down Results

Figure 3(a) displays the results of the rhX titration and filtration yield comparison for the average of two batches run with the Scale-Down (SD) model and in Manufacturing (MFG). It is evident from these graphs that the SD model provides an accurate method for determining titration yield. Figure 3(b) shows the turbidity profile evolution throughout the course of titration for one particular CHF pool at both scales. Similarly, there was close agreement between scales when measuring the enzyme activity and total protein during titration, adding further evidence to the accuracy of the scale-down titration model. However, filtration yield is higher at the small scale. This in turn results in the overall discrepancy between the small scale and large scale processes.

Figure 3(c) shows the particle size distribution of the precipitate formed during one titration of the same starting pool of CHF at manufacturing scale and small-scale. The mean particle size is slightly lower for manufacturing scale. This may be due to the higher impeller tip speed, and thus, higher maximum shear rate at full-scale. It also could be a result of immediate analysis of the small-scale samples, whereas the full-scale sample was analyzed two days later after storage at 4°C (39°F). In both cases, the majority of particles formed are above the 6 to 15 µm range in diameter (152 to 381 mil), the nominal rating of the particular depth filter used.

The onset of the occasional clogging of the membrane filter directly following the depth filter also was investigated by monitoring the turbidity of the depth filtrate. While the first batch was completed without any filtration difficulties, the membrane filter did clog during the second batch, resulting in the need to replace the clogged filter cartridges before completing the batch. However, when this second batch was "reproduced" at the small scale with identical filter fluxes and loads and identical starting material, no filtration problems were observed. Figure 4 displays the turbidity profiles of the filtrate from the depth filter for the two manufacturing batches. Turbidity of the filtrates at small-scale was undetectable.

One theory for this discrepancy is that the process-scale depth filter is not performing to the same degree as its small-scale counterpart, resulting in considerable breakthrough of particles, which then are retained in the membrane filter. To further investigate how the depth filter cartridge could contribute to the difference in yield seen across the scales, one of the used process-scale depth filter cartridges was retrieved and an "autopsy" was performed.

Depth Filter Autopsy

Figure 5(a) shows a picture of the depth filter cartridge (lens-style lenticular) after completion of the first batch. Upon inspection, it became evident that the filter was not performing as it should with a significant amount of area around the center of each cell remaining free of precipitate cake build-up.

Because of the lens-shape of the lenticular cells, the gap between cells is wider at the perimeter of the cartridge than in the center region. Apparently, the gap spacing close to the center region was not sufficient to allow passage of the precipitate for cake formation. Thus, the surface area at the center of the cartridge is largely underutilized. It is evident how such a cartridge design could impact filtration, as the effective flux and load would be higher at process scale than what was utilized at bench scale. Either of these effects by themselves could result in the reduced adsorptive capacity of the depth filter, and so the cumulative effect could explain the poorer depth filter performance at process scale. By cutting sections of defined dimension (2" × 2" or 5 cm × 5 cm) from different areas on the used cartridge and extracting and assaying the residual rhX, the concentration of rhX was determined in the residual liquid contained within the filter

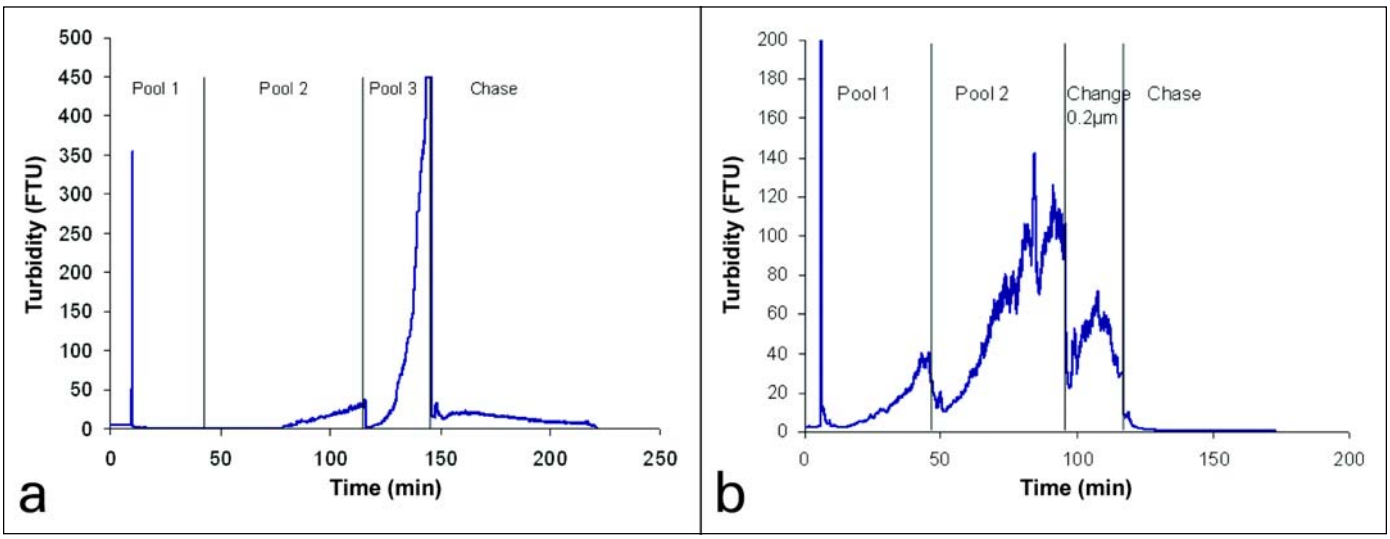

Figure 4. In-line turbidity of filtrate from depth filter, **(a)** Batch 1, **(b)** Batch 2.

Contributors to Product Loss	Batch 1	Batch 2
Filter Sheet (Retained Liquid)	4.1%	5.0%
Precipitate Cake (Retained Liquid)	2.3%	2.2%
Filter Housing Venting	2.7%	2.8%
Filter Cartridge Change-Out	0.0%	3.0%
Sum of Losses	**9.1%**	**12.9%**
Overall Yield Loss Determined by Mass Balance	**10.7%**	**13.7%**
Difference Between Yield and Volumetric Loss Quantities	**1.6%**	**0.7%**

Table B. Filtration Yield Analysis.

at four different areas from the filter cartridge that were caked to different extents. Figure 5(b) shows the results of this assay. In this graph, the concentrations of rhX have been normalized to the final concentration measured in the chase buffer as it left the depth filter. Ideally, the residual rhX concentration in the filter would be equal to the final concentration of chase buffer, giving a normalized value of 1. There is a significant amount of product left behind in the filter and heterogeneity with respect to position within the filter cartridge. The amount of product left behind on the filter at any given position correlated directly to the relative extent of caking above that piece of media.

It is likely that the exclusion of precipitate cake at the center-most depth filter media creates a *path-of-least-resistance* for the chase buffer, which then flows straight through the center region of the cartridge without sweeping residual soluble rhX from the precipitate cake or liquid holdup contained within these covered regions of the depth filter media. In Table B, the impact of this path-of-least resistance phenomenon and of other sources was determined on the rhX yield for the filtration step of the process. It was assumed that the 75% of the total filter surface area was covered with cake and 80% of the volume of the wet cake was liquid. All of these sources of product loss would only be encountered in the full-scale process, and nearly all of the difference between the small-scale and process-scale filtration yields were accounted for by the chase buffer path-of-least-resistance phenomenon (7% loss).

Evaluation of Filtration Process Modifications

The next objective was to explore several potential modifications to the process with the goal of recovering that lost 7% and bringing the pH adjust yield more in line with the small-scale yield and reduce the incidence of membrane filter clogging. The modifications investigated were:

1. Replace the depth filter cartridge with a cartridge design that allows more uniform cake distribution across its entire surface area.
2. Replace the existing dead-end filtration process with a microfiltration/diafiltration process.

Alternative Depth Filter Cartridge Designs

Two alternative depth filter cartridge designs were studied: a lenticular design in which each cell is enclosed in a rigid polypropylene cage (Figure 6) and a fully encapsulated non-lenticular design. The caged lenticular design allows uniform spacing between filter cells eliminating the tapered spacing between the lens-style cells. The fully encapsulated design eliminates the need for a central filtrate core altogether and thus, also has more desirable flow properties. While candidate depth filter grades using the encapsulated design were tested and identified, the cage-style lenticular design was eventually chosen because it could utilize the same depth filter media and be used in the existing filter housings. These were distinct advantages when considering implementing a process change to an approved commercial process. This cage-style cartridge was evaluated at the pilot scale, maintaining filter flux and load consistent with the process scale.

Cage-Style Pilot-Scale Results

A filter autopsy was performed on the spent filter cartridge

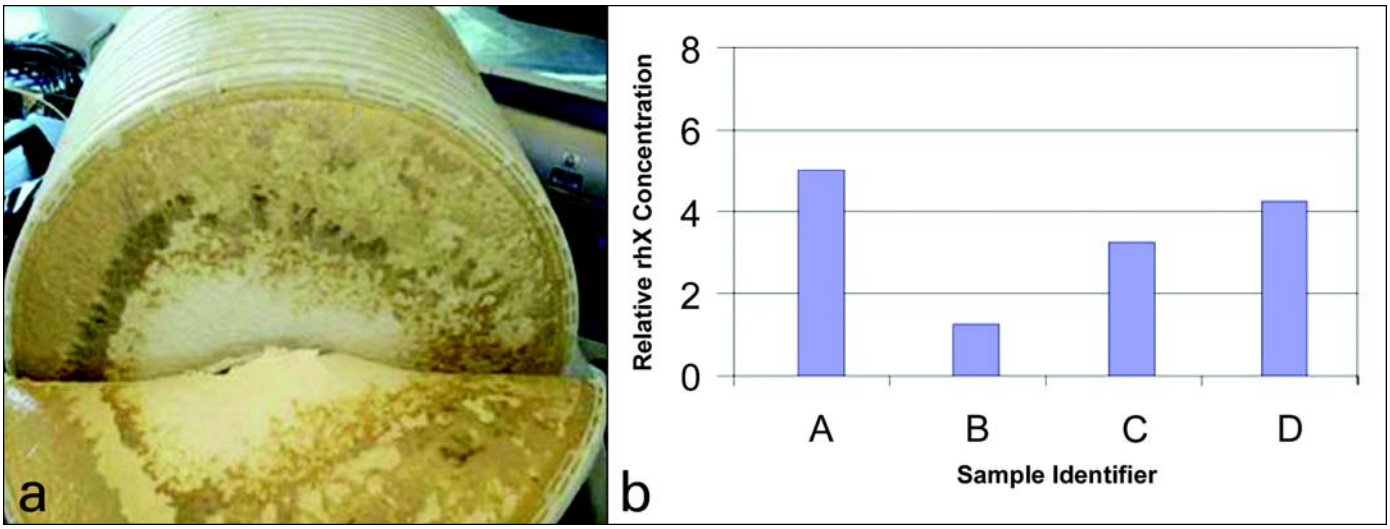

Figure 5. (a) Photo of spent depth filter showing heterogeneity of precipitate cake distribution in between lenticular cells. (b) Normalized rhX residual concentration at various spots in the filter cartridge: A = Bottom cell, center region, B = Bottom cell, side region, C = Top cell, center region, D = Top cell, side region.

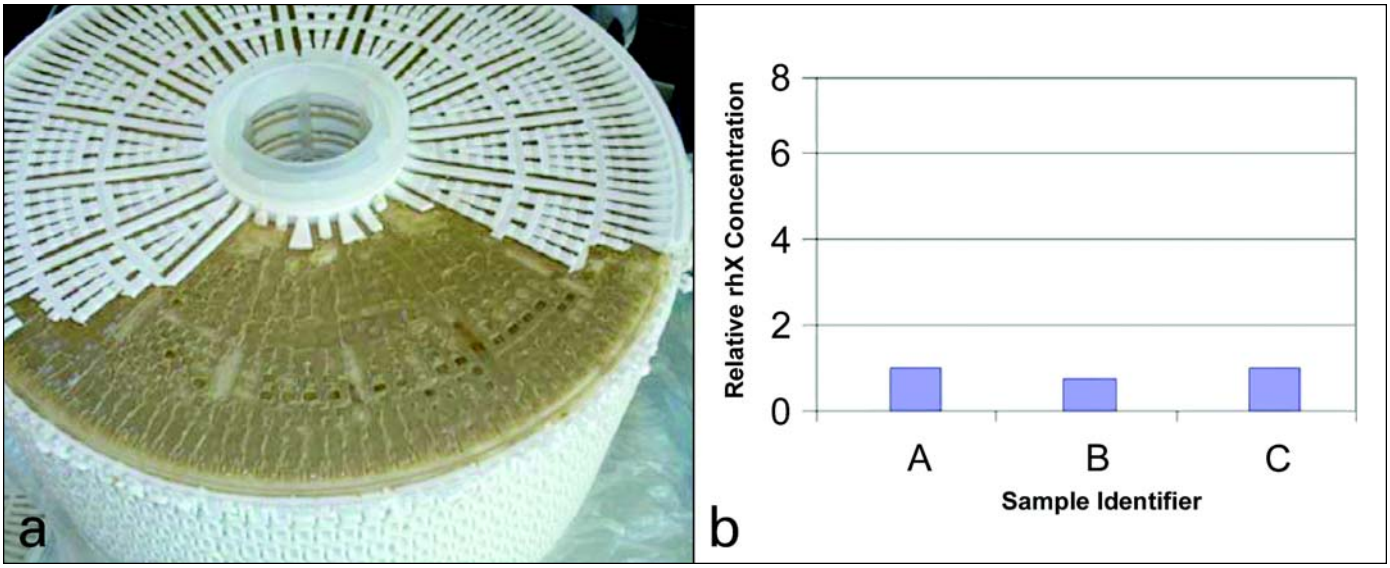

Figure 6. Used depth filter cartridge cake distribution (a) and residual rhX measurements from filter autopsy; A = Bottom pad, B = Center pad, C = Top pad (b).

using the same method previously established. Figure 6 shows a photo of one of the cells with the polypropylene cage partially removed. Upon opening the filter cartridge, it was evident that the filter media was more evenly utilized (the bare spots are places where the filter cake stuck to the plastic mesh cage that was cut away). Samples were taken from various spots in the filter cartridge and the residual rhX was measured as previously. Again, the residual rhX concentration was normalized to the final concentration of chase buffer leaving the filter.

These results support the theory for how the previous depth filter's design contributed to yield loss. The overall product yield for this trial was ***94%*** (compared to an average of 88% for the two manufacturing batches followed). The improved design of this cartridge appears to allow a more uniform build up of the cake on the filter sheets that, in turn, prevents the formation of a path-of-least-resistance, allowing for a more effective chase buffer flow distribution and recovery of residual rhX within the cake and filter sheets. Depth filter breakthrough also was not observed during the filtration, *and there was no pressure build-up on the 0.2 µm filter capsule even with 40% less relative surface area*. This is a good indication that the use of this cage-style cartridge at the process scale should result in fewer membrane filter clogging incidents.

Microfiltration/Diafiltration

Three trials of a hollow fiber microfiltration/diafiltration unit operation were performed at bench-scale using CHF supplied from manufacturing. A diagram of the TFF system is displayed in Figure 7. The process can be summarized as follows:

- CHF is titrated per SOP to the target pH.
- The titrated CHF was filtered by hollow fiber TFF until approximately 66% of the liquid volume had been collected as permeate, resulting in a 3X concentration of particulates. 0.65 µm (15 mil) hollow fiber membranes with an effective membrane area of 460 cm^2 (71.3 in^2) and a flowpath length of 30 cm (11.8 in) were used.

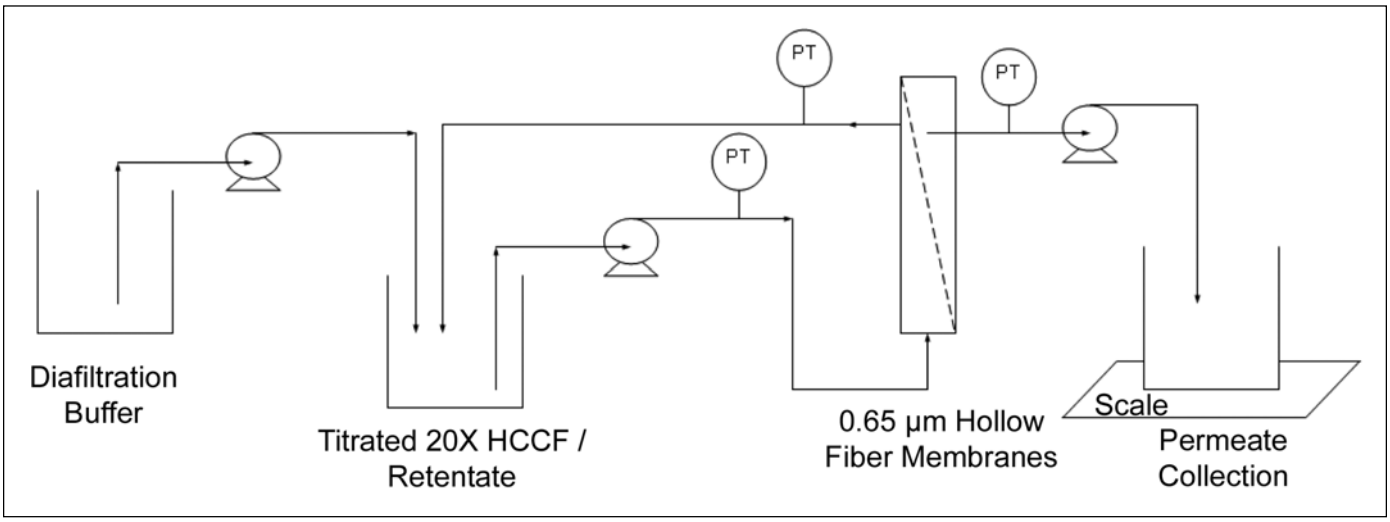

Figure 7. Microfiltration/diafiltration system setup.

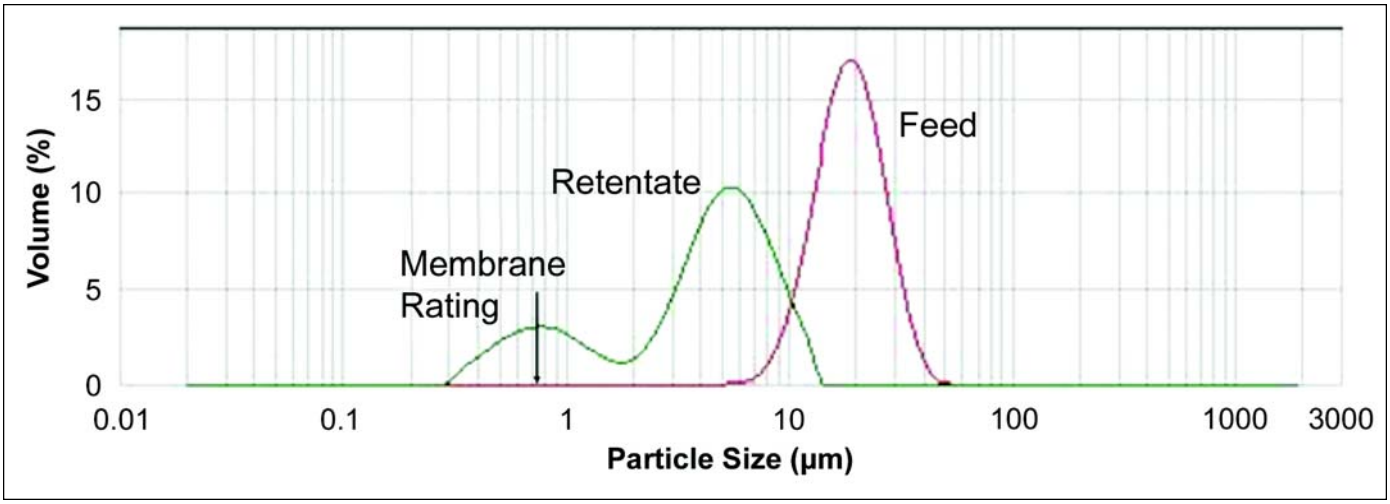

Figure 8. Particle size distributions of the initial titrated CHF (feed) and intermediate retentate following microfiltration.

- Chase buffer was used as a diafiltration buffer. Diafiltration buffer was added to the retentate at the same rate at which permeate was removed. In total, 5 diavolumes of buffer were used.
- The diafiltration rate and recycle rate were controlled to maintain the transmembrane pressure within vendor specification.

MF/DF Results

The MF/DF filtration process resulted in near complete recovery of rhX for all three trials with an average measured yield for the three trials of 115%. The >100% result could be due to sampling if the mixture was not uniformly mixed, or it could be due to the resolubilization of the rhX which was initially entrained in the precipitate following titration. The yield of HCP impurities also was higher (87% for MF/DF as opposed to 83% for bench-scale depth filtration), indicating that some HCP may be subject to the same resolubilization phenomenon, or this may be a consequence of the removal of the adsorptive capacity of the depth filter media, which is positively charged.

Particle size analysis of the initial pH adjusted CHF (feed) and intermediate retentate was performed and Figure 8 shows the results of this analysis. It is apparent from the changes in particle size that the shear force encountered during TFF is of great enough magnitude that the precipitate is broken up into smaller particles. A considerable number of these particles are smaller than the 0.65 µm nominal rating of the hollow fiber filter, which could increase the particle burden on the 0.2 µm membrane filter. Hence, there is the potential for full recovery of the rhX with MF/DF, but the impact on the downstream processing needs to be evaluated in light of the higher HCP recovery.

Conclusions

Through a combination of scale-down analysis and process monitoring, the lens-style lenticular depth filter cartridge design was identified as the main contributor to the additional yield loss seen at process-scale. A new lenticular cage-style filter design was evaluated at pilot scale and allowed for more uniform accessibility of the filter media. This in turn led to a significantly lower level of rhX left behind in the filter holdup, and thus, a significantly higher rhX recovery. Changing to the new design should result in improvements in yield and a reduction of clogging incidents. The microfiltration/diafiltration process is promising based on the product yield obtained in initial bench-scale experiments, but the impact on downstream purification operations needs to be determined before proceeding any further. Table C summarizes the key findings and recommendations of this study.

Abbreviations

CHF Concentrated Harvest Fluid

Filter Technology	rhX yield	Other Benefits	Potential Issues with Adoption	Decision
Lens-Style Depth Filter Cartridges (2 process-scale batches)	88%	Status quo	N/A	N/A
Cage-Style Depth Filter Cartridges (one pilot-scale trial)	94%	Potential reduction in 0.2 μm membrane filter clogging due to more efficient utilization of depth filter surface area.	Minimal – Same depth filter media as current process. Cost increase is not significant compared to yield enhancement. Lower extractables than current filter.	Submitted as a process change.
Microfiltration/diafiltration (Three bench-scale trials)	115%	TFF could result in more consistent, reliable filter performance, fewer operational issues.	Unknown impact on 0.2 μm membrane filtration due to small particle generation. Unknown impact on product quality. Lower HCP removal and increased volume could impact capture chromatography.	Further studies needed to assess impact on product quality and on downstream purification processes.

Table C. Process modification evaluation summary

rhX	Recombinant enzyme biopharmaceutical "X", one of BioMarin's approved products
HCP	Host Cell Protein
P/V	Mixing Power per unit Volume

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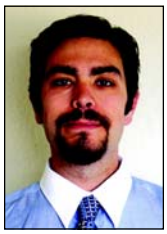

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Case Study: Parenteral Facility Upgrade Project with Fill Line Install

by Keith Weseli and Michael DiGiovanni

This article presents a case study illustrating project management and commissioning and qualification processes that allowed for accelerated completion of a renovation project.

Project Summary

As part of an overall parenteral facility upgrade, which spanned a number of years, this case study focuses on the start-up, commissioning, and qualification of a new aseptic filling line for this operational facility.

The location for the new aseptic filling line is in an area of the plant where two aseptic filling lines already existed. These lines connect to multiple freeze dryers and capping lines and supported the filling, freeze drying, and capping of multiple products. The majority of products on these lines are dried, but there are some liquid presentations. Multiple fill volumes and stopper/vial combinations were accommodated. The long term goal for the new filling line is to replace both existing filling lines.

The first phase called for the replacement of one filling line and the implementation of a new process designed to reduce the number of aseptic connections. The existing filling line used 14 different vial/stopper combinations ranging from a 3 ml vial to a 50 ml vial and required line speeds ranging from 80 to 300 vials per minute. This line was the only line fully validated to fill a number of products for the facility and the corporation. Therefore, successful design, commissioning, qualification, and start-up were critical. The second existing line is scheduled to be decommissioned 12 to 18 months following the successful installation of the new filling line.

One major goal of this project was to optimize the qualification documentation by focusing on key regulatory requirements rather than a combination of regulatory and operational requirements. While this focus significantly reduced the number of requirements tested as part of the qualification effort, it did not effectively identify key operational performance metrics early in the project's development phase. However, the Commissioning and Qualification (C&Q) team was able to identify and integrate these key operational requirements into the C&Q process and used them to effectively improve the performance of the system prior to installing it into the production facility.

The new process for connecting the product fill tanks to the filler to reduce aseptic connections presented additional challenges. A number of new equipment items were introduced to operators and the level of automated control of the fill line was increased. These changes brought about additional aseptic equipment preparation challenges and added an additional layer of commissioning, qualification, and validation activities to the project.

Table A. Commissioning, qualification, and validation activity locations.

Activity	At Off-Site Testing Facility	At Production Facility
Requirements	X	
Design Documents	X	
Commissioning Testing (Receipt, installation checks, throughput, startup and performance tests)	X	X*
Installation Qualification	X	X*
Operational Qualification	X	X*
Performance Qualification		X
Cleaning Validation		X
Process Validation		X

*All documentation and testing activities necessary to qualify the system and verify acceptable performance were completed at the off-site testing facility. After installing the unit in the final location, minimal IQ documents were re-executed to insure all equipment was accounted for and installed properly. Additionally, some OQ and Comm testing was re-executed to verify performance in the final location was as consistent with what was seen in the test facility.

Installation for the new line was accomplished during a full maintenance shutdown of the production facility. However, the location for the new line was in a common aseptic freeze dry area which was required to return to production as quickly as possible. Initial start-up, commissioning, and qualification through Operational Qualification (OQ) of the new line were accomplished during the maintenance shutdown. However, Performance Qualification (PQ) and Process Validation (PV) activities on the new line had to be accomplished, while aseptic manufacturing operations were occurring on the line that was not removed during the shutdown. PQ utilized the Manufacturing Execution System (MES) with the new equipment filling water. PV was accomplished in aseptic conditions filling actual drug substance. Troubleshooting and testing a line in an operational aseptic environment proved to be extremely difficult. Testing activities could not disrupt production demands during this period. Operational resources were challenged every day to continue production, while trying to learn and support the qualification and validation of the new line. Refer to Table A for a breakdown of commissioning, qualification, and validation activities that were accomplished in each location.

Objective

Due to the criticality of the project, the filling line was first installed in a former aseptic production plant located off-site. The objective was to reduce the potential for significant start-up delays by completing as much design, installation, start-up, and commissioning activity as possible in this off-site testing facility. The construction downtime, which involved a much larger overall scope, was to last eight weeks. This would allow time for construction and additional commissioning and qualification activities in the actual facility during the shutdown period. Intensive static and dynamic airflow pattern testing also were executed in the actual facility to prove that airflows throughout the actual production facility were not adversely affected by the installation of the new line. The production area and the remaining fill line, were then returned to service in an aseptic state. Once aseptic, media fills were performed on the existing line and production began again on this existing line. The new line then progressed through a series of PQ tests, media fills, and PV. The schedule called for the new line to begin making marketable medicine approximately eight weeks after the facility was returned to aseptic conditions. With a full maintenance shutdown taking place at the same time as the construction activities, multiple commissioning and qualification activities to qualify new equipment installations, airflow pattern testing, and the start-up of the aseptic environment, it was critical that the project develop and maintain one integrated schedule with proper sequencing and interdependencies.

Testing Strategy

Planning

The principles in the ISPE Baseline® Guide to Commissioning and Qualification were followed in planning, testing, and verification activities for this renovation project. An overarching project validation plan was developed, which provided the outline for all commissioning, qualification, and validation strategies. Test plans were developed for systems or groups of systems, which contained the detailed approaches to commissioning, qualification, and computer systems validation. The test plans dictated that all requirements were tested and only those associated with higher risk, compliance requirements, and could affect product quality, were tested during qualification. The test plans also laid out which tests would occur in the offsite testing facility and which would occur in the production facility. Each test plan was summarized following testing. For equipment that was tested in the off-site facility, separate test summary reports were gener-

Test Case Run Number:	
Software Release #:	

Dose Control and Stoppering Test	
Test Case	
Vial Size (check one)	☐ 3 ml ☐ 5 ml ☐ 10 ml ☐ 50 ml
Recipe (check one)	☐ Product A ☐ Product B ☐ Product C ☐ Product J ☐ Product D ☐ Product E ☐ Product F ☐ Product G ☐ Product G ☐ Product I
Stopper Type (check one)	☐ Type 1 ☐ Type 2 ☐ Type 3 ☐ Type 4 ☐ Type 5 ☐ Type 6 ☐ Type 7 ☐ Type 8
Use of Inline Filtration (check one)	☐ Inline Filtration Used ☐ Inline Filtration Not Used
Description	Filler Service: Dose Control and Stoppering Test

Figure 1. Test case cover sheet.

ated and approved—one for the off-site testing and one for testing in the production facility.

Planning documents were approved by affected functional groups' leadership with final approval from Quality Assurance. User Requirement documents were developed and the verification that the design met the requirements was accomplished via Design Qualification (or Design Review for indirect impact systems). Planning, requirements definition, and verification of design adequacy took standard approaches. The remaining subsections discuss some unique aspects of this project.

Benefits of Off-Site Testing

The project team had a number of key challenges it needed to overcome in order to deliver the new fill line successfully. The use of an off-site testing facility was a critical piece in overcoming these challenges, and provided significant benefit to the facility.

The new fill line was being installed in an existing, validated, and fully operational aseptic filling operation. While there was some ability to build inventories of key products to allow for an extended production outage, due to strong demand for these products and capacity constraints in the existing facility, an eight week shutdown was all that could be accommodated. With a significant construction scope, including architectural modifications, installation of a new filling line, installation of multiple aseptic filling hoods, and other items, it was necessary to limit the amount of start-up problems to ensure the project could be completed in eight weeks. It also was important that once the facility had been restarted, issues that needed to be addressed on the new line could not affect production on the sister line in the same aseptic area. These issues drove the need for an off-site testing facility to ensure the unit was operating properly, was validatable, and could be operated effectively by the operations personnel once it was installed.

From a cost perspective, the use of the off-site testing facility added very few additional costs to the project, but provided significant savings. There was no additional cost for the off-site facility since it was already owned and operated by the organization installing the fill line. However, there was some additional construction costs associated with the moving and final installation of the fill line since the system was fully assembled and operational in the test facility. This was the only redundant activity for the engineering and construction portion of the project. Additionally, there was very little duplication of validation documentation from one site to the other through the effective use of commissioning testing, and the focusing of qualification efforts on key process requirements and not on engineering requirements. The

Recipe ____________ Vial Spec. ____________

Date ____________ Stopper Spec. ____________

DOSING - Alarm & Intervention Log

Initial Conditions:

Surge/Fill Tank Pressure Setpoint ______

Horizontal Nozzle Start Position ________

Vertical Nozzle Start Position _________

Tare Arm Start Position _____________

Gross Arm Start Position ____________

Time	Vial #	**Alarm Points**	Tare fail to re-zero	Gross fail to re-zero	Fill Adjust Limit Exceeded	Tare did not read stable weight	Tare scale did not return to zero	Tare weight outside specification	Gross did not read stable weight	Gross scale did not return to zero	Needle scale error	Gross scale fails to increment	Raised Needle	Carrier Belt Overtorque	Other Alarms	**Aseptic Interventions**	Adjust Needles	Adjust needle rack	Adjust tubing on needles	Clear Overtorque	Other Interventions	Comments
Total for Sheet																						
Total for Run																						

Figure 2. Dosing performance tracking tool.

use of test cases helped to greatly reduce the costs associated with these redundancies by allowing the team to minimize the number of test cases needed by establishing a format that allowed for both commissioning and qualification testing of multiple variables in one test case, by focusing qualification testing around critical process parameters, providing an efficient documentation process for commissioning testing, which allowed for trouble shooting and re-execution of test cases without revisions. The real savings for the overall project came from a significantly reduced inventory build prior to the outage, the ability to more efficiently identify and resolve problems in a non-aseptic environment, and the ability to transition to a full production mode sooner, eliminating over-time, outsourcing of products, operational inefficiencies, and the need for changes after completion of the project thus delay final validation of the new filling line. These larger savings off-set the minor additional costs associated with the off-site testing facility and also made the project possible.

The Use of Test Cases Instead of Protocols

The ISPE Baseline Guide® to Commissioning and Qualification defines commissioning as "a well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the End-User that results in a safe and functional environment that meets established design requirements and stakeholder expectations." Performance testing is a key aspect of the commissioning process. The typical way to document this testing is in a protocol which has a series of test cases and execution instructions. This protocol can be a very lengthy document to ensure that all of the system's functional requirements and specifications are tested. This can lead to an arduous approval process as differences of opinion regarding one specific test case can impede the approval of the entire protocol, resulting in schedule delays. Another potential shortcoming of this approach is that if a testing gap is discovered (i.e., a requirement was not tested) the testing protocol must be revised or addenda must be created depending on the process established by the project team.

To avoid some of these drawbacks, this facility upgrade project implemented a process whereby test cases were written and approved individually rather than within the context of a testing protocol. This sped up the document development process significantly. Another advantage of this process was that test cases could be run multiple times without the creation of additional documentation. This was crucial to the project given the diversity of products filled by the line. The same test case could be executed for each of the nine product recipes and their associated vial/stopper combinations without assembling a testing protocol that would have been hundreds of pages in length. Recipe, vial type, stopper type, etc. were documented by simply checking a series of boxes on the first page of the test script - *Figure 1*. Figure 1 is the first page of a test case that was approved prior to execution and post-execution reviewed and approved (not shown). The test cases aided the project team in determining which recipes would be the most challenging from whatever performance aspect the team wanted to examine. For example, the team could run the same test case on Recipe X and Y and analyze the percentage of vials displaying missing stoppers by simply comparing the test cases. The results were then examined without the burden of generating new testing documents or writing a summary report. The test cases also could be used to document testing at the test facility and in the main production facility, further reducing the amount of new documentation that would need to be created. Moreover, the use of test cases facilitated assessing the impact of changes without new testing documentation. If a physical change was made to the system, test cases for the same recipe executed before and after the change could be directly compared. Re-execution of failed test cases or re-execution to verify performance after a physical change also was simplified through this process.

The use of test cases also facilitated the testing of the inline filtration system, which was the system implemented to significantly reduce the number of aseptic connections required by the process. This system pressurized a manufacturing tank, allowing product to be filtered by a dual filtration assembly into a smaller fill tank located in the fill room. The control system actively controls fill tank pressure. Besides reducing the number of aseptic connections required, the inline filtration system was believed to provide the additional benefit of tighter dosing control, due to active pressure and level control on the smaller filling tank. To prove this theory, the standard filler commissioning test was used. A direct comparison of dosing results using the inline filtration system and its active pressure control could be made to previous filler runs completed prior to installation of the new system. The performance testing results confirmed that the new system did indeed provide tighter dosing control for the filler. The use of test cases instead of protocols allowed the inline filtration system to be tested in parallel with testing of the filler, thus reducing the time to effectively test the integrated system. Since the inline filtration system was not completed until several months into the testing period at the off-site test facility, the time saved by parallel testing of the systems was crucial.

Using the Off-Site Test Facility

The owner of the final facility operates and maintains multiple production and development facilities around the world. There are a number of legacy production facilities still in place, and recently the owner had designated one facility in particular for development activities. This facility was approximately 30 miles from the final production facility. The opportunity to conduct commissioning and qualification at an off-site test facility provided some distinct advantages for the project team. First, being physically removed from the production facility allowed the project team to fully concentrate on the task of commissioning the new filler without the distractions of the day-to-day production routine. Using the off-site testing facility gave the project team access to experienced personnel who had been involved in similar projects

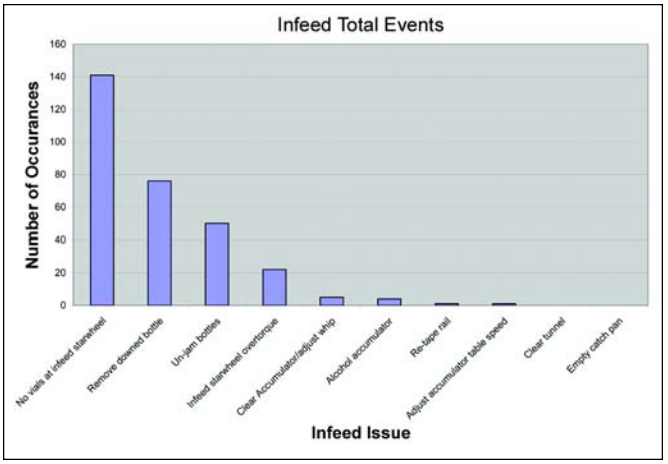

Figure 3. Infeed Pareto chart.

and had operational knowledge that benefited the project team. The facility allowed for the replication of production conditions for performance testing. Vials were washed and sterilized prior to filling operations so vial handling characteristics of clean, sterilized glass were analyzed (if desired, the equipment allowed for manually loading vials directly onto the pre-fill accumulation table). Stoppers were autoclaved and prepared according to operational procedures so performance of the stoppering system could be effectively compared to production rates. Unidirectional airflow hoods were turned on so the performance of the check-weigh scales would be comparable to that in the Grade A production environment.

To ensure that testing results from the testing facility could be considered valid after the equipment was moved into the production facility, the project team took a detailed inventory of all equipment prior to packing for the move. Since the test-facility and final production facility were only about 30 miles from one another, the team was able to have significant oversite and involvement in the movement of the equipment. The team witnessed the movers to ensure that care was taken as the equipment was loaded for movement. A commissioning receipt verification was conducted as the equipment arrived at the production facility, and installation checks were done following equipment placement in the building. These efforts mitigated risks associated with moving the equipment and accepting testing conducted in two different locations as equivalent. Project teams regularly make such risk-based decisions when deciding to leveraging testing conducted on a vendor's factory during FAT.

Testing Beyond the Requirements

The requirements documents developed for the project were intentionally focused specifically on regulatory requirements rather than operational requirements. While this strategy greatly reduced the amount of regulatory documentation and limited the scope of qualification/validation testing, it left a gap with the overall functional requirements which are normally tied to commissioning activities and operational expectations of the system. The commissioning and qualification test cases were written to align with the User and Functional Requirements associated with the filler. However, things like the number of alarms, the number of aseptic interventions, and the percentage of vials automatically rejected by the control system, which are certainly important from an operational and business perspective, were not specified. The project team quickly realized that they could "meet established design requirements" while failing to meet "stakeholder expectations."

The installation, start-up, and validation of this new line were critical for the plant. The existing filling line was the only line the company had validated to fill a number of key products. Therefore, it was very important for the project team as well as the operations team to accurately understand how well the machine would perform after installation. To effectively communicate the capability of the new filler, the project team had to develop a tool to document the system's performance above and beyond what was requested in the test scripts. The project team worked with the plant's operations team to develop acceptance criteria focused around the line's overall performance. These criteria included missing stopper rates for each run, number of aseptic interventions, total yield for the fill, and others. The team developed a process that allowed commissioning test executors to efficiently track the issues encountered during the test run. Four separate tools were created—one for filler infeed, one for dosing performance, one for stoppering performance, and one for tray loading performance. The dosing performance tool is shown in Figure 2 for illustrative purposes. This documentation process allowed for the commissioning executors to test in parallel with the formal testing script. Results of commissioning were then attached to the test script so this additional information was captured. After several test runs, these documents enabled the team to quickly generate Pareto charts for various issues. With the Pareto charts, the team was then able to effectively focus on critical issues, solve them, and then re-execute runs to ensure changes were effective. With a clear set of operational expectations, regulatory requirements, documented solutions and their effectiveness, management was able to understand in detail the risks with the new fill line from a performance perspective and make a sound decision as to whether to move forward with the project during this shutdown period or wait until the next available shutdown period given the inventory demands of the facility.

Solving Technical Problems

The Pareto charts became the primary decision tool for the project team to address technical and performance problems witnessed at the off-site test facility. Using these charts, the team addressed several problems in a relatively short period of time. Examining the Infeed Pareto chart (Figure 3) illustrates the approach the team took to solving technical issues. A quick glance at the Pareto shows that the two most occurring alarms and aseptic interventions were "No vials at infeed starwheel" and "Remove downed bottle." Through testing experience, the C&Q team knew that this in fact was one in the same problem. When a "No vials at

infeed starwheel" alarm was received, this was usually due to a downed bottle jamming the flow of vials from the pre-fill accumulation table to the filler infeed starwheel. When this occurred, operator intervention was required to remove the downed vial. The infeed transition did have a downed vial escapement, but the jam was often created because the vials fell downstream of the escapement.

Again from the testing, the C&Q team also knew that this problem was primarily related to the 10 ml vial. Qualitative data demonstrated that more than 50 percent of the occurrences of "No vials at infeed starwheel" were associated with testing runs using the 10 ml vial. This vial is tall and has a relatively high center of gravity. If there was any interruption in the flow of vials through the infeed transition, the vials upstream of the interruption had a tendency to wobble and fall. The project engineers designed a vial neck guide at the vial escapement that prevented vials from tipping over. This guide was installed over the infeed vial guide and grabbed vials so that if there was motion due to a break in the stream of vials, the vials would not fall over. Using the test tracking tools, the team documented a significant reduction in the number of "No vials at infeed starwheel" and "Remove downed bottle" alarms following the implementation of this physical change to the system. Similar troubleshooting during the testing phase at the off-site test facility, as well as change management tracking using the repeatable test case execution, also were employed.

Managing Components

Procurement is a functional area involved with any capital project. One generally assumes that this function will acquire the components of the process systems. While this was true for this facility upgrade project, the team also had to manage testing components – specifically coordinating the acquisition and use of vials and stoppers for testing. Since the majority of the testing took place at an off-site test facility, the project team had to interface with the procurement group to ensure testing supplies were available. The procurement team then had to balance the requests of the project team with the needs of the manufacturing facility, which was ramping up production to meet inventory needs prior to the upcoming shutdown. Clearly, procurement had to defer to production when there were conflicts with a given vial or stopper.

A logical solution to this situation would simply be to order more vials and stoppers from the vendors. However, the lead time for these items is quite significant – on the scale of months, not weeks. While this was an option, it was not a panacea for the project team and the tight demands of the schedule. Planning for testing needs relatively far in advance became a necessity for the project, not a luxury. With only four focused months of testing at the test facility and two months of construction and C&Q testing in the new facility, precise planning was a necessity and there was not much time to deal with procurement issues.

With the wide variety of vials and stoppers in use on existing production lines, other performance issues had been observed and were being addressed by other project groups. These groups often wanted to conduct studies on how potential replacement container closure systems would function with the new filler, even though these would not immediately be employed in production following the shutdown period. Despite the pressing production needs following the shutdown, the commissioning team had to examine the big picture and allow potential improved vials and stoppers to be run on the new machine. This enabled the characteristics of these components to be examined without production downtime, which would be required if these studies were conducted once the filler was placed in the manufacturing facility.

Lessons Learned

Executing the Commissioning Tests

Separating business needs from regulatory/quality requirements provided a number of key benefits for the project. It greatly reduced the amount of regulatory documentation without reducing the effectiveness of the regulatory effort. The definition of the operational requirements late in the project proved to be a major obstacle, and added significant inefficiencies to the project early on. While the team was able to recover from this deficiency, as a whole, integration of operational requirements into the C&Q effort can be done without reducing the regulatory optimization effort, and ensures a more operable, efficient, and maintainable system in the future. Another objective of the project was to provide better integration of the mechanical qualification and computer system validation effort. While progress was made in this area, there was clearly more that could have been done.

The commissioning test cases were generally executed by operators familiar with the existing filler and procedures. This use of experienced production staff eased the technology and knowledge transfer process that occurred at the end of the project. The knowledge operators brought to the commissioning team cannot be overstated. Their expertise in the areas of aseptic technique and documenting aseptic interventions was essential for developing robust testing data and defining operational requirements that were not part of the regulatory effort.

Human Resources

Although there were operators who supported the commissioning phase of the project, a full fill team could not be spared by the production facility to support full-time commissioning testing given the pre-shutdown production schedule. Therefore, the commissioning contractors often had to assume the role of operators. This required the commissioning contractors to quickly learn the functionality of the machine which should be expected of any professional commissioning team while maintaining their objectivity during the testing process. The ability of the commissioning team to run the equipment enhanced troubleshooting efforts and the resolution of operational issues.

Other critical resources for the project included Equipment Engineers and Maintenance Mechanics with a very

solid background in parenteral equipment, maintenance, filling processes, and equipment troubleshooting. Automation engineers with the ability to cross the boundary between process/equipment issues and instrumentation and coding were invaluable toward ensuring the process and the system worked in harmony. This group was very important during the troubleshooting phase of the project. Their understanding of the machines, ability to perform effective root cause analysis, and identify effective solutions quickly led to significant improvements in performance over very short periods of time. Lastly, a responsive Quality organization made rapid turnaround on testing documentation possible.

Coordination with End User

Integration of a new filling line into an existing facility cannot be done without the commitment and support of the future system owners. Their understanding of the day-to-day business of making medicine in the particular facility where this system was installed is invaluable. They are the best equipped to articulate issues, provide clear direction around priorities. They also understand the operational and regulatory limitations and improvements of the system, and their effect on the overall operability of the area.

About the Authors

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Integrating Industrial Engineering and Lean Techniques at a Contract Pharmaceutical Manufacturer

This article presents the application of industrial engineering and lean techniques to a contract pharmaceutical manufacturing facility.

by Valerie Maier-Speredelozzi, Cyrus Agarabi, Thomas Needham, and Sirine A. Saleem

Introduction

Current Good Manufacturing Practices (cGMPs) were developed to ensure quality pharmaceutical products and keep the public safe. The regulatory approach by the US Food and Drug Administration (FDA), combined with an environment that did not encourage manufacturing innovation, resulted in a pharmaceutical industry that did not keep pace with technological evolution, and ultimately had a restrictive effect on daily operations and process improvements for pharmaceutical manufacturers. Companies were apprehensive to be the first to initiate major changes in their production environments, without knowing how regulators would respond. In response, the FDA released two documents to encourage more innovation in pharmaceutical manufacturing: Guidances for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance[1] and Pharmaceutical cGMPs for the 21st Century-A Risk-Based Approach.[2] These guidances have excited many in the pharmaceutical industry who realize the potential to continuously improve processes, as occurs in other manufacturing industries. Consequently, the focus changed from product testing and release to understanding the product, the manufacturing process, and operations.[3,4]

Other industries have successfully developed innovative approaches to continuously improve and remain competitive, so it is important to learn from their successes and failures. A facility producing pharmaceutical products under cGMPs was evaluated to gain a "baseline" understanding of current manufacturing practices. Critical and problematic areas were identified as well as potential opportunities to incorporate external industry practices to improve the manufacturing process with a focus on the Toyota Production System®.

There is considerable opportunity to investigate the implementation of current practices and knowledge found outside the pharmaceutical industry for incorporation into novel processes in line with the FDA's cGMP regulations and PAT guidance.[5] The concept of incorporating external industries' practices has been recently proposed.[6] However, research focused on these principles and their effects on manufacturing operations and pharmaceutical product development has not been explored. It is pivotal to approach improvements to pharmaceutical manufacturing processes, while still complying with cGMP and FDA regulations, as well as other regulatory agencies around the globe.

Background

This section provides an overview of current

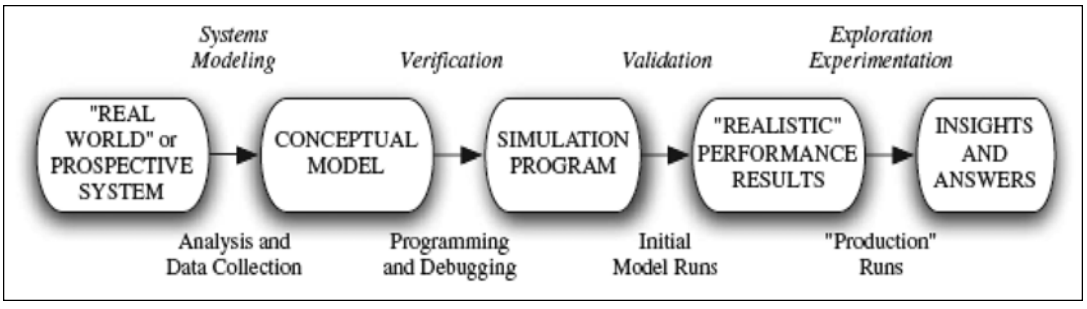

Figure 1. Simulation overview.[15]

practices and tools from outside the pharmaceutical industry that were investigated for a contract pharmaceutical company (XYZ Pharma) to improve its current manufacturing system. An extensive overview of these principles and tools can be found in books on lean manufacturing.[7,8,9,10]

Lean Manufacturing and its Tools

Toyota was a leading developer in the use of lean manufacturing, which has been widely adopted with applicability to any industry as the "Toyota Production System®." Production is considered lean if it is accomplished with minimal waste,[11] and if it utilizes far fewer resources, such as worker effort, production, storage space, or equipment investments while striving to achieve defect free processing.[12] Taiichi Ohno of Toyota®[7] identified seven forms of waste: defects, waiting, motion, over-processing, over-production, inventory, and inefficiency. Several lean techniques can be used in the pursuit of achieving zero waste such as the following:

- Autonomation (or Jidoka) has two distinct meanings: 1) A change from a manual process to a machine process. 2) Automatic control of defects or automation with a human mind.[8]
- Error-Proofing: This technique places various checking devices on equipment and tools to remove the potential for error and ultimately the creation of defects.
- Just-In-Time (JIT) systems: This technique requires a holistic approach to ensure accurate production, ordering, and stock quantities to ensure that the right parts needed in an assembly are available at the exact time they are needed and only in the amount needed.[7]
- Kanban (sign board): This technique is a communication tool to convey information about picking up or receiving the production order.[7]
- Kaizen (good change): This technique is defined as continuous improvement.
- "5S:" This technique is used during a Kaizen event to reduce hidden wastes in the plant through a cleanup activity.
- System Configurations: This technique is essential to identify a system's bottlenecks and focus on improving them in order to realize the full potential of the system.

These various lean tools were each considered for possible application at XYZ Pharma, following the preliminary application of another lean tool, Value Stream Mapping.

Value Stream Mapping® (VSM)

The first step in achieving lean manufacturing is to understand the current system by applying VSM. This process involves recording all activities involved with manufacturing a product from raw materials to finished goods. A VSM is created to evaluate total efficiency instead of individual efficiencies. The map is comprised of three basic elements: 1. Product flow, 2. Information flow, and 3. Material flow.[9] Furthermore, it includes two classes of work: work that adds value to the product and non-value added work (waste). By addressing both types of work, a strategy can be devised to implement lean tools to minimize waste and create a long term vision. Eventually, this can be shown through a future state map which would employ the improvements and their estimated effects on the system.[9] It should be noted that to create an accurate model of the three flows in the map, there must be accurate data collected from the production floor. This is *accomplished* by using "Gemba" which is defined as the "actual place" and is the first step used by Toyota® when solving a problem.[10] The concept reinforces the need for firsthand knowledge and challenges conventional management methods of system reports and computer analysis.

The created VSM might be the foundation of a simulation model that enables the monitoring of Work In Progress (WIP), production lead time, cycle time, changeover time, efficiency, etc.[13] As depicted in Figure 1, simulation will allow visualization and incorporate detailed information about the system while closely conforming to the individual aspects.[14] This will facilitate experimentation with theoretical scenarios to identify problematic areas and potential failures.

Additionally, using other methods such as Quality by Design (QbD) and Design of Experiments (DOE) may help in determining the critical factors and interactions identified from a VSM or simulation model results that achieved statistical significance. Such significant factors will become the focus of the future state model.

Company and Process Background

The pharmaceutical company in this study is referred to as XYZ Pharma and primarily serves as an OTC contract manufacturer for more than 100 products. They are housed in a 25,000 sq.ft. production facility with a detached 75,000 sq.ft. warehouse building nearby. There are approximately 55 permanent and temporary employees working three overlapping shifts (5 am to 2 pm, 7:30 am to 4 pm, and 2 pm to 10:30 pm). There are between 20 and 30 operators during the shifts to run the filling and packaging machines. Only a select group of operators have been trained on the newest filling machine, and their operating times are limited to the second shift. The 12 person Quality Control (QC) department functions to ensure the quality of all incoming shipments, all cGMP requirements during production, and the quality specifications of all outbound products, including maintaining documentation and a "quarantine" area. One driver is responsible for operating XYZ Pharma's truck, which travels between the main warehouse building and the production facility approximately every two hours with raw materials, finished goods and recyclables.

This study will evaluate the manufacturing of a poloxamer based topical gel, referred to as Product X, produced in three 30,000 tube batch sizes for one 90,000 tube job. This product is similar in formulation and manufacturing processes (Figure 2) to many other products manufactured at XYZ Pharma and is representative of the system. Raw materials undergo a 23 step proprietary process to formulate the bulk drug. During production, the QC inspector periodically checks on the manufacturing specialist to verify his work. The formulation process is completed when the product has been entirely

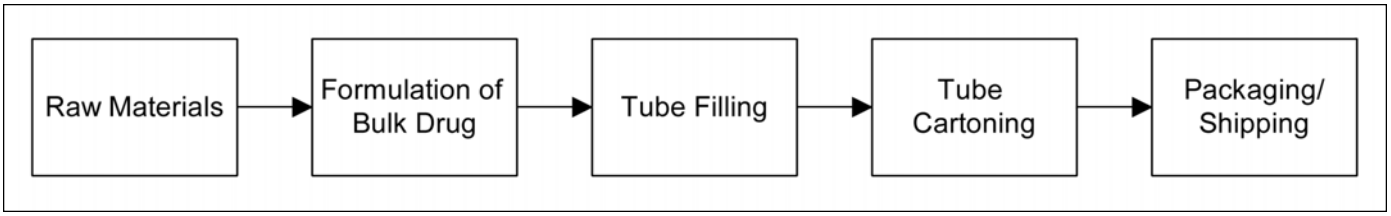

Figure 2. Overview of manufacturing of Product X.

transferred into a stainless steel storage vat through a milling process. A mechanic is responsible for the setup of the filling equipment and must prime the machine with product and make adjustments to ensure accurate filling within specifications. The company currently has two different types of tube filling machines: three older machines and one new, which have both been used to manufacture Product X. The majority of employees are trained on the older machines, which can be run on all three shifts with only minor adjustments after the initial setup. The new system is only run by a select number of operators and generally runs during the 7:30 am to 4:00 pm second shift. The older machines are capable of producing 35 tubes per minute of Product X using two to three operators, while the new system produces 70 tubes per minute using between two and four operators. If a filled tube passes the inspection criteria, it is put into a plastic storage tote on a pallet. Each pallet holds up to 20 plastic totes, and the company owns 52 totes. If the totes are filled before the next process (cartoning) is running, then operators must assemble boxes and fill those instead of totes. A mechanic must setup and adjust the cartoner to accommodate the size and feed rate of the cartons, and the subsequent tape machine. Cartoning occurs at a load rate of 78 to 82 cartons per minute and can operate through all three shifts with six to eight operators. Finished goods are placed in the production holding area under quarantine to await final assay results and reconciliation of quantities. The product may be moved via an internal shipping truck to the warehouse facility to await final release of the lot from quarantine to allow shipping to the distributor.

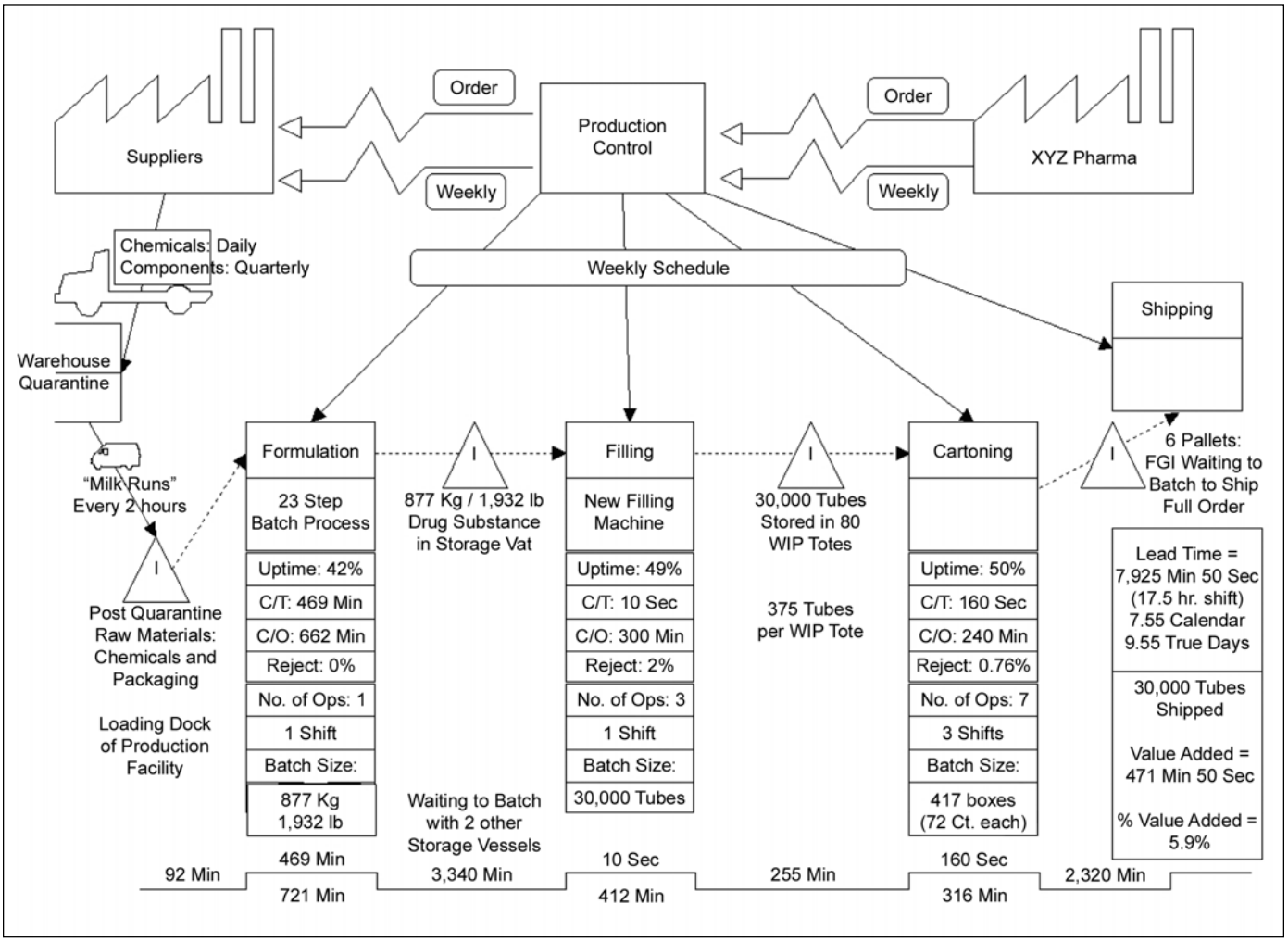

Figure 3. Current state VSM.

Current State VSM

A current state Value Stream Map (VSM) of the system for Product X at XYZ Pharma is shown in Figure 3. Data for this VSM was collected through time studies and retrieved from the master batch records of four recent production runs of Product X. The suppliers are located at the top left, and the XYZ Pharma customers at the top right. Information flows across the top of the diagram from right to left, and downward in the form of weekly schedules for each department. Materials and product flow across the diagram from left to right through the various processing operations. Each major operation has a "process box" underneath with metrics that help to quantify the time and resources required for that production stage. Uptime percentage was calculated by dividing the value added time (of the batch) by total production time, both value and non-value added. Non-value added time for a single operation was comprised of breaks, lunch, machine breakdowns, and setup/change over times. Along the bottom of the VSM, a "ladder diagram" shows value adding processing time (high points) and non-value adding time (low points) of the entire production process, which includes batching delays, time spent in inventory, which is represented by triangles on the diagram, waiting, or other wastes. The percent of value adding time for the entire process is 5.9% which is actually very typical for many "current state" non-lean facilities.

The current state VSM gives the Cycle Time (CT) of an individual tube through processing, except during formulation where the entire batch is undergoing value added work at the same time. The map shows that the greatest wastes of time are the buildup of WIP in the system before the filling line and after the cartoning process, where finished goods pallets are stored until the entire batch is complete and ready for shipment. The lead time of the system was calculated to be 7925 min and 50 sec. When divided by the total amount of operational hours from 5:00 am to 10:30 pm (17.5 hours), the lead time is roughly 7.5 days. The current state is based on a five day work week with Saturday and Sunday as days off. This translates into a "real world" lead time of 9.5 calendar days for one batch. One order for this product generally consists of three batches requiring minimal inter-batch changes once the initial set-ups have occurred, resulting in decreased holding times to avoid starving down process machines. Therefore, the second and third batches are produced faster, and the entire three batch process requires approximately 11 days of processing or 15 calendar days.

Simulation for the Current VSM

The simulation utilizes collected data and compiled master batch records to create a model which depicts the current state of the system. All processing times, waiting times, and personnel assignments have been created through observation and verified through company documentation. A portion of the facility layout and the simulation locations which have been built are shown in Figure 4. A Computer Aided Drafting (CAD) model of the facility layout, including accurate distances between departments, was developed. This layout was then imported into the commercial simulation software package as a backdrop for the simulation model. Travel times for employees moving product between processing operations were entered into the model, and a visual representation of the movement of product through the facility was available as the simulation model ran. The flow of materials follows the current VSM in Figure 3 as discussed earlier.

The results of the current state simulation help to gain an understanding of the steady state of the system as shown in Table A. The simulation runs overnight and on the weekends even when the virtual equipment is not operating to realistically represent the current state in the facility, which does not operate on the weekends. Thus, a batch that is in production on Friday may not be filled and cartoned until Monday, increasing the lead time. The simulation was run for 999 replications, the maximum allowed by the commercial software package, and the calculated average throughput time through the system was found to be 370.92 hours or 15.45

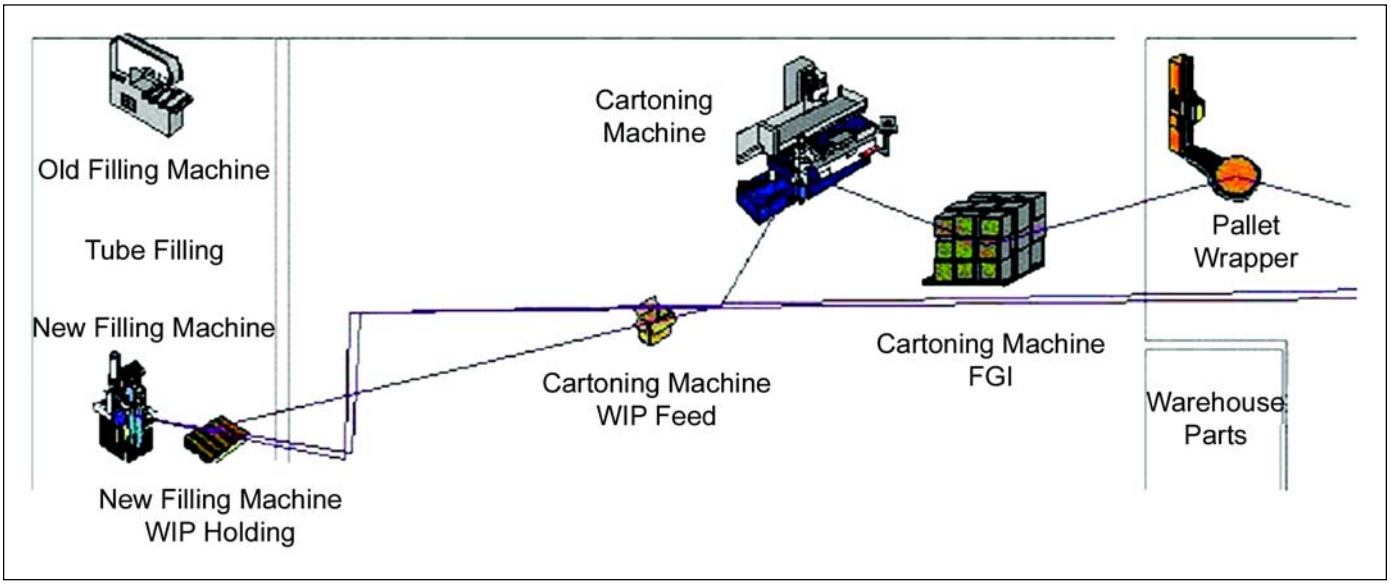

Figure 4. Current state simulation layout.

Location Name	Avg Time per Entry (MIN)	% Utilization
Inventory Transfer and Holding		
Production Warehouse Area	3081.99	0
Formulation Holding Area	934.16	12.79
Storage Vat Load	977.77	13.39
Vat Holding Area	7097.92	31.64
New Filling Machine WIP Holding	54.86	0.64
Cartoning Machine WIP Feed	353.97	4.06
Cartoning Machine FGI	203.02	14.32
Equipment		
Kettle	1397.93	19.14
New Filling Machine	1816.03	24.58
Cartoning Machine	142.85	16.49
Pallet Wrapper	27.14	2.26
Total System Throughput Time	**370.92 hrs**	**15.45 days**

Table A. Results of the current state simulation.

days. In order to ensure that the simulation adequately represented real world conditions, the average time per batch, 123.88 hours, is multiplied by three to give a total order time of 371.65 hours. The average time from the simulations was analyzed to be 99.8% similar to that from the master batch records.

The largest periods of non-value added time are when the operation waits to batch. The time that formulated bulk drug product spends in the transfer vat waiting to be brought to the filling line is very long. Also the time spent waiting for the batch of wrapped and palletized finished goods is considerable. Due to the infinite capacity of the production warehouse area in the model, the utilization percent is not calculated. This was purposely avoided to prevent blockage of incoming, outgoing, and stored materials, which would require a separate in-depth material handling study out of this project's scope.

Furthermore, Table A shows that the two highest utilization percentages of equipment or inventory transfer and holding locations are the vat holding area and the new filling machine, respectively. These areas appear to be bottlenecks in the current system and should be viewed as areas for improvement for the future state by introducing parallel machining capabilities. This is possible because the company had actually replaced a slower old filling machine with a faster new filling machine. Both machines were already validated, so utilizing them simultaneously to fill one batch of Product X in less time would be acceptable within FDA guidelines and would not require a new investment. While the production warehouse area does not have a calculated utilization percent, the average time per entry is the second highest and also should be considered as a potential area for improvement.

Areas for Improvements

After developing the current VSM and running the simulation, critical and problematic areas were identified as well as potential opportunities to incorporate lean tools to improve the manufacturing process. These areas for improvements include:

- shrinking traditional batch sizes to create a more semi-continuous production system
- improving efficiency of "milk run" truck deliveries
- reducing inventories by decreasing storage vessel batch sizes and decreasing WIP buffers
- cleaning and organizing facilities by applying the 5S techniques
- improving equipment by using visual controls and Single Minute Exchange of Dies techniques to decrease setup times
- incorporating automation that would result in improved product quality and fewer operators needed on machines
- adding parallel machines at the equipment bottleneck
- cross training personnel so that most operators would be trained on multiple pieces of equipment, allowing them to operate during any shift and rotate when needed

The Future State Simulation

To develop the future state model, a Design of Experiments (DOE) methodology was used to systematically vary the state of certain factors or operational parameters in the simulation. After analyzing the areas for improvement, three critical factors were identified:

Factor A – parallel manufacturing by reinstating use of an old filling machine
Factor B – cross training of personnel
Factor C – changes in move batching rules during production

Some of the other lean improvements for the facility that were considered above were evaluated and suggested to the company, but the implications and results of these changes would be more difficult to model in a simulation environment. For the three selected factors, the simulation model could be altered by adding machine resources, changing the rules that govern which virtual operators can operate which equipment, and changing the size of move batches. It is important to note that the validated batch size of Product X, constituting a full production run on a master batch record for FDA documentation purposes, has not been changed. What is changed with Factor C is that the quantities of work-in-process that can be moved between operations are reduced. For instance, the first tube of Product X that is filled no longer needs to wait for the last tube in the batch to be completed

	Factors		
Scenario #	A	B	C
1	0	0	0
2	0	0	1
3	0	1	0
4	0	1	1
5	1	0	0
6	1	0	1
7	1	1	0
8	1	1	1

Table B. 2^3 factorial design of three factors selected for experimentation.

Scenario	1	2	3	4	5	6	7	8
Avg. Throughput (Hr)	371	189	284	105	406	161	290	110

Table C. Rounded average throughput times (Hr) of all simulation scenarios.

Location Name	1	2	3	4	5	6	7	8
Inventory Transfer and Holding								
Production Warehouse Area	3082	598	2242	164	3061	629	2198	136
Formulation Holding Area	934	1584	943	1458	939	1076	939	1140
Storage Vat Load	978	631	986	154	979	119	980	87
Vat Holding Area	7098	0	4537	0	8912	0	5021	0
New Filling Machine WIP Holding	55	0	97	0	304	33	235	1
Cartoning Machine WIP Feed	354	11	493	33	1127	207	785	171
Cartoning Machine FGI	203	226	132	99	222	235	126	171
Equipment								
Kettle	1398	3266	1411	1909	1404	1560	1404	1576
Hopper	0	658	0	147	1262	385	734	112
New Filling Machine	1816	33	1021	9	46	31	22	9
Old Filling Machine	0	0	0	0	44	27	32	20
Cartoning Machine	143	117	112	63	172	142	118	75
Pallet Wrapper	27	22	31	25	26	40	41	169

Table D. Average time per entry (minutes) of all simulation scenarios.

before it is moved to the cartoning operation.

Subsequently, a 2^3 factorial design of the critical three factors was selected for evaluation in a simulation as shown in Table B where 0 refers to the current state and 1 refers to the suggested improvement.

The impact of the three critical factors on the average throughput times and average time per entry is shown in Table C and Table D, respectively. Table C summarizes the average throughput times of 999 simulation replications for each of the eight scenarios. Scenarios 4 and 8 show the greatest improvement over the original current state throughput time (Scenario 1). Scenario 8 is a future state with all three factors changed, which is comprised of parallel machining, cross training, and changing the batch rules. Scenario 4 is the same as scenario 8, except it does not use parallel machining methods.

Table D compares all of the simulation scenarios and shows the average time per entry, which gives the average time (in minutes) spent at a given location by each component traveling through the system. This is helpful in evaluating the effects of the significant rule changes in the various scenarios on processing and holding times.

The changing of the batching rules to a more continuous approach resulted in considerable time savings. For example, the average time per entry (min) that a box of finished goods inventory spends waiting after completion of operations at the cartoning machine using Scenario 4 was approximately 50% of the time as the current state, Scenario 1.

The utilization (%) of locations resulting from the simulations is given in Table E. This is useful to identify possible new bottlenecks created in the system after changes have been made. Many manufacturers strive to reach high utilization rates for expensive machinery and research has shown that this can result in a large buildup of WIP in front of the

Location Name	1	2	3	4	5	6	7	8
Inventory Transfer and Holding								
Production Warehouse Area	0	0	0	0	0	0	0	0
Formulation Holding Area	13	42	17	69	12	36	16	54
Storage Vat Load	13	67	18	30	12	16	17	17
Vat Holding Area	32	0	26	0	36	0	29	0
New Filling Machine WIP Holding	1	0	1	0	3	0	4	0
Cartoning Machine WIP feed	4	0	7	1	12	5	12	7
Cartoning Machine FGI	14	32	13	25	14	37	12	40
Equipment								
Kettle	19	86	25	91	18	52	25	74
Hopper	0	70	0	28	16	13	13	23
New Filling Machine	25	74	18	36	25	45	19	26
Old Filling Machine	0	0	0	0	23	37	19	26
Cartoning Machine	16	26	17	25	18	37	18	31
Pallet Wrapper	2	3	3	7	2	8	4	45

Table E. Utilization (%) of locations.

machine to avoid starvation.[16] This buildup of WIP has negative effects on the system as can be seen from the batching used at XYZ Pharma. It is interesting to note that increasing the utilization of holding and transfer areas is not the goal of lean manufacturing and implies that raw materials or WIP is occupying holding areas, which adds to non-value added time.

Scenario 4 provides the lowest throughput time (Hr) out of the eight tested scenarios. Following the continuous improvement philosophy, the next phase of improvements would address the new locations which have subsequently become bottlenecks in the system. The addition of cross training and a change in the batching rules has shifted the bottleneck to the formulation step. The utilization of the kettle has increased from 19% to 91% between Scenarios 1 and 4, which strongly suggests further improvements to setups, cleaning and removal of other non-value added operations. If minimization of non-value added time does not relieve the formulation bottleneck, parallel machining should be investigated. Within the inventory transfer and holding areas, the utilization of the formulation holding area experiences a large increase from 13% in the current state (Scenario 1) to 69% in the future state (Scenario 4). Further improvements would consist of a more precise JIT system, which would bring the correct amount of materials for formulation at the time that the manufacturing operator requires them. Scenario 4 improves upon the current system by spreading out the arrival of the raw materials, but inventory is still held in the formulation holding area. If this JIT system was instated, the current formulation holding area could be converted into a processing area or could be used for other purposes.

Statistical Analysis of Results

To determine whether the three critical factors and their interactions are significant, a full factorial design was analyzed. The coefficient of determination, or adjusted R^2 value, was calculated to be 0.89, indicating that 89% of variability in the data can be accounted for by the model. Also, the calculated P value is less than 0.05; so therefore, the hypothesis that this model is adequate has less than a 5% chance of being rejected.

The Analysis of Variance (ANOVA) statistical results in Table F show that all three main factors, parallel manufacturing, cross training personnel, and a change in batching are significant. The interaction between each of these factors is also examined by this statistical method. The interaction between parallel manufacturing and changing batching rules is significant, as is the interaction between cross training

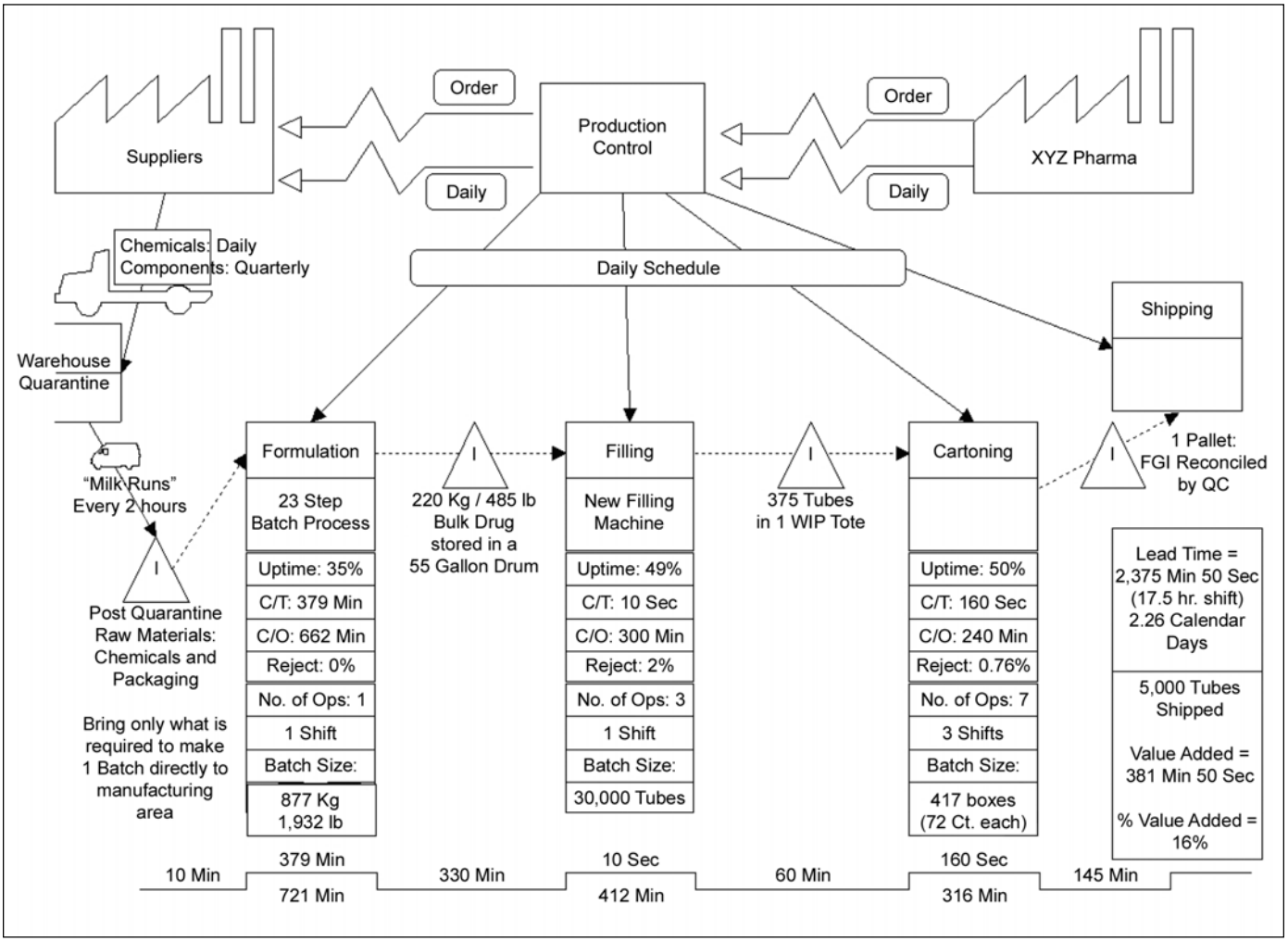

Figure 5. Future State Value Stream Map based on Scenario 4.

Source	Nparm	DF	Sum of Squares	F Ratio	Prob > F
Parallel MFG	1	1	40767	28.7772	<0.0001
Cross Train	1	1	14217695	10036.16	0.0000
Batch	1	1	77386070	54626.21	0.0000
Parallel MFG*Cross Train	1	1	1147	0.8099	0.3682
Parallel MFG*Batch	1	1	514934	363.4881	<0.0001
Cross Train*Batch	1	1	582003	410.8311	<0.0001

Table F. ANOVA table results of the three critical factors.

personnel and changing the batching rules. The interaction between parallel manufacturing and cross training is not a significant interaction. The nonsignificant interaction is most likely due to the overpowering effect of changing the batching rules.

Future State VSM

The envisioned future state VSM was created as illustrated in Figure 5 based on results found from Scenario 4. This scenario yields the lowest simulation throughput time, which is the primary goal for a contract manufacturer. It is well established that in contract manufacturing, overproduction is not a concern because XYZ Pharma only produces what their customers have ordered. This scenario utilizes cross training and change in batching rules to decrease lead times. One difference from the current state with regard to cross training is the increase in shifts that are available for the new filling machine to operate, due to a greater number of operators able to run the machine. The most significant factor that was found through the statistical analysis was the batching rule changes. These changes affect the entire process from arrival of raw materials to departure of finished goods inventories. Arrival of raw ingredients are limited to quantities required for formulation of bulk drug at that time and are stored directly outside of the manufacturing areas. The replacement of the transfer vat with a smaller, more flexible, and mobile drum has decreased waiting times during transfers and setups, subsequently decreasing the cycle time by approximately 90 minutes. Another benefit of earlier bulk drug substance arrivals are the completion of final adjustments to the filling equipment sooner. Waiting times also have been decreased because WIP is no longer waiting to batch prior to movement. Bulk drug in drums, WIP totes, and finished goods pallets are all moved individually, and require fewer quantities to be moved. The cumulative effects of these changes result in a lead time of approximately 2130 minutes, which is about a 75% reduction of time. It is important to note that this future state value stream map indicates the time to produce the first pallet of finished goods inventory. In the future state, the company may not have to batch the finished goods prior to shipping. Therefore, this estimate is useful to determine how quickly finished goods would be ready to begin shipping if there was flexibility with the customers to receive goods in more frequent smaller delivery amounts, while still complying with regulations, and if it did not increase transportation costs. The classic Economic Order Quantity model continues to apply with a trade-off between holding inventory, while large batches are completed versus paying order set-up costs for more frequent, smaller batches. For FDA validation purposes, the defined batch size has not changed, but movement within the facility is allowed in smaller transfer vessels and in smaller quantities of tubes and cartons.

Recommendations were made to the company, Pharma XYZ, based on the results of the Value Stream Mapping and simulation activities. The company, which is too small to employ industrial or manufacturing engineers of their own, benefited from seeing models of both the current state and an envisioned future state of their operations, which employs various potential lean techniques. The project was completed as part of a graduate student thesis project, and a team project for a class, and, had no cost to the company. To date, they have not specifically implemented the described recommended changes, as their focus is on daily production and regulatory compliance, as opposed to process improvement.

Conclusions

The focus on product quality is extremely high in the pharmaceutical industry to avoid potentially fatal and costly defects. With the advent of pharmaceutical quality systems, the industry is moving away from end product testing and toward in process testing, which has been used for many years by other industries. Some pharmaceutical production facilities have a "Job Shop" layout, where all formulation equipment is grouped near each other and products are transported in large vats for filling and on palletized totes of tubes for other work in process. A redesigned layout would place all of the equipment needed for a particular product in close proximity to each other in order to achieve a more continuous flow through the facility.

Lean manufacturing techniques should be explored in the pharmaceutical industry to improve current systems. Lean techniques also should be utilized early in the development of new systems. This case study represents a number of possible opportunities for specific areas of improvement as well as suggesting an overall change in the manufacturing mindset. The pharmaceutical industry can learn a great deal from outside industries, such as using industrial engineering and lean techniques to enhance competitiveness and thereby help to ensure solvency.

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Retrofitting CIP into API Plants

by Nigel A. Fletcher

This article describes the physical modifications and additions retrofitted into existing plants to incorporate CIP technology and some of the techniques that can be used to 'stretch' the existing CIP systems for best effect.

Introduction

With the ever increasing demand for improved quality, the API industry has turned its attention to cleaning. Every aspect of cleaning is being considered from the use, or not, of detergents, to the methods used and how these affect the final quality of the API product. This is not a problem for new plant designs where cleaning and Cleaning-In-Place (CIP) can be integrated into the design, but it is a different matter for API facilities already in production.

Five to 10 years ago CIP was simply something that only really happened in plants producing high quality products or those that produced sterile, aseptic, or special products. Many plants appear to have paid scant regard to cleaning, restricting cleaning to boiling out the reactors, and cursorily, spraying centrifuges and dryers to remove 'gross' contamination. Little attention was paid to out-of-the-way places in nozzles, valve bodies, or vent lines etc. because the strict quality requirements in place now were not in place then. This was possibly because the APIs produced tended to be less potent and could tolerate a small amount of contamination from another product without there being a serious risk to the end user.

Although there are simple solutions to the cleaning problem, the most difficult part is retrofitting CIP into a plant not originally designed to be cleaned. This particularly applies to the integration of CIP as part of plant retrofits, turnaround optimizations, or plant extensions. Let us be clear at this point that CIP is being added to plants not only to improve product quality, but also in the case of multipurpose plants, to reduce the time between product campaigns. Thus, CIP retrofits are being seen as a way of improving plant productivity (paying for itself) as well as satisfying improved quality requirements. This article will provide some examples of potential solutions that could be used to improve cleaning. Many 'solutions' in this article are specific to a particular plant or installation, but are intended to illustrate cleaning/CIP can be retrofitted even in older plants. In the examples used, operator time has been reduced and plant turnaround times have been improved. Time savings range from a few hours to as much as several shifts. The precise time saving is, of course, dependent on the extent of the plant modification, when it is modified and how much automation has been included in the change. Many of the changes outlined in this article were installed piecemeal to fit with the manufacturers' budgets and manufacturing timetables.

Things have changed in the

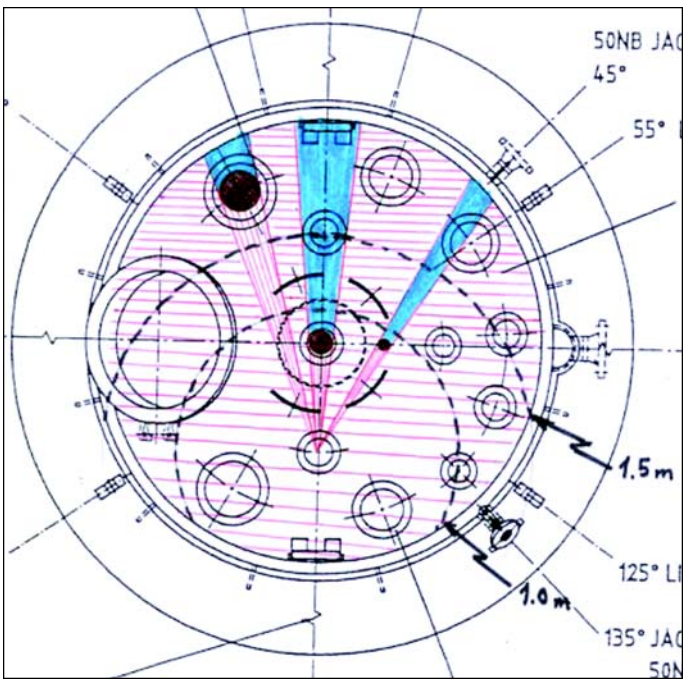

Figure 1. Spray pattern in a typical API reactor.

past five to 10 years in quality terms and there is a significantly greater requirement for plants to be demonstrably clean and prepared for processing the next product. While this QA requirement is perfectly reasonable, it has led to a situation where new plants have to be designed and constructed to integrate CIP into their operation, but older plants have been left behind. As these plants often have a considerable residual life before they are decommissioned, the operating company is left with the situation of having to implement a cleaning regime in a plant that was not designed for it. It is at this point that consultants get called in to 'solve' the situation as they are specialists and the operating company personnel are unlikely to have the necessary time nor expertise to perform the analysis and design required.

Having identified the problem, the client usually asks if the recommended solutions also can improve/reduce the exposure to the operator, reduce the turnaround time between product campaigns, reduce solvent usage, reduce waste disposal costs, and reduce environmental impact from cleaning operations/wastes. Ideally, the consultant's proposals will achieve all of these, but their main purpose must be to improve product quality.

Where the Problems are Found

Since there are many areas in an API plant that need cleaning and the potential solutions would number in the thousands, this article will focus on a few examples in a number of key areas in an API plant, including:

- reactor heads and some of the associated overheads
- Nütsche-type filters
- centrifuges
- dryers

Other considerations are the protocols used for the cleaning and the 'solvents' used. These critical areas are often overlooked or, worse, treated as unimportant. Undervaluing of the cleaning protocol often manifests itself in 'one protocol cleans everything' or 'if it is wetted by the CIP, then it will be cleaned.' The same applies to the choice of cleaning solvent where 'one solvent does all the cleaning,' i.e., is the 'universal' solvent. These inappropriate attitudes are all too prevalent and the industry needs education in this area; however, this subject will not be addressed in this article.

API Reactors

Reactors in API plants have a relatively common design, whether fabricated in glass-lined carbon steel or stainless steel, and generally consist of a vertical shell, closed top and bottom with dished ends. Nozzles on the top head provide the majority of the access to the vessel. These nozzles are closed by valves, agitators, baffles, or dip-pipes, and are often cited as the areas where the client company has most problems with residues. Other 'dirty' areas are crusty product rings part way up the vessel sidewall and underside of the agitator blades.

All of these areas can be cleaned, but there are two principal approaches that can be adopted. The first is the most simple – open the manway and lower a high pressure rotary spray unit into the vessel. These provide thin jets that impact on the walls in a defined pattern that progresses over the whole interior surface. Cleaning is achieved mainly by 'impact cleaning.' This is very effective and many suppliers of these types of units will show photographs highlighting what has been achieved by their units. This is a perfectly acceptable solution with many benefits, but there are two reasons why many companies will not adopt this solution. The first is that these systems use water and there is a concern that the dirt will not be properly dissolved and removed especially from 'difficult' areas deep in the recesses of nozzles. Secondly, the vessel to be cleaned needs to be opened to allow the insertion of the (bulky) spray unit. If the product to be cleaned is highly potent or toxic, then there is a serious risk that the operators could be exposed/contaminated. These objections can be overcome, but the cost and the operational inconvenience can be high and so the integration of these systems is low.

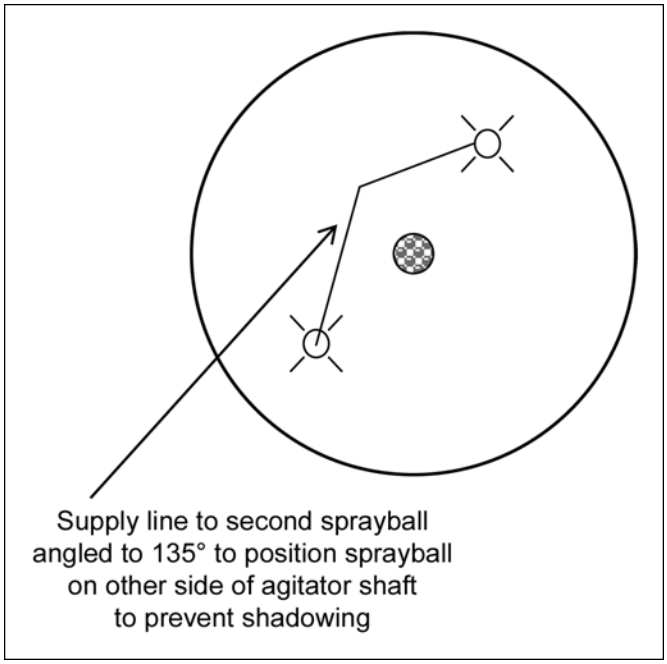

Figure 2. Second sprayball installation in a reactor with only one access nozzle for CIP sprays.

The second technique is to permanently install sprayballs or nozzles to allow CIP. This technique is commonly used, but can fail easily. The first difficulty to overcome is that there is often only one nozzle that can be adapted to install a spray device. This is doomed to failure as a simple pattern analysis shows - *Figure 1.* Objects such as the agitator shaft impede the spray and the vessel is left dirty in the 'shadow' area. The dark areas in the Figure show the untouched and uncleaned areas. A point also worth noting from the pattern is that if the throw of the spray device is inadequate as shown by the 1.0m and 1.5m dotted lines, it is quite clear that parts of the vessel will not be cleaned adequately.

If only one nozzle is available, the installation of a second spray device is possible (Figure 2) by means of an internally

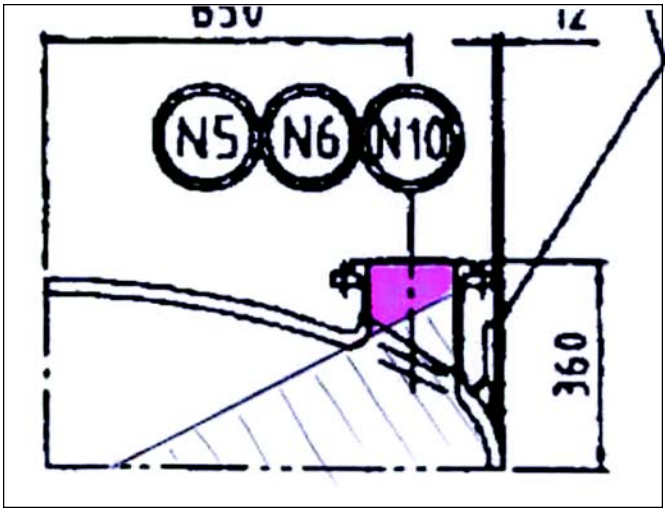

Figure 3. Nozzle shadowing resulting from the spray not fully penetrating into the nozzle.

mounted angled supply line from the first sprayball's dip-pipe. This adds a second spray on the opposite side of the vessel so effectively eliminating the shadow area of the agitator shaft and other obstructions.

This is not a perfect solution because the installation of piping inside this type of vessel is not ideal and finding a second nozzle would be a better solution. This can involve a difficult analysis of the vessel processes and may require some re-piping of the top head of the vessel.

However, it is rare that the simple installation of two sprayballs will clean the top head nozzles as Figure 3 suggests. Although the shadow area in the nozzle, shown in Figure 3, is small, it is difficult to clean. There used to be a mistaken belief that 'rebound' washing would occur in these areas. This idea meant that the spray hitting one side of the nozzle would bounce off the nozzle wall and hit the side in shadow. Thus, the shadow areas would be wetted, and so in time, would be

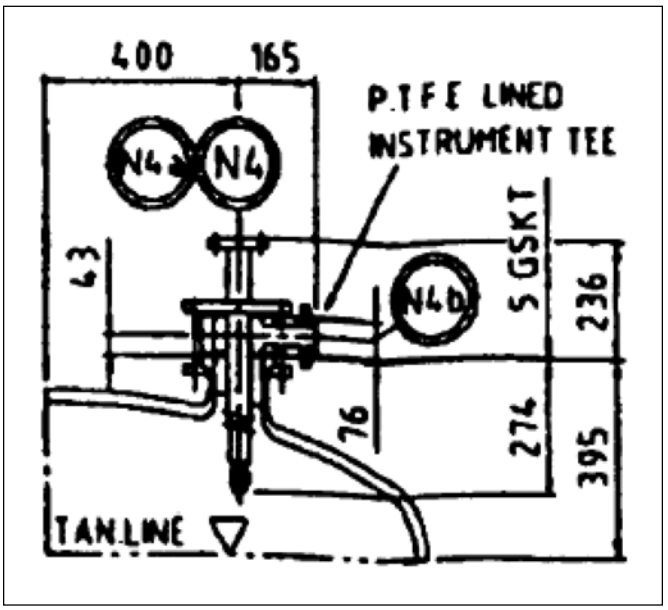

Figure 4. 'Flushable' nozzle which includes an instrument tee which can be connected to the cleaning system.

cleaned. While rebound washing can occur, it only happens where the jets or sprays are moving at high velocity.

High velocity jets usually only occur locally to the sprayball so by the time they reach the deeper recesses of a nozzle, they simply do not have the energy to rebound according to the theory. Thus, rebound washing does not generally work. So if this method is not feasible, then this means that an alternative must be found. Washing the deep parts of a nozzle is, of course, trivial if the nozzle can be directly flushed by solvent from a bulk system or can be flushed by condensate from a condenser. Where this is not possible, the use of a spray ring (Figure 5) or a standard instrument tee (Figure 4) should be considered.

Both of these installed at the top of the nozzle allow cleaning fluid to be introduced to produce the desired cleaning effect. The spray ring, supplied by a number of manufacturers, can be used to flush nozzles that have dip-pipes or baffles.

Putting all the above ideas together achieves very good cleaning of the top head and nozzles of a reactor. However, this does not address other reactor cleaning problems, such as a crusted ring of product on the side wall or deposits on the underside of the agitator blades. In these cases, the use of high pressure washers or traditional boil-out techniques are probably the most effective short-term solutions. If the crusted materials are sufficiently soluble, the solvent running down the walls from the sprays in the top head may slowly remove the crusted ring. At this point, it is worth commenting that the choice of cleaning solvent is critical for these more difficult cleaning duties and an area where many fail. Detailed analysis of the cleaning problems is required at this point. This is not covered in this article.

Whatever solution has been adopted, the spent CIP solution flows out of the base of the vessel through the bottom outlet valve. The supply of cleaning solution from the sprays must be such that flooding in the bottom of the vessel is avoided. If flooding does occur, this can give rise to re-deposition of dislodged product and a cleaning failure.

This bottom outlet valve is another area where contamination occurs and the selection of the right valve can improve this situation. For example, a ball valve can be purchased with side ports to allow flushing of the body cavity. If the valve type is unchangeable, repeatedly opening and closing the valve during the cleaning sequence may help. If this technique does not work and no alternative valve can be installed, dismantling and manual cleaning may be necessary.

Nütsche Filter Cleaning

A review of Nütsche-type filters reveals that they closely resemble vessels. The Nütsche filter and filter-dryer are similar machines in many respects and suggestions in this section apply to both types. However, the dryer has the added capability of heating cleaning solutions. The top head is very similar to that of a vessel with numerous nozzles, dip-pipes, and an agitator. Thus, the solutions that serve to clean vessels also serve to clean the top heads of filters and filter-dryers. However, there are exceptions including which is the

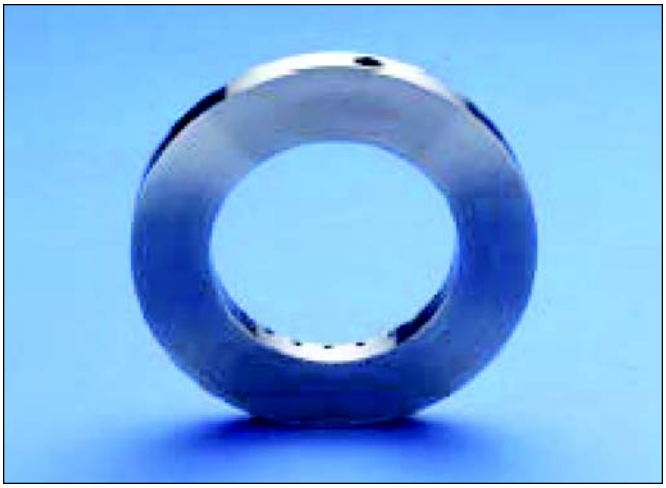

Figure 5. Proprietary spray ring to be installed inside the bolt circle of the nozzle and connected to the cleaning system by a short branch.

dust dome or filter that serves to remove dust fines from the vented gas during depressurization or in the case of a filter-dryer, the dry product fines from the drying operation.

The cleaning of this filter is not trivial and the author is unaware of a guaranteed way of achieving complete cleaning of the filter elements. The author is aware of customers' trials that are examining the use of sinter elements and how they may be cleaned in place. The author understands that some results have been validated, but many pharmaceutical manufacturers still have concerns about the cleanability of these elements. If we accept this limitation, we need to consider what we can achieve. This may be gross cleaning of the elements and wetting them in situ (so called Wet-In-Place or WIP) so that they can be removed manually for disposal or washing externally. It must be remembered that there are two sides to the filters – the so-called dirty and clean sides.

For cleaning purposes, both these sides must be wetted although the clean side is not so critical in this respect. Figure 6 shows the access door to the filter dome, normally used to change the filter elements. The door/cover has been modified to include a sprayball (see tri-clamp connection). This spray provides a 180° pattern spray that will wet a reasonable proportion of the elements, but not all of them. Ideally, this unit will have an internal pipe which holds the sprayball and possibly a second sprayball inside the ring of filter elements. However, this configuration is difficult to arrange because the piping and sprays must not interfere with the filter elements. Another spray needs to be installed on the opposite side of the housing to improve the overall wetting of the elements. It is difficult to be precise as the number of elements varies according to duty, size, and make of the Nütsche filter.

An important point to note is that the modification to install the sprayball is restricted to a part (the access door in this case) that can easily be removed from the machine for modification in the engineering workshop. If the filter is a filter-dryer, it is also possible to use the explosion relief hatch (if installed) as a suitable nozzle that can be modified to provide sprays into the filter dome. A similar modification can be made to the top head of the filter dome on the clean side where a 180° pattern sprayball can be installed to spray the top end of the filter candles. This gets the internal surfaces of the filter candles wet as well as the top head of the filter dome. Thus, spraying both sides of the candles means that they are safer to remove for manual cleaning or disposal.

There is an important point to be noted in relation to the two modifications described above. Where possible, all CIP retrofits should be carried out either by insertion into existing nozzles or by modification of parts that can be removed from the plant to a suitable workshop. In the case of the filter dome, this means the filter access door/hatch and the top head, which is usually flanged and bolted to the body. Where a nozzle needs to be modified – then whatever its function – it can often be modified to include an extra connection for CIP. This is where the experience of the consultant can be useful to recommend a solution that needs unusual or lateral thinking.

Peeler Centrifuges

If the Nütsche filter is not the main means of isolating the product from its mother liquor, a centrifuge is used. These come in a variety of types, but the two principal types encountered are the inverting bag or peeler centrifuges. This article will consider the latter, peeler, type. Retrofitting CIP into and around the inverting bag centrifuge will be considered in another article.

The peeler centrifuge is very complex internally. There is the feed pipe, the solids peeler mechanism, solids level measurement device, wash fluid inlet, splash guard(s), and basket assembly. If the machine is reasonably modern, there also may be some internal spray devices for CIP/cleaning although these may not be as useful as they appear. All of these items are housed in a large outer housing, which wraps around the basket and out of the bottom of which passes the mother liquor to an external collection system. The housing is closed by a full face door, which acts as the mounting point for the peeler mechanism, feed pipe etc. and has a large diameter seal with the main housing.

This main seal is the source of many problems. There are few centrifuges where this seal does not leak, if not regularly, then frequently enough to be a source of irritation to the operating staff. This leakage is a problem for cleaning as the most effective CIP mechanism for this type of machine is to partially flood the machine and turn the basket round slowly. This 'washing machine' action is very effective for cleaning the basket and filter media although not always successful for the solids outlet chute. If it can be engineered and will tolerate it, without leaking, then reverse flooding the solids outlet chute can be very effective. If flooding is used , a short internal spray may be needed to reduce the risk of a residual 'ring' at the surface of the cleaning 'pool.' This final washdown also will remove re-deposited solids after the flood solution has been drained away. The list of difficult areas to wash in the peeler centrifuge can be summarized as follows:

- behind the basket
- clamping bars for the filtration media
- solids discharge chute

Figure 6. Nütsche dust filter showing the access cover fitted with a cleaning nozzle.

- around mounting screws for internals
- behind cover plates, e.g., end of the peeler arm
- inlet and outlet nozzles on the main housing

Flooding the machine can deal with some (but not all) of these quite effectively, and if the machine cannot be flooded due to a poor door seal, other measures need to be considered.

If there is an inert gas nozzle on the back of the housing, this can be adapted to incorporate a low profile spray nozzle with 180° spray pattern, which can provide a reasonable wash behind the basket. If this is not available, the vapor vent on the top of the housing can be adapted in the same way with a low profile, 180° spray pattern, spray nozzle. This does not target the back of the basket in the same way, and results can be mixed, but can be improved if the basket is rotated slowly, simultaneously with spraying. Recirculating the cleaning fluid helps combined with spraying for 15 to 20 minutes. Do not continue with a single CIP operation for more than 30 minutes continuously because it rarely increases the quality of the end result. These methods cover washing behind the basket, but do not address cleaning areas inside the basket.

If the machine has been fitted with a spray arm for injecting wash fluid during operation, it can be used to provide a very satisfactory method of introducing cleaning fluid to the basket. An example is shown in Figure 8. This can be used to wash the media clamping bars, but it should be pointed out that this system does not usually operate at a sufficiently high pressure and so this may require a pressure boost from either a pump or increased pressure in the source vessel. Choice of cleaning fluid is critical as the cake wash sprays will not provide impact cleaning jets so the cleaning fluid must be able to dissolve the product.

In the example shown in Figure 8, the centrifuge has been fitted with various spray devices. One above the slurry feed for general washing of the internal area of the basket and a second one immediately behind the peeler arm (seen in the top left of the photograph) and these provide for fairly good cleaning of the internals of the machine. However, they do not clean mounting screws or studs or behind cover plates. A reported problem is the ingress of product behind the cover plate at the end of the peeler arm. Commonly, these plates are mounted with a metal to metal seal which is not always a good seal. The result is that a brown, sticky residue can be found behind the plate when the maintenance team carry out work on the mechanism. This leakage is caused by distortion or damage of the cover plate. The solution is to retrofit a very thin (0.25-0.5 mm), full-face PTFE gasket under the cover plate with its edge flush with the outer face of the peeler arm and cover plate. When the cover plate is re-bolted, then the gasket performs as any other gasket and seals the gap effectively. This eliminates the cleaning problem permanently.

A similar problem is seen around the mounting screws for the peeler knife where product is forced due to the product pressure during the peeling operation. While the fitting of a PTFE gasket may solve this problem, it is likely to return and so a simpler arrangement is to try to space the knife away from the support bracket. This larger gap/space is a lot easier to wash out than the narrow one where the knife is bolted directly to the support.

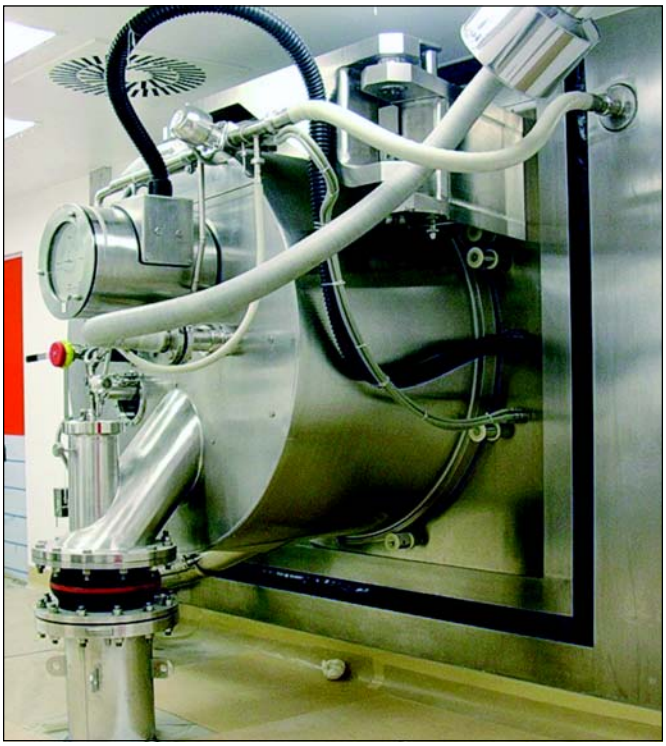

Figure 7. Typical peeler type centrifuge.

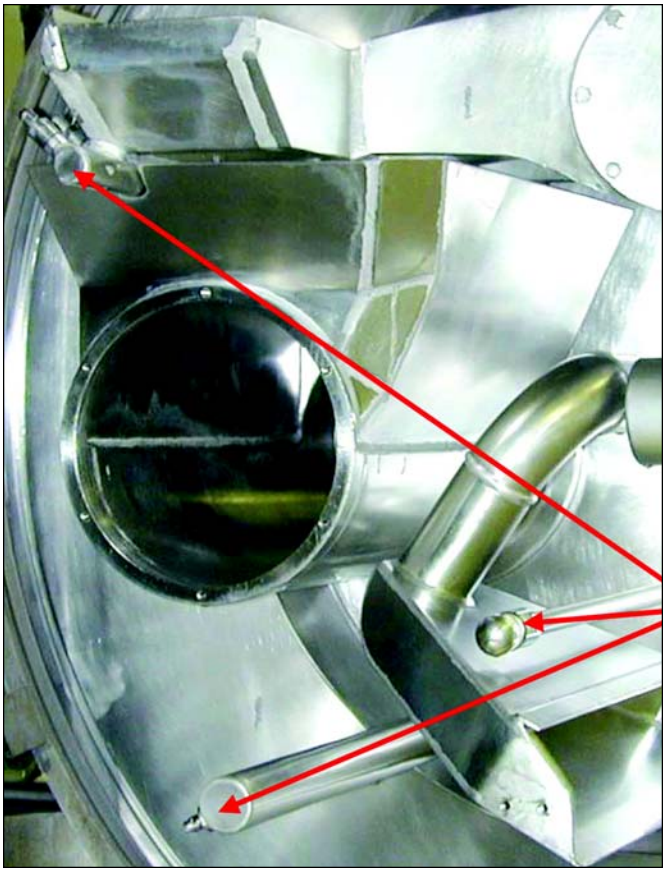

Figure 8. Typical spray installation in centrifuge body as shown by the three arrows.

Centrate Liquor Outlet and Piping

The inlet and outlet (mother liquor) nozzles need to be considered. Generally, the inlet nozzle is not too much of a problem as the slurry is fed into the machine at a reasonable velocity; so, this nozzle does not get particularly contaminated and can be cleaned by pumping cleaning solution through it at high velocity with solution recirculation if possible. The outlet or mother liquor nozzle is rather different. The flow at the start of the centrifuging operation is high, but when the main dewatering phase finishes, the liquors pass through this nozzle as a spray or at low flowrate. This leaves the nozzle and downstream mother liquor system contaminated. Normally, this is not a problem as it is rare that the mother liquor is the desired product and the mother liquor system is usually beyond the GMP boundary. However, if the product is the mother liquor or there is a cloth/media failure and the batch needs recovery, the cleanliness of the mother liquor system becomes important. The ideal solution is to flood the base of the centrifuge together with the mother liquor system. However, this is not always possible and an alternative solution must be found. Normally, the mother liquor outlet has an elbow on it pointing down for gravity drainage of the liquors or, occasionally, the elbow is horizontal. In either case, the solution is to replace the elbow with a tee. This is an opportunity to create a new access point onto the system into which a spray device may be fitted. The only disadvantage with this method is that the tee where the

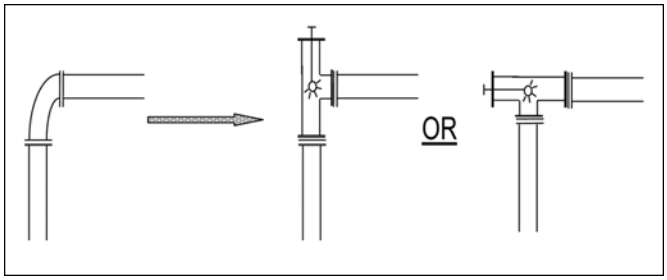

Figure 9. Spray installation in elbow.

spray unit is fitted becomes a 'dead area' or an area for contamination and must be cleaned. Alternatively, a short spray 'bubble' can be fitted on the end of the elbow which virtually eliminates the dead area. These alternatives are shown in the illustrations in Figures 9 and 10.

The spray bubble can be mounted on a short reach tri-clamp nozzle 'stabbed' into the line on the corner of the elbow. Its spray pattern can be adjusted to jet into the centrifuge outlet and also simultaneously down the mother liquor piping.

Vertical and Horizontal Axis Dryers

The final item of equipment to consider is the dryer, which is available in a number of different formats. Typically, there are two types in most pharmaceutical plants: the vertical axis conical dryer and the horizontal axis paddle dryer. It can readily be seen that the conical dryer has many similarities with the reactor and the solutions for cleaning these machines are broadly the same as for the reactor. Flood washing is a common method, but suffers the problem of a large volume of contaminated waste solvent. A considerably better method is to use a tank washer lowered into the body through a suitable nozzle and to recirculate the wash solution.

This type of machine is not difficult to wash compared to the horizontal axis paddle dryer. This is because the blades on a paddle dryer are usually arranged to sweep nearly 100% of the internal surface of the dryer body. This is a problem because there is no point to introduce a spray device to

Figure 10. Bubble spray unit.

Figure 11. Extending spray unit which extends when the cleaning solution pressure is high enough.

intrude inside the body. This means that you cannot use the most effective method of cleaning with the paddles turning. If the paddles are static, there is a concern that areas may be missed due to 'shadowing' and not cleaned properly. A common solution to this situation is to flood the body and agitate the solution using the paddles. This is effective, but uses a large amount of solution and can take a considerable amount of time if the method uses total flooding. The target in such a situation is to reduce both time and solvent usage.

If the idea of flooding is disregarded, two possibilities can be examined: static or dynamic washing. In the case of static washing, the paddles are brought to a standstill at a known position and a sprayball inserted into the body through the top manway or a nozzle on the top of the machine. In this case, the spray is operated, removed, the paddles rotated 90°, the spray reinserted, the spray operated a second time, and this sequence repeated until the desired end result achieved. Washing solutions can be re-circulated or reused until exhausted so that the total volume of solution is kept low. There are clear risks with this approach, for example, operating the paddles without having withdrawn the spray device. These can be reduced by careful operating practice and having a PTFE dip-pipe and sprayball, which will shear off if struck by the paddles without damaging the dryer. Alternatively, the sprayball can be the type which extends from a housing mounted on the nozzle when there is sufficient pressure of cleaning solution. An example is shown in Figure 11. This type usually rotates and provides good coverage of the internals. The same sequence of withdraw, rotate paddles, insert and wash, can be used with this type, but it requires less operator input and can be automated.

While static washing techniques have many benefits, the alternative dynamic washing technique is usually more effective. This is because the cleaning fluid can often contact all the internal parts of the machine compared to the shadowing of the spray in the static situation. But as stated above, this is more difficult as the opportunities for this in the paddle dryer are so limited.

Only if the body has nozzles at each end that can be adapted is there a realistic opportunity of undertaking dynamic cleaning. It should be noted that a spray mounted in the end of a cylinder can only spray about half the cylinder and opposite end as it is operating from inside a nozzle. The simple diagram in Figure 12 illustrates this with the dark areas showing unwashed sections. Thus, two such sprayballs would be required to cover the whole of the interior of the dryer.

The throw and spray angle of the spray devices need to be selected carefully. The illustration omits the paddles and these would interfere with the spray patterns from the two spray devices. However, as they are rotating during the washing cycle, the interference is significantly reduced for in one position the paddles obstruct the spray, but a few degrees of rotation later they are less of an obstruction. This aspect of the cleaning has to be checked by spray pattern analysis for the paddles in a number of positions. This method does rely on the availability of nozzles or manways. Even a manway positioned low down on the body can be used, providing the manway plug can be modified and the cleaning operation is performed with the dryer body being kept fully drained so the spray does not become submerged.

As with the other items of equipment covered in this article, there are many other areas of dryers that need cleaning and they need to be considered separately. These

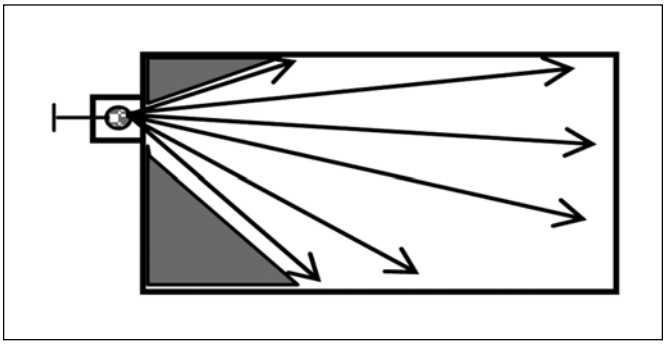

Figure 12. Spray coverage in the cylindrical body of a dryer.

include the solids outlet valve, solids outlet chute, the shaft seal area inside the body of the machine, filter dome, and other nozzles on the body.

Other Equipment and CIP Nozzles

There are many different types of spray nozzles with some nozzles providing uniform mists and others providing highly directed jets. The consultant has to choose which type best suits each particular installation. For example, a spray head with a solid cone spray with narrow included angle may be the correct choice to clean an isolated side nozzle. Each type will achieve a certain degree of cleaning so it is important that when considering a particular installation that the nozzle is chosen to give the correct coverage, the right 'direction', the right fluid velocity if impact cleaning is required, and the right physical size to fit the nozzle or chosen location. If impact cleaning is required, many spray nozzles need to be located well within two meters of the 'target.' Beyond this point, spray nozzles lose much of their energy and become unsuitable for impact cleaning. If the 'target' is more than 1.5 to 2.0 meters from the nearest spray, then as stated above, it may be more appropriate to choose a rotary or powered jet unit which is ideal for this type of duty. Sprayball or spray nozzle selection may take some time to find, but the results will be better if the correct nozzle is used. Where this is not achievable, it is possible to work directly with sprayball manufacturers to achieve the precise flows and spray patterns to solve specific cleaning problems.

The selection of spray device becomes more critical as other items of equipment are considered. Many, including those considered in this article, have either complex structures or deep, difficult to clean areas and specialist advice is usually required to ensure a successful solution to the cleaning problem. Gasket areas are frequently a problem, including body gaskets for vessels or equipment or nozzle gaskets. The gasket is rarely a perfect fit in the flange and there is often a recess or pair of crevices (one either side of the gasket), which can become contaminated with 'product.' Gasket areas have to be very specifically addressed and the solution will depend on gasket location and the cleaning technique used.

For gaskets in a horizontal plane, the risk is usually lower than vertically orientated gaskets. With a vertical gasket the bottom position allows settling of contamination into the crevices and the removal of this contamination is very difficult. Critical to this cleaning is the selection of the correct cleaning agent to dissolve the 'dirt'; frequent refreshing of the solution in contact with the dirt so that the maximum dissolution driving force is available; good agitation of the solution during cleaning, and if possible, the use of high velocity jets for cleaning to give a scouring action. The use of the same techniques is also applicable to horizontal gaskets, but the use of burst washing is advantageous as this allows contaminated cleaning solution to drain away before new solution is introduced. These techniques do achieve most of the cleaning required except where the product is highly potent. In this case, dismantling may be the only method to ensure removal of the product. The author has noted that process transfer piping gaskets are virtually never considered a problem although these gaskets are also in contact with slurries and product solutions. Transfer piping also includes sample points, drains, instrument branches, and various other crevice areas. These are often ignored as they are not visible, but they can be as much a source of problems as any equipment gasket.

Conclusions

Retrofitting of CIP is most successful when simple solutions are adopted with relatively little engineering work on the plant. Most retrofits use existing nozzles or access points into the process, or where this has not been possible, then simple 'stab-in' connections. If the CIP retrofit is too complex, too expensive, or requires a long shut-down period, there will be little incentive to perform the work as it will be perceived to be too difficult. Retrofits should be designed so that they can be performed during a campaign turnaround, during a short shut-down, or as a last resort, during the annual plant shut-down. In other words, the easier it is to fit the modification, the more likely it is to be performed and the greater the chance of the client/operating company realizing the desired CIP goals. Successful CIP retrofits are effective and pay back all of their costs in improved quality and shortened turnaround time.

As mentioned earlier, the protocol used for cleaning also is important. For example, washing continuously may not be as effective as burst washing. The protocol may or may not use detergent, acid or alkaline wash solutions, and these have to be considered when retrofitting CIP or cleaning systems into the plant to ensure they can be removed at the finish of the cleaning sequence. The selection of the correct 'solvent' is, similarly critical, and time may have to be spent reviewing and considering alternatives to achieve the best results. This activity is not a trivial one and requires experience and a structured approach.

In summary, when retrofitting CIP to an existing plant, the consultant has to consider every aspect of the cleaning process, including the plant equipment, the operational requirements, PED (or equivalent pressure equipment codes), and HSE issues. Thus, retrofitting CIP must start with the desired end result or target and accommodate the physical limitations of the plant and result in the potential changes that need to be incorporated into the cleaning protocol. The key to a successful result is not to be too narrow in thinking about physical solutions. Problems have to be analyzed systematically and the resultant solutions kept as simple as possible.

About the Author

Nigel Fletcher joined Foster Wheeler in 1975 and has worked on pharmaceutical projects for more than 25 years. He has extensive experience in very large and very small specialized API and aseptic facilities design. He has been Process Manager for a large number of projects, including multi-

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Solving the Terminology Conundrum

by Robert Adamson, Nuala Calnan, Robert E. Chew, and Steven J. Wisniewski

This article discusses the terms "commissioning," "qualification," and "verification." Do the terms refer to the same or different ideas? How should the pharmaceutical and biotechnology industries use these terms in a consistent and meaningful way? This article provides a compilation of how these terms are used in regulations and by various industries, and provides a proposal for clear definitions to be used as ISPE updates and creates Baseline® Guides.

Introduction

In today's biopharma and pharmaceutical industries, three related, but distinct terms are in common use: commissioning, qualification, and verification. Inconsistent interpretation and application of these terms leads to misunderstandings and inefficiencies on the part of vendors, service providers, and manufacturing personnel from company to company. This article, through a review of the industry definitions and associated practices, is intended to stimulate discussion on resolving this terminology conundrum and provide key input to pending publications of ISPE Baseline® Guides.

In 2001, ISPE issued the Baseline® Guide Volume 5: Commissioning and Qualification, that provided definitions for two of these terms: Commissioning and Qualification. In 2007, ASTM E2500-07: A Standard Guide for the Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment was issued. This standard introduced the term "verification" as a new term for demonstrating suitability and fitness for intended purpose, in place of the terms commissioning and qualification.

The terms "verification" and "commissioning" are used in many industries and have a fairly consistent meaning. The term "qualification" has been used by the regulated pharmaceutical and biotech industries, and can be found in EU regulations, as well as US, EU, and ICH guidance documents. Do these terms mean the same thing (more or less) or do they convey three different necessary and unique meanings?

This article is divided into two parts:

1. definitions and use of the terms found in published regulatory and guidance documents
2. analysis of the terms in light of current practices

The authors invite readers to respond to this discussion, either through the ISPE Commissioning and Qualification Community of Practice (C&Q COP) discussion board, or via direct communication. Such input will be considered when any related updates to the Baseline® Guides are undertaken.

Part I – Definitions and Citations

Qualification

The term qualification, while not specifically found in US GMP regulations, is found in EU regulations, ICH Q7A, and ICH Q9, as well as WHO and other country regulations and guidance documents.

US – FDA

The US GMPs do not explicitly mention the term qualification – in that there is no specific regulatory requirement to produce documents labeled installation, operation, or performance qualification. However, there are clear expectations of a process that demonstrates fitness for intended use and assures proper performance.

US GMPs require that:

- *Facilities be "suitable... to facilitate cleaning, maintenance, and proper operation."*
- *Equipment is to "be of appropriate design... to facilitate operations for its intended use." (21 CFR 211.42, 211.63, 606.40, 606.60, 820.40, 820.60).*
- *Automated systems are required to be "checked according to a written program designed to assure proper performance" (211.68).*

The medical device regulations (21 CFR 820) require that: *"computer software programs shall be validated by adequate and documented testing" (820.61).*

21 CFR Part 11 requires [for those systems to

which Part 11 applies]: *"Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered record."*

The 1987 FDA guidance on process validation first introduced the term qualification in these terms:

Installation qualification studies establish confidence that the process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. After process equipment is designed or selected, it should be evaluated and tested to verify that it is capable of operating satisfactorily within the operating limits required by the process. This phase of validation includes examination of equipment design; determination of calibration, maintenance, and adjustment requirements; and identifying critical equipment features that could affect the process and product. Information obtained from these studies should be used to establish written procedures covering equipment calibration, maintenance, monitoring, and control. ***In assessing the suitability of a given piece of equipment*** *[emphasis added], it is usually insufficient to rely solely upon the representations of the equipment supplier, or upon experience in producing some other product. Sound theoretical and practical engineering principles and considerations are a first step in the assessment.*

The Food and Drug Administration's (FDA's) current thinking on the topic of Active Substances Used as Starting Materials is represented by the ICH Q7A guidance, which includes references to Qualification.

EU – EMEA

EU Volume 4: EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Annex 15 (Qualification and Validation), while specifically referencing both qualification and validation, further outlines in its lead Principle Statement that:

"...manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations... A risk assessment approach should be used to determine the scope and extent of validation."

The Annex goes on to describe the following validation and qualification activities as:

- *The first element of the validation...* ***could*** *be design qualification.*
- *Installation qualification should be performed on new or modified facilities, systems, and equipment.*
- *Operational qualification should follow installation qualification.*
- *Performance qualification should follow successful completion of installation qualification and operational qualification.*

The annex includes specifics regarding the *content* and *execution* of qualification work. Content requirements include the items typically found in an IQ, OQ, or PQ protocol, such as installation verification, collection of equipment manuals, calibration, materials of construction, testing across operating ranges, etc. Execution requirements include:

- *Written protocol specifying critical steps and acceptance criteria.*
- *Protocol reviewed and approved (does not specify by whom).*
- *A report written summarizing results, including recommending changes necessary to correct deficiencies, and documenting changes with appropriate justification.*
- *Formal release to the next step in qualification or validation as a written authorization (does not specify by whom).*

ICH Q7A has been incorporated into the EU GMPs as **Part II: Basic Requirements for Active Substances used as Starting Materials**, which also includes specific references to qualification activities.

ICH Q9 has recently been adopted by the EU as part of its Vol 4 GMPs as **Annex 20.**

ICH Harmonized Tripartite Guidelines

The ICH International guidance documents contain additional references to qualification. ICH Q7A, *GMPs for Active Pharmaceutical Ingredients* states that:

"Before initiating process validation activities, appropriate qualification of critical equipment and systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

- *Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended use.*
- *Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified.*
- *Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.*
- *Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.*

The recent ICH Q9, *Quality Risk Management*, includes an appendix of applications of quality risk management; Appendix II.4 describes how to use quality risk management for facilities, equipment, and utilities, including:

"We leave it to industry to debate these proposals; it is important that we achieve a consistent understanding and application of these terms. Once the debate is complete, it is for ISPE to incorporate the results into upcoming Baseline® Guides."

"...to determine the scope and extent of qualification of facilities, buildings, and production equipment..."

ISPE Baseline® Guide

The 2001 Commissioning and Qualification Baseline® Guide defines IQ, OQ, and PQ in similar terms:

- *Installation Qualification: the documented verification that all aspects of a facility, utility or equipment that can affect product quality adhere to approved specifications (e.g., construction, materials) and are correctly installed.*
- *Operational Qualification: the documented verification that all aspects of a facility, utility, or equipment that can affect product quality operate as intended throughout all anticipated ranges.*
- *Performance Qualification: the documented verification that all aspects of a facility, utility, or equipment that can affect product quality perform as intended meeting predetermined acceptance criteria.*

World Health Organization (WHO)

World Health Organization (WHO) Guidance on Validation defines Qualification as *"Action of proving and documenting that any premises, systems, and equipment are properly installed and/or work correctly and lead to the expected results."*

Commissioning

EU – EMEA

EU GMPs Annex 11, *Computerised Systems* positions commissioning as a component of computer validation:

[The computer validation life] "cycle includes the stages of planning, specifying, programming, testing, commissioning, documentation, operation, monitoring and modifying."

ISPE Baseline® Guide

The 2001 Commissioning and Qualification Baseline® Guide defines Commissioning as *"A well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user that results in a safe and functional environment that meets established design requirements and stakeholder expectations."*

The material that follows this definition positions commissioning as a process that includes inspections, operational testing, and performance testing.

Commissioning as defined by non-drug industries:

- *Building commissioning provides documented confirmation that building systems function according to criteria set forth in the project documents to satisfy the owner's operational needs* (Building Commissioning Association).
- *Commissioning means to verify that the building's energy related systems are installed, calibrated and perform according to the owner's project requirements, basis of design, and construction documents* (LEED requirements).
- *Building commissioning is the process of ensuring that building systems and equipment are designed, installed, tested, and capable of being operated and maintained according to the owner's operational needs* (US Department of Energy).
- *Process of ensuring that new buildings and their systems perform as designed* (Oak Ridge National Laboratory).

Verification

US – FDA

21 CFR Part 820 (U.S. medical device quality system regulations) defines Verification to mean: *"confirmation by examination and provision of objective evidence that specified requirements have been fulfilled."* This definition may be contrasted with the Part 820 definition of Validation, *"confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled."*

EU – EMEA

EU Volume 4: EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Annex 15 (Qualification and Validation), Glossary, includes the same definitions for DQ, IQ, OQ, and PQ as originated in the ICH Q7A document, which defines these activities in terms of a *"Documented Verification."*

ASTM E2500 defines *Verification* as: *"A systematic approach to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses all types of approaches to assuring systems are fit for use such as qualification, commissioning and qualification, verification, system validation, or other."*

According to ISO 9000:2000 Verification is defined as the: *"Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled." Objective evidence is defined as "data supporting the existence or verity of something."*

IEEE Standard 1012-2004, *Standard for Independent Verification and Validation*, defines Verification as: *"Process for determining whether the soft-*

ware products of an activity fulfill the requirements or conditions imposed on them in the previous activities."

Of note, the definition of Validation in IEEE standard 1012-2004 is: *Validation – process for determining whether the requirements and the final as-built system or software product fulfills its specific intended use.*

Part II – Analysis in Light of Current Practices

The question is, do these three terms – verification, commissioning, qualification – describe the same or different things?

The simplest term to analyze is *verification*. For the most part, the definitions of verification are consistent (as found in 21 CFR 820, ISO 9000, IEEE 1012-2004, and other sources). These definitions focus on the idea of "confirming, through objective evidence, that a specified requirement has been met (fulfilled)." ASTM E2500 defines Verification using the same base word: "to verify." The standard assigns a broader mission for verification, "a systematic approach to verify... systems and equipment are fit for intended use, properly installed, operating correctly... an umbrella term."

The term *commissioning* is more complex – different organizations in our industry assign different meanings to commissioning. Some view it as the work that is necessary to make a piece of equipment ready to start, i.e., the pre-functional inspections and checks (sometimes referred to as pre-commissioning). Other organizations are more aligned with the 2001 Commissioning and Qualification Baseline® Guide definition, which positions commissioning as a project lifecycle activity that consists of a planned, managed, and documented approach to bringing equipment or systems to a full operational state, and demonstrating conformance with specifications and user requirements. Depending on system complexity, the start-up, setting to work, regulation and adjustments, cycle development, and related work can be significant, not to mention the actual inspections and testing activities. Using this idea of commissioning means it may include a number of diverse activities requiring significant planning and coordination. Other industries define commissioning in terms that emphasize the performance testing of a system or group of systems against end-user requirements.

Finally, *qualification*, as shown above, is specifically mentioned in EU regulations as well as ICH Q7A and ICH Q9. Although the word Qualification is not explicitly mentioned in US GMP regulations, the concept of equipment and facilities being ***suitable for their intended use*** is clearly referenced. Furthermore, US GMPs do contain a requirement to validate certain automation systems, and everyone recognizes that the typical current industry practice is to include installation, operation, and performance qualification.

How do we reconcile this *Terminology Conundrum*? Are we to adopt the stance that if one uses the term "verification," that this implies a science- and risk-based approach as defined by ASTM E2500, whereas use of the terms "commissioning" and "qualification" implies a more traditional approach not based on science and risk? Or do these three terms describe three different ideas or processes, each of which can have a useful place in our approach to delivering equipment, systems, and automation that are ***suitable for their intended use?***

1. Irrespective of an organization's regulatory compliance strategy of using either a program labeled "Verification" or "Qualification," facilities and equipment will still need to be *commissioned* as defined above. Therefore, a well planned, managed, and documented effort to start-up and place into service a system, equipment, or combination thereof, including automation, will need to be undertaken – *commissioning*. This phase includes safe start-up, setting to work, regulation and adjustment, cycle development, etc., which contribute to achieving a full operational state.

2. A significant amount of valuable verification work may occur during this commissioning process, e.g., physical inspections, documentation reviews, operational testing, and performance testing. Retention of the term *commissioning* for this complex process of placing equipment into operation may therefore be appropriate, and for this term to extend to and include, the verification work that may occur at this time.

3. Assignment of the term *verification* to the act of confirming, through objective evidence, that a particular specification has been met is appropriate, given the common understanding of the meaning of this term and its use by the medical device regulations, ICH guidance, etc. This confirmation can take many forms: physical inspection, operational testing, performance testing, as well as other methods such as review of a material certification document, software code inspection for conformance to programming standards, etc.

    a. This *verification could* occur at any point in the overall lifecycle of, design, fabrication, installation, pre-start-up, start-up, or initial operation of the overall system or process.

    b. This *verification should* occur at the most appropriate point in the overall lifecycle – as defined and justified though the Quality Risk Management (QRM) process.

    c. This *verification* work *may* occur during factory acceptance, site acceptance testing, installation, or formal commissioning phases of the project.

    d. This *verification* work is performed under *Good Engineering*

Practice (GEP), and executed by appropriate Subject Matter Experts (SME).

4. A common requirement of all of the regulatory references above is that facilities, equipment systems, and associated automation are documented and authorized as *suitable for the intended use*. The determination that systems are *suitable for their intended use* present a difficulty in ensuring that there is a clear understanding of what suitability means. Suitability for use can be defined in many ways, and there may be different possible design solutions, which will achieve a desired result. We strongly recommend that *suitability for use* is not equivalent to meeting a particular engineering design specification. Instead, we propose that *suitability for use* be defined in terms of ability to meet product and process requirements necessary to manufacture a quality product, and ability to provide sufficient control of risks to the patient (this is what ASTM E2500 has as its approach). Suitability for use is therefore linked to:

   a. A specific manufacturing process and product (or class of products).

   b. It is based on knowledge of the process and an analysis of risk to the patient.

Qualification should mean that equipment has been found to be suitable for its intended use, based on the design criteria (process requirements or equivalent) and the verification work that was performed throughout the delivery process, in particular including that which occurred during the commissioning phase. *Qualified* no longer means the completion of an IQ/OQ/PQ protocol as traditionally formulated – leveraged or otherwise, but is instead a state or condition of certified suitability for use. Graphically, these three terms relate as illustrated in Figure 1.

The question is, can we adopt this

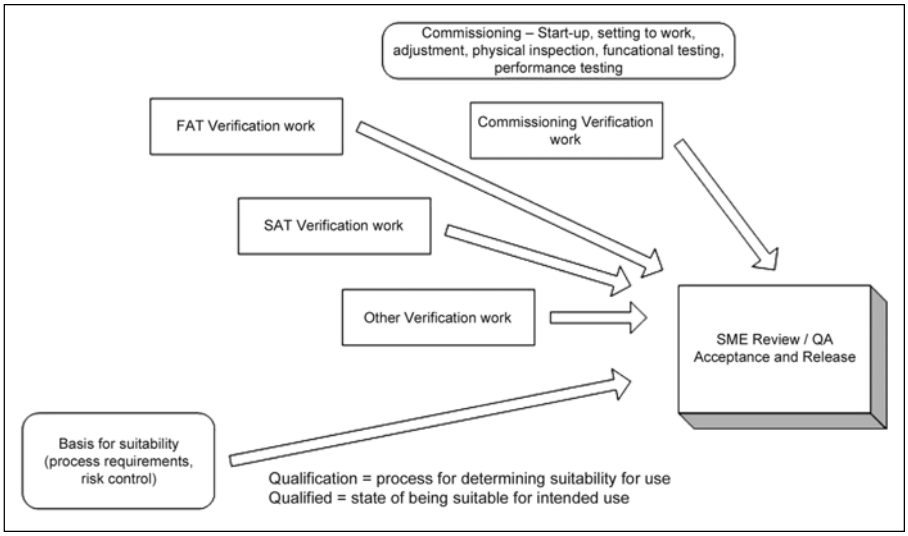

Figure 1. Relationships between the concept of verification, commissioning, and qualification.

use of the word *qualification* without invoking the non-value added practices of the past? Can people get past the habit of creating separate IQ, OQ, and PQ protocols, and instead adopt the idea that qualification is a "state" achieved as shown above? Or should we adopt a different definition? Or drop the use of the term altogether (as ASTM has done), and leave it to the operating company to explain how their program nonetheless meets the intent of EU and other global regulations?

For those who feel the need to have some form of qualification documentation, the determination that equipment is suitable for its intended use could be equivalent to either the Acceptance and Release phase described in ASTM E2500 or to the Qualification Summary Report phase currently undertaken in many traditional compliance programs, as illustrated in Figure 2.

Both these representations and the relationship of the terminology meet the intent of all regulations for demonstrating *Suitability for Use* and do not present non-compliance concerns within the ICH or EU regulated regions. Design qualification also can fit into this scheme should that be desired. Therefore, the idea that suitability for use can be determined based on patient risk

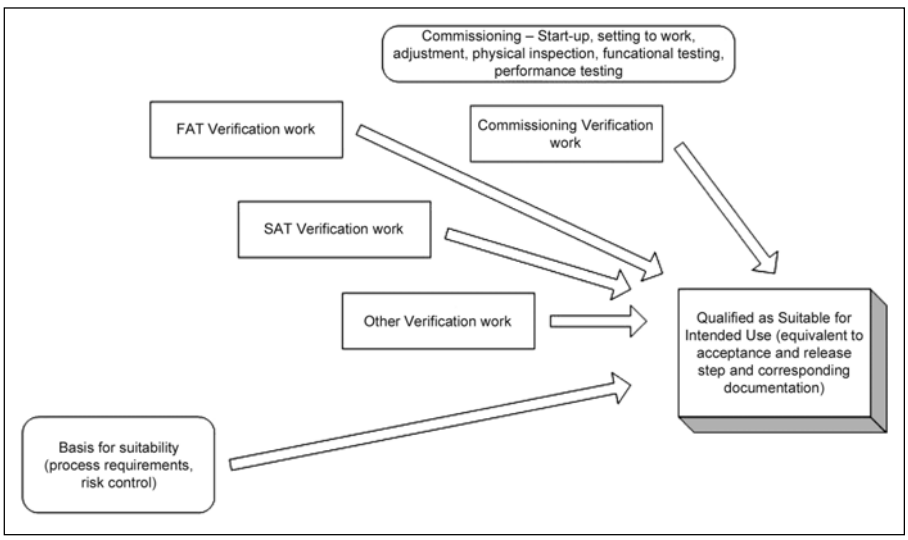

Figure 2. Verification, commissioning, and qualification as distinct steps. Note that in this model, there is no extra qualification-related field work or documentation when compared to the ASTM E2500 process. It is simply a repackaging of the acceptance and release phase for those organizations that require a document labeled "qualification protocol/ report."

and process requirements is well grounded in EU regulations and ICH documents, and is supported by US regulations and guidance documents.

We leave it to industry to debate these proposals; it is important that we achieve a consistent understanding and application of these terms. Once the debate is complete, it is for ISPE to incorporate the results into upcoming Baseline® Guides.

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The authors invite readers to respond to this discussion, either through the ISPE Commissioning and Qualification Community of Practice (C&Q COP) discussion board through **www.ISPE.org/cops** or via direct communication.

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ICH Officials Announce Adoption of Q10 at ISPE's Washington Conference

by Rochelle Runas, ISPE Technical Writer

The final draft of the much anticipated ICH Guideline Q10 (Pharmaceutical Quality Systems) has been adopted by the ICH Steering Committee, ICH officials announced 5 June at the ISPE 2008 Washington Conference: Engineering Regulatory Compliance, Washington, D.C., USA.

During the ISPE educational session, "Regulatory Perspectives on Hot Topics, Regulatory Trends, and Observations," members of the ICH Q10 Expert Working Group, including Joe Famulare, Deputy Director, Center for Drug Evaluation and Research (CEDER) Office of Compliance, US FDA; Moheb Nasr, Office of New Drug Quality Assessment (ONDQA), CEDER, US FDA; and Robert Baum, Executive Director, Pfizer, Inc., delivered the news live via teleconference from the ICH Steering Committee Meeting in Portland, Oregon, USA.

"We have successfully reached Step 4," Famulare told 70 ISPE education delegates. "There is a consensus, we've signed off on it, and it is ready for publication."

Famulare, Nasr, and Baum gave the latest update from the meeting, including highlights of the new document. Q10 includes a revised section on transfer of ownership of products to include additional information addressing quality. The document also includes a robust section on outsourcing with the key message that ultimate responsibility falls on the manufacturer.

Q10 describes a model for an effective quality management system for the pharmaceutical industry that can be implemented throughout the different stages of a product lifecycle. Implementation should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

Having reached Step 4, Q10 moves immediately to the final step (Step 5: Implementation) of the process, which is regulatory implementation. This step is carried out according to the same national/regional procedures that apply to other regional regulatory guidelines and requirements, in the EU, Japan, and the US.

ISPE's Product Quality Lifecycle Implementation (PQLI) initiative is helping industry define areas where they can provide the technical framework for implementation of QbD in regulatory submissions, and turn the ICH Guidelines Q8, Q9, and Q10 into a cross-functional and practical reality.

More information on Q10 is expected to be posted soon on the ICH Web site, www.ich.org.

French Medicines Agency Voices Support for ISPE's Risk-MaPP Guide Principles

by Rochelle Runas, ISPE Technical Writer

Representatives from the French Medicines Agency (AFSSAPS) have voiced support for risk-management principles that underpin ISPE's upcoming ISPE Baseline® Guide Volume 10: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP).

"AFSSAPS is in favor of a risk-management method," said Vincent Gazin, Head of the Clinical Toxicology Unit, AFSSAPS, at the ISPE 2008 Washington Conference: Engineering Regulatory Compliance held June 2 – 5 in Washington, D.C., USA. "We agree to have a scientific discussion more than an interpretation of regulatory text."

The need for dedicated facilities for the manufacture of certain classes of high hazard compounds has been the subject of much debate in recent years. The rationale for separating certain compounds has not always been clear and regulators in the US and Europe are working on revisions to parts of their Good Manufacturing Practice (GMP) guidelines addressing this issue.

The ISPE Risk-MaPP Baseline® Guide shows how the rational use of a science-based risk assessment process can be used to assess compounds, on a case-by-case basis, to support manufacturing strategies that allow for the use of multi-product facilities.

In January the EMEA released a "State of the Status of the Revision of Chapter 5 of the GMP Guide Concerning "Dedicated Facilities," indicating that the EMEA will provide a list of products that mandates "dedicated facilities." The development of this list is pending input from toxicological/pharmacological experts, including Gazin.

The EMEA anticipates that a text will be submitted to the European Commission at the end of 2008 or the beginning of 2009 for public consultation.

At the ISPE educational session, "Risk-MaPP: Application of the new ISPE Baseline® Guide Volume 10: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP)," Gazin and Nicolas Chauviere-Courcol, Mechanical Engineer, gave a presentation on how risk management principles are applied in the toxicological unit of AFSSAPS.

Concludes on page 7.

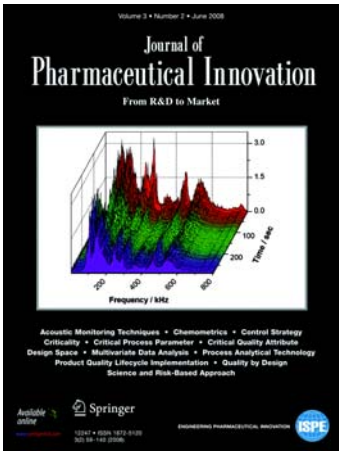
JPI Publishes Ground-breaking Scientific Papers on Reshaping Pharmaceutical Quality

The June 2008 issue of the Journal of Pharmaceutical Innovation (JPI) has published the first scientific papers outlining the progress made on ISPE's Product Quality Lifecycle Implementation (PQLI) initiative.

Written by subject matter experts representing the global pharmaceutical manufacturing industry, these papers present preliminary practical scientific and technological approaches to implementing ICH documents that address Pharmaceutical Development (Q8 and Q8(R)), Quality Risk Management (Q9), and Pharmaceutical Quality Systems (Q10).

The June issue is available in print and with Open Access on SpringerLink (available at http://www.springer.com/journal/12247) with the possibility to comment.

The Product Quality Lifecycle Implementation (PQLI) initiative was launched by ISPE in June 2007 to help industry find practical technical solutions to the challenges of implementing guidelines put forth by the ICH. The first three Task Teams formed focused on Criticality, Design Space and Control Strategy, and how these areas are linked; a Legacy Products Task team has also been formed as the fourth topical area.



Through PQLI, ISPE is providing technical frameworks to facilitate the implementation of Q8, Q9, and Q10 for new products and processes, as well as for existing approved products which could benefit. PQLI will provide better understanding of Quality by Design (QbD) applied to new products and processes, and is developing cross-functional tools valued by both the Industry and Regulatory Authorities worldwide.

PQLI is projected to be at least a five-year initiative that has started with highly interactive fact-gathering sessions held in the USA and Europe. Working groups will continue to collect and process information for distribution as white papers, articles to be published in ISPE's Journal of Pharma-

Continued on page 3.

Employers and Industry Professionals Realize Value of the CPIP℠

As acceptance for the Certified Pharmaceutical Industry Professional℠ (CPIP℠) credential gains momentum worldwide, industry professionals and employers remark on its significance as a powerful tool for professional development and top job performance.

"We intend to strategically use the CPIP credential now and in the future to qualify our team and support their on-going professional development," said Donovan Wearne, CEO SeerPharma Pty., Ltd.

"Our company has a dual career ladder, allowing technical staff to advance to levels that were once only open to individuals on a management track. I challenged those aspiring to Senior Principal Consultant levels to pursue the CPIP credential as a sign of their commitment to being recognized by our industry as a professional with a high proficiency level," said Ken Ewan, Director, Corporate Engineering, Amgen. "The CPIP program's seven knowledge areas allow our managers to identify the focus each technical staff member needs to advance their careers."

"Our industry benefits from employees certified in diverse knowledge, and with the ability to apply this knowledge across all segments of our industry," said Ali Afnan, PhD, U.S. FDA. "In addition, it allows employers to be able to recognize top performers, attain better product quality, industry-wide recognition, and commitment to innovation. Certified employees will become more valuable as team leaders, develop keener awareness, and perform their job more efficiently."

Visit www.ISPE-PCC.org for up-to-the-minute CPIP news, exam information, test dates, and more.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

JPI Publishes Ground-breaking Scientific Papers...

Continued from page 2.

ceutical Innovation and Pharmaceutical Engineering Magazine, leading to detailed technical documents, and training programs that will be produced by ISPE for the industry worldwide.

With the publication of these articles, the ISPE PQLI Task Teams are seeking additional feedback prior to developing their respective positions into technical documents.

The Criticality article describes a mechanism for categorizing and delineating criticality for quality attributes, variables, material attributes and process parameters in accordance with a risk-based approach reflective of QbD principles articulated in ICH Q8R. The article introduces the adoption of a Criticality Analysis Decision Tree to categorize criticality relative to a variable's impact to quality and delineate levels of criticality with respect to relative risk.

Design Space discussions considered the linkage of the patient experience with product quality. It also focused on how risk assessment methodologies integrate with process design principles, provided perspective on selection of mechanistic versus empirical approaches, and clarified how they

Concludes on page 4.

ISPE Singapore Conference and Region's Industry Remains Strong

More than 300 industry professionals from the Singapore region and beyond attended the 8th edition of the ISPE Singapore Conference 1 – 3 June at SUNTEC, Singapore.

"Enhancing Regional Pharmaceutical Manufacturing Excellence," co-organized by ISPE and Reed Exhibitions, addressed the latest regulatory, technological, and practical issues facing both multi-national and regional pharmaceutical manufacturers in API, secondary, and biotech manufacturing, through workshops and various sessions.

More than 35 international regional speakers drawn from the US FDA, WHO, Singapore Health Sciences Authority (HSA), and the pharmaceutical industry shared their insights and views on various issues.

In addition, many of the delegates had the opportunity to visit international pharmaceutical manufacturing facilities based in Singapore. The Interphex Asia 2008 exhibition was also held 2 – 3 at the same venue, in conjunction with the conference.

The strong attendance at the ISPE Singapore Conference is indicative of the speed of pharmaceutical production in Singapore. Despite competition from emerging cheaper manufacturing facilities in markets such as China and India, multinational corporations are already investing some $1.3 billion US dollars in plants in Singapore, and pharmaceutical manufacturing output doubled last year, according to a Channel News Asia report.

Industry professionals engaged in a workshop session during the ISPE Singapore Conference.

A good turnout of delegates at the conference.

The pharmaceutical manufacturing industry in Singapore is expected to stay strong for the next five years, according to Gus Abdallah, Past President, ISPE Singapore Affiliate. "Over the next five years, I would say you are looking at a similar increase, just with the number of pharmaceutical companies coming in here, and speaking with pharmaceutical companies, they really intend to push the output from Singapore, so I see a very health increase," Abdallah said in an interview with Channel News Asia.

Gus Abdallah, Past President, ISPE Singapore Affiliate, on Channel News Asia.

ISPE Manchester Conference to Focus on Product and Process Quality

The ISPE Manchester Conference on Product and Process Quality will be held 15 – 18 September at The Lowry Hotel, Manchester, UK. There will be six seminars on:

- Innovations in OSD Processing
- Barrier Isolation Technology
- Science- and Risk-based Approach for C&Q: Application of the New Baseline® Guide: Installation and Verification in Support of ASTM E2500
- Applying GAMP® 5 Risk-based Approaches in Practice
- Investigational Products – Delivering Quality by Design
- PAT Data Management – Impact on Business Processes Used for Improving Product and Process Quality

The following are descriptions of each seminar.

Innovations in OSD Processing

Learn about new technologies in OSD manufacturing, innovative Quality by Design approaches to product and process design, innovation in other processing industries. The two-day seminar will feature sessions on:

- Nano-chemical Approaches to Controlled and Targeted Drug Delivery
- Lyopan – A Lyophilisation Technology for producing Fast-melting Tablets
- Continuous Processing of OSD
- Scientific Approach to Process Design
- DEM Modelling
- Real Time Statistical Process Control
- QbD and ISPE OSD Baseline® Guide

There will also be case studies on design Space, real-time release, and real time performance management in the process industry.

Barrier Isolation Technology

Through technology updates, case studies, discussion groups and industry comment, this seminar will present the latest developments in barrier isolation technology. Vendors will briefly introduce the latest and most innovative technologies, while case studies will focus on the implementation of recently developed isolators.

Concludes on page 5.

JPI Publishes Ground-breaking Scientific Papers...

Continued from page 3.

may be applied to legacy products, and biotech products. The team also discussed a number of useful methods for depicting design space. The team recognizes that organizations may choose different, scientifically defensible means to arrive at design space.

The Control Strategy team has proposed a Model process to enable a clear logic to be used on how a Control Strategy differentiates between patient and business requirements, as well as showing the linkage from Critical Quality Attributes, e.g. via Critical Process Parameters, to individual controls such as analytical, PAT, engineering, procedural or other controls. The Model illustrates how the Control Strategy embraces ICH requirements (product and systems). It will also provide a discussion bridge between disciplines such as development scientists and controls engineers.

The Legacy Products team has started work and will produce a paper later in 2008 in JPI. The team is considering how to derive business benefits by reviewing knowledge about a product and/or process and proposing opportunities for flexibility in a post approval regulatory application for an approved product. A suggested workflow process will be produced and supported by case studies.

"The publication of these papers is a milestone event as it will bring together an industry view of a risk- and science-based design approach for pharmaceuticals," said James C. Spavins, Vice President, Global CMC, Pfizer. "The use of risk-based analyses to determine design constraints and then determine appropriate controls is a foundational process for the advancement of science and technology - it is time for pharmaceutical professionals to have an aligned view."

The Journal of Pharmaceutical Innovation (JPI) is an international, multidisciplinary peer-reviewed scientific journal dedicated to publishing high quality papers emphasizing innovative research and applied technologies within the pharmaceutical and biotechnology industries. JPI's goal is to be the premier communication vehicle for the critical body of knowledge that is needed for scientific evolution and technical innovation. The journal brings together in a single source the most exciting work from a variety of fields - from R&D to market. JPI publishes Perspectives, Case Studies, Research Letters, Research Articles, and Reviews in the following categories: materials science; process design, optimization, automation, and control; product design; facilities; information management; regulatory policy and strategy; supply chain developments; and education and professional development. JPI is published by ISPE in collaboration with Springer.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

ISPE Manchester Conference to Focus on Product and Process Quality

Continued from page 4.

Sessions will include sterile transfer, electron beam technology, clean-in-place applications, and a range of topics such as the influence of humidity on concentration and the decontamination trusses.

Science- and Risk-based Approach for C&Q: Application of the New Baseline® Guide: Installation and Verification in Support of ASTM E2500

This seminar offers an exclusive opportunity to receive an overview of the Baseline® Pharmaceutical Engineering Guide for Installation and Verification – An Implementation Guide in Support of Science and Risk-based approaches for C&Q and In Support of ASTM E2500, which is currently in development.

The new guide will coexist with the current C&Q Baseline Guide and provides guidance on the implementation of risk-based approaches and verification of a system under the ASTM Standard E2500 – Standard for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment. The seminar also focuses on how the new Guide incorporates concepts from ICH Q8 and Q9 guidance, and provides procedures to improve delivery of regulated manufacturing capacity.

This is a topic of great interest to the industry as the ASTM E2500 standard was published in 2007 and delegates will be interested to understand more about ISPE's response. It is also of major significance due to the ongoing debate as to whether the previous guide and methodology are to be followed or whether the industry should move to this new paradigm.

Applying GAMP® 5 Risk-based Approaches in Practice

This seminar will provide delegates with current thinking and examples on how the risk-based approaches described in GAMP 5 may be applied in practice. The sessions will demonstrate that the specification, design, implementation, operation, and subsequent retirement of a computerized system require careful planning and organization within a structured framework. If managed correctly, this not only ensures compliance with regulatory requirements but also enables technological advance and encourages innovation.

The seminar will offer the first opportunities for the industry to present and discuss the impact of GAMP 5 and how it is being put into practice. It will also cover two pieces of legislation that are likely to appear in the near future – EU Annex 11 and the Revised 21 CFR Part 11.

Investigational Products – Delivering Quality by Design

This seminar will cover the future of clinical supplies, address efficiencies and improvements in labelling processes, and include a regulatory update workshop on the proposed changes to Annex 13 (a key document for those in clinical supplies).

Supporting those working with investigational products (IP) and clinical trials, this seminar will work with delegates to understand clinical trials regulations in Europe, and develop better ways of working in line with these regulations. Using case studies and real examples, the focus will be on sharing experiences from the wide range of companies involved in the manufacture, packaging and distribution of investigational medicinal products. Through networking events, interactive workshops, and seminar presentations led by key opinion leaders, including those from within our industry and clinical/hospital environments, this seminar provides a unique and valuable forum to challenge existing preconceptions, explore alternative approaches and to share "best practice" ideas.

PAT Data Management – Impact on Business Processes Used for Improving Product and Process Quality

One of the challenges resulting from the PAT initiative is what to do with all of the additional data that is being generated and how to use these data for quality and other business decisions. This session looks at the progress that has been made in supporting the manufacturing processes utilizing PAT generated data.

It concentrates on the business challenges in implementing PAT systems to design, analyze, and control manufacturing operations to improve the processability and product quality. Case studies will help delegates understand how companies have utilized data management throughout their development and manufacturing environment as well as discussing the challenges of integrating these data in the business processes.

A full day will be devoted to PAT data management. A half-day will consider how PAT can be applied to make better business decisions. A further half-day will involve an interactive European Community of Practice (COP) meeting, which will give participants the opportunity to discuss PAT implementation with equally minded scientists. It will also give them valuable information which they can take back to their local COP to work on PAT issues in more detail.

For more detailed information, visit www.ISPE.org/manchesterconference.

ENGINEERING PHARMACEUTICAL INNOVATION ISPE

Mark Your Calendar with these ISPE Events

August 2008

6 Greater Los Angeles Area Chapter, Social Regulatory Aspects of Clinical Research and Overview of FDA Good Clinical Practice Guidelines, David Geffen School of Medicine, Irvine, California, USA
8 Japan Affiliate, 17th SAM and GMP Meeting, Yamaguchi, Japan
8 Puerto Rico Chapter, Site Tour and Training on "How to Conduct an Effective Investigation (CAPA)," Guayama, Puerto Rico, USA
12 – 14 Brazil Affiliate, GAMP® Forum Three-Day Event, Mercure Apartments, Sao Paulo, Brazil
18 – 19 Argentina Affiliate, Course II: Water for Pharmaceutical Use and ISPE Baseline® Guide and Regulations, Laboratorios Rontag Auditorium, Buenos Aires, Argentina
21 Puerto Rico Chapter, Technology Showcase, San Juan, Puerto Rico, USA
21 San Diego Chapter, Vendor Night, Hilton La Jolla Torrey Pines, La Jolla, California, USA
22 San Diego Chapter, Golf Tournament, Twin Oaks Golf Course, San Marcos, California, USA
27 Nordic Affiliate, Conference on Cleaning, Helsinki, Finland
28 DACH Affiliate, Workshop on "New Technologies in Manufacturing Effervescent Tablets" and site visit at Hermes, Wolfsberg, Austria
28 – 30 INTERPHEX *India* 2008, HITEX Exhibition Centre, Hyderabad, India
21 San Diego Chapter, Vendor Night, Theme: Football Tailgate Party, Hilton La Jolla Torrey Pines, La Jolla, California, USA
22 San Diego Chapter, 11th Annual Golf Tournament, Twin Oaks Golf Course, San Marcos, California, USA

September 2008

2 UK Affiliate – Central Region, Visit to Superconducting Magnets Facility at Siemens Medical Amysham, Oxford, United Kingdom
4 Puerto Rico Chapter, Full-Day Biotechnology Program, Guaynabo, Puerto Rico, USA
9 San Diego Chapter, Padres versus Dodgers Game, San Diego, California, USA
9 San Francisco/Bay Area Chapter, Commuter Conference on "Alternative Delivery and Contracting Methods – IPD, DB, DBOM," UCSF Mission Bay, San Francisco, California, USA
11 Ireland Affiliate, UCB/Schwarz Plant Tour and Golf Outing, Shannon, Ireland
12 DACH Affiliate, Workshop at Bosch on "Containment/Asept. Filling of Liquid Products," Crailsheim, Germany
15 – 18 ISPE Conference on Product and Process Quality, The Lowry Hotel, Manchester, United Kingdom
16 Boston Area Chapter, Six Sigma Seminar, Genzyme Corporate Center, Cambridge, Massachusetts, USA
16 Chesapeake Bay Area, Annual Golf Tournament, Whiskey Creek Golf Club, Ijamsville, Maryland, USA
16 – 17 Great Lakes Chapter, Vendor Show and Education Program, Indianapolis, Indiana, USA
18 Brazil Affiliate, One-Day Event on "HVAC in a Pharmaceutical Industry," Mercure Apartments, Sao Paulo, Brazil
18 Pacific Northwest Chapter, Vendor Night, Bellevue, Washington, USA
19 Pacific Northwest Chapter, Golf Tournament, Echo Falls Golf Course, Echo Falls, Washington, USA
19 Rocky Mountain Chapter, Annual Golf Tournament, Indian Peaks Golf Course, Lafeyette, Colorado, USA
22 Argentina Affiliate, Workshop with Topics on "Plant Design, Construction, New Alternatives Manufacturing Facilities and Regulations, Laboratorios Rontag Auditorium, Buenos Aires, Argentina
22 – 25 ISPE New Jersey Classroom Training, Holiday Inn Somerset, Somerset, New Jersey, USA
24 – 25 INTERPHEX *Canada*, including educational programming by the ISPE Central Canada Chapter, Palais des congres de Montreal, Montreal, Quebec, Canada
24 – 25 Spain Affiliate, Project Management Conference, Spain
25 Italy Affiliate, Pharmaceutical Management Forum, Florence, Italy
25 San Diego Chapter, Dinner Meeting – "Amylin Ohio Case Study," San Diego, California, USA
30 Nordic Affiliate, Conference on Project Management, Helsingborg, Sweden

October 2008

2 Greater Los Angeles Area Chapter, Golf Tournament, Strawberry Farms Golf Club, Irvine, California, USA
6 – 9 ISPE Milan Classroom Training, Crowne Plaza Milan Linate, Milan, Italy
7 – 8 Nordic Affiliate, Event on EuPAT3, Stockholm, Sweden
8 UK Affiliate – Northwest Affiliate, Joint ISPE/IChemE Day Seminar on Sustainability, Science and Industry Museum, Manchester, United Kingdom
8 Boston Area Chapter, Annual Product Show, Gillette Stadium Clubhouse, Foxboro, Massachusetts, USA
10 Puerto Rico Chapter, Site Tour and Training "Maintenance and Reliability – Predictive Maintenance," Puerto Rico, USA
10 – 11 ISPE China Conference, Organized in conjunction with the 13th China International Pharmaceutical Industry Exhibition (China Pharm), Beijing, China
16 Ireland Affiliate, Workshop/Seminar on "Regulatory Environment," Crowne Plaza Dublin Airport Hotel, Dublin, Ireland
16 South Central Chapter, Plant Tour and Dinner, Austin, Texas, USA
16 San Diego Chapter, Full Day Risk Validation Class, Biogen Idec, San Diego, California, USA
16 – 17 2008 Istanbul Classroom Training, Sheraton Istanbul Maslak Hotel, Istanbul, Turkey
22 Italy Affiliate, Event Topic: ISPE Maintenance Baseline® Guide, Verona, Italy
22 Nordic Affiliate, Conference on GAMP®, Oslo, Norway
23 DACH Affiliate, Workshop at Bosch on "New Technologies for Powder Filling," Waiblingen, Germany
26 – 29 2008 ISPE Annual Meeting, Boca Raton Resort, Boca Raton, Florida, USA

Dates and Topics are subject to change.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

The BTEC Experience

by Jeff Odum, ISPE North American Education Advisor

The week of May 12th was a historical one for ISPE. That week, ISPE and North Carolina State University held a first-of-its-kind public training event for the biotech industry. Three courses were offered by ISPE and BTEC instructors at the Golden Leaf Biomanufacturing Training and Education Center (BTEC).

The BTEC training program offered the courses Biopharmaceutical Manufacturing Facilities, Process Validation in Biotechnology Manufacturing, and Getting the Most from your Bioreactor. The program included lectures and hands-on activities at a state-of-the-art cGMP pilot plant facility, the first commercial-scale bioprocess training center in the United States. The intimate class sizes provided individuals with an opportunity to share best practices and benchmark their efforts against peers.

I had the pleasure of being teamed with Dr. Michael Flickinger, the Director of BTEC, to deliver a course on Biopharmaceutical Manufacturing Facility Design, using the BTEC as a "working model" for implementation of many of the design principles of the Biopharmaceutical Manufacturing Facilities Baseline® Guide. The focus of the course was simple: allow a small group of experienced industry professionals the chance to test their knowledge via a unique design problem.

A focus of the course was to use the Biopharmaceutical Manufacturing Facilities Baseline® Guide as a text for study of how to address design issues faced by many companies. The BTEC served as a great teaching tool, one that gave students the opportunity to "roll up their sleeves" (as best you can when gowned up) and dive into the internal workings of a manufacturing operation. The students were divided into two teams and given a chance to redesign the facility based on a unique case study scenario.

BTEC training participants ready themselves for their hands-on coursework.

And to make it interesting, a distinguished panel of five industry professionals served as a selection jury for choosing the best approach to meet the design criteria. My thanks to Glen Williams (Biolex), Ed George (Wyeth), Steve Errico (Eisai), John Wagner (Merck), and Mitch Lower (Biogen IDEC) for their participation and insights.

The experience was great. Having a working, commercial-scale teaching facility at your disposal allows you to do so many more things than you could do simply using a lecture format. The students dove into the design problem head first and did a fantastic job in not only coming together as a team, but in developing two sound design solutions for the case problem.

I'd like to extend my sincere thanks to BTEC and all of the instructors for their expertise and dedication to this successful, ground-breaking training event.

...Risk-MaPP Guide Principles

Continued from page 1.

While AFSSAPS has not yet officially reviewed the Risk-MaPP Guide, Gazin's comments during his presentation indicated his support for the Guide's principles.

Gazin commented on the following text taken from the Risk-MaPP draft September 2007:

> *Pharmacological and toxicological descriptions (dose-response, no-observed-adverse-effect level (NOAEL) and ADI) should be used to assess compounds instead of hazard labels. Terms such as potent, cytotoxic, cytostatic, and other product class definitions tend to induce an emotional response that might imply that these compounds are always difficult to handle and require the highest level of control.*

"Emotional responses should be rationalized," said Gazin. "Toxicity depends on the quantity as well as on the duration and the route of exposure. NOAELs and usual toxicological reference values should be integrated in a risk management program. But the choice of NOAELs and toxicological reference values (such as ADI) could be different among toxicologists."

"The objective is to have harmonization between assessors," said Gazin. "When we are talking about scientific data, it is easier to have harmonization."

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Your Questions, Your Answers

A sampling of interactive discussions taking place online among colleagues through ISPE's Communities of Practice.

Recognizing the challenge of the pharmaceutical industry to achieve continuous improvement and productivity, ISPE has implemented Communities of Practice (COP) as an online forum to enable colleagues in specific disciplines to rapidly exchange information and solutions to everyday problems.

Through professional networking and peer collaboration, ISPE COPs produce discipline-specific content that deepens members' knowledge and expertise, increases quality and continuous improvement in the industry, and achieves ISPE's core purpose of leading global innovation.

Currently, there are 17 active COPs in areas of pharmaceutical expertise such as Active Pharmaceutical Ingredients (API); Biotechnology (Biotech); Commissioning and Qualification (C&Q); Containment; Critical Utilities (CU); Disposables; Engineering Standards Benchmarking; Good Automated Manufacturing Practice (GAMP®); Good Control Laboratory Practices (GCLP); Heating, Ventilation, and Air Conditioning (HVAC); Investigational Products (IP); Packaging; Process Analytical Technology (PAT); Process/Product Development (PPD); Project Management (PM); Sterile Products Processing (SPP); and Sustainable Facilities. Initiatives for the COP in the field of Oral Solid Dosage is in development.

By engaging in ISPE COPs and becoming active in their communities, participants have the ability to connect with like-minded professionals through an interactive online community that offers global networking opportunities and access to a discipline-specific body of knowledge. As the following pages of this article demonstrate, Members of the diverse COPs are actively participating in a continuous discussion of ideas to solve everyday problems. They are frequently using COPs to validate industrial measures, reference guidelines, convey best practices, develop technical documents, and keep abreast of current issues and important trends and developments of the community discipline.

Joining one or multiple ISPE COPs is the first step to connecting with peers and colleagues around the world. With the accelerated growth of pharmaceutical domains such as biotechnology and generics, the demand for lean manufacturing methodologies, and the extraordinary costs in producing drugs, COPs represent an effective outlet for the dissemination of valuable content produced by and for ISPE COP Members. ISPE COPs continue to be a progressive and efficient response tool in the competitive environment of pharmaceutical engineering.

You do not have to be an ISPE member to join and participate in ISPE COPs; however, ISPE Members gain full access to all functionalities of the COPs.

To join and become active in your ISPE Communities of Practice, visit www.ISPE.org/cops.

Active Pharmaceutical Ingredients (API) COP

Validated Status of a Manufacturing Process

Q Typically, when a process is validated, the passrate for the number of batches manufactured per year should be high (i.e., maybe >90%). What should be the passrate for batches manufactured in order to consider a process in a validated status?

A There is more than one area to be considered as part of a periodic validation review to deem the process validated. One of them is the product quality review including analytical results, process capability, trends, out of specifications, reworks, yield etc.

This data should be reviewed to determine if a change in the validation status is indicated by

trends in any of the above. In addition, the trended analytical data in the Product review should be compared with the analytical data from the most recent PQ exercise. If a statistically significant shift is seen (even if the result remains within specification) then an investigation into the probable root cause must be undertaken in accordance with the Investigation of Non Conformances and Deviations procedure. If the investigation determines that the process can no longer be considered validated, then a revalidation exercise should be executed.

A A batch failure rate of 10% would suggest that the process was out of control. It is likely that a trend could be found in the 10% of failures: all late at night, all just after start-up, etc. That trend would be the part of the process that is out of control.

A A 10% failure rate would indeed be very high. The question is "Is there an acceptable failure rate or conversely an acceptable passrate" that would deem the process to be in a validated status. In a nutshell, is there a quantifiable number (in terms of % passrate) that the community recognized to say that the process is validated or out of control?

A As we all know, some processes are more robust than others. A robust process may be out of control when <1% failures occur. A new process for an innovative drug just being launched may still need optimization so a much higher failure rate may be seen in Year One, but the company would want to improve upon that annually. Perhaps the Six-Sigma approach to failure would be a useful target for processes.

Biotechnology (Biotech) COP

Emergency Showers in Class A/B Area

Q I am involved in a discussion with our site safety personnel about installing an emergency shower and eyewash in Class A/B (Class 100) areas in a pilot plant facility. My understanding is that the presence of the shower/eyewash would increase the risk of microbial failures in the environmental monitoring of the area. No one I have talked to has seen any showers/eyewashes in these areas in other facilities. Under what circumstances are there showers/eyewashes in Class A/B (Class 100) areas? Can someone provide me with references from regulatory guidelines on this issue?

A Grade A/Class 100 areas are typically kept small due to the high capital and operating costs, and the challenges of maintaining that level of classification. I am not aware of anyone installing an emergency shower or eye wash in this type of area. Grade A/Class 100 areas usually have a surrounding or background area of Grade B or Class 10,000. Emergency showers and eye washes have been installed in Grade B/Class 10,000 when required for operator safety. You may be able to install these safety systems just outside of the Grade B/Class 10,000 area, but they must be readily accessible in an emergency situation. ANSI Standard Z358.1-2004 provides guidelines for safety equipment fixtures and installation practices. I would first confirm that the operations pose a safety hazard that requires installation of these safety systems.

Commissioning and Qualification (C&Q) COP

Cleanroom vs. Environmentally Controlled Room

Q This may not be the correct COP for this topic, but has anyone else been asked to stop using the term cleanroom and instead use the phrase Environmentally Controlled Room? In my case, I am referring to ISO 7. Up until the beginning of this year, we used the term cleanroom as defined in ISO 14644-1. Just recently we have been asked to change to environmentally controlled rooms, but I have yet to find the rationale for the change.

A Actually, we use the term "cleanroom" environments up to and including ISO 8.

A I will try to explain what I understand about these two terms. I was also asked to change the term and here is the explanation:

ISO 14644-1 and 2 refer to the particle size and amount of it in the air or space while the controlled environment goes beyond; we have to continuously monitor the microbial growth and routing of the cleaning agents, but also we have to monitor the temperature, humidity, differential pressure, and air flows to keep the environment under control and avoid cross contamination. If you read USP chapter 1116 Microbiological Evaluation of Clean Room and Other Controlled Environments, there is an explanation of these two terms. The difference of Clean Room and Environmentally controlled rooms reside in the amount of controls you set for that particular area. You may have a room that is Class ISO 8 where you don't have to control cleaning as you need to control it in an ISO Class 8 room where you have a critical step of your process. I will say that the difference resides in the controls that you need to establish due to your process steps.

Containment COP

Segregated vs. Stand Alone Potent Facility

Q Does anyone know of any current or proposed regulations in North America or EU which require/propose a stand alone facility for manufacture of GMP potent and/or cytotoxic products (oral solid dosage forms)? At one point the FDA was talking about this and I hear rumors from my EU friends from time to time.

A First, what is the definition of potent? Industry cannot agree and the regulators do not have a definition.

The current trend is to use risk assessment to determine the need for stand alone/segregated facilities. Industry actually needs to come up with a common definition for segregated and stand alone facilities!

I would suggest you attend the 2 – 5

June 2008 Containment Technologies Forum in DC as Edwin Melendez, the FDA "expert" in "potent" compounds, will be presenting the FDA's views on risk-based approaches. Last year Edwin answered many questions in a casual Q&A at the end of the session. He clarified many points, like dedicated facility does not necessarily mean a separate facility to the FDA. I believe some of that Q&A is available on this site.

If you look in the Community News/Community Files portion of this site you will see that the EMEA are currently evaluating which compounds to list as requiring dedicated facilities. The issue is on hold until Toxicological studies are performed. During the June Risk-MaPP session in DC, Vincent Gazin, Toxicologist from AFSSAPS, will be presenting on the status of these studies... come hear first hand what is happening and you may even be able to sway his opinion!

Hope to see you in DC; I really think you will get more than this question answered!

A I don't recall seeing you at the DC conference, so I wanted to let you know that ISPE recorded all the sessions and is selling all the proceedings (the CD will have a sound file and a PDF file of the presentations for all 10 sessions), so if you are interested, please contact ISPE.

For your information, the next containment technology session will be 2 – 5 March 2009 in Tampa.

Critical Utilities (CU) COP

Hydrocarbon in Compress Air

Q We are looking for a method to know the hydrocarbon content in compress air. Do you have any reference?

A There are tubes that you hook up to your compressed air. Once you run a certain quantity through the tube you can tell the concentration of hydrocarbon by the color change. One supplier is Draeger and they have a quality article I came across that might be useful. http://www.draeger.com/ST/internet/pdf/CS/en/DraegerReview/DR94/DR94_article_4.pdf

A Are you looking for levels in mg/m3 or in ppm? The Draeger tubes will give the levels in mg/m3 and then must be converted to ppm if required. The problem with Draeger tubes is that it is hard to get an accurate concentration level. Also, you must know the type of oil you are testing for. The type can have a direct effect on detectability of the Draeger tube.

A Which ISO 8573 Class should the compress air comply for a use in pharmaceutical facilities (sterile and non sterile areas) (maximum oil content).

A ISO 8573 part 1 identifies classes of compressed air with allowable levels of contaminants. Some would suggest a Class 2 or better for hydrocarbons. As far as testing for hydrocarbons, ISO 8573 parts 2 and 5 are the testing methods.

At the Annual Meeting at ISPE when I was presenting on this, one person suggested that if a sterile filter is 0.2 micron, why should the filtration need to be any greater than this? So this appears to be the standard his company was using. Most coalescing filters will offer a 0.01 mg/m3 rating basis 70°F temp and clean. Some would say to minimize risk; you should have the most stringent Class, which is Class zero, so this is up to your risk tolerance. Oil Free compressors do not add hydrocarbons to the air and are the least risk, while oil injected compressors need clean up equipment. Intake is another concern. Make sure your compressor is not taking in hydrocarbons as even oil free compressors put out what they take in (concerns would be powder lubricants used in the facility that get airborne or intakes near loading docks which will absorb exhaust fumes).

Disposables COP

Retrofitting Disposables

Q Please share your experiences/opinions during retrofitting disposables in existing SS facilities. What are the challenges involved in it?

A The most challenging issue is creating appropriate interfaces from single use items to existing stainless items, especially for aseptic systems, if that is your context. There are several ways of doing it. We commonly set up the stainless systems with the interfaces ready to go, called "pigtails," to which we can perform tubing welds or use an aseptic single use connector. We also use different single use SIP connectors at standard SIP ports. Depending on the room classification and bioburden requirements of the process one can simply connect using a plastic triclamp connector on the disposable item.

Engineering Standards Benchmarking COP

Global Approach

Q How does your company address the design and construction of facilities globally when facing the different international regulations?

a. Controlled environments (i.e. particulate control, viable & non viable monitoring, temperature and humidity controls)?
b. Environmental, health and safety issues (i.e. local codes vs. corporate requirements)?

Respond to this question by joining this newly developed COP. Questions and answers are welcome under the section "Community Discussions," on the Engineering Standards Benchmarking COP site.

GAMP® COP

Infrastructure Qualification

Q Some years ago there was a lot of discussion about infrastructure qualification. An ISPE GAMP® Good Practice Guide ("IT Infrastructure Control and Compliance") was published, giving great guidance on how to achieve a qualified platform.

Since then I haven't heard much about infrastructure qualification. I was just wondering if any of you have:

- experienced that infrastructure qualification is a hot topic in your corporation/among your customers
- heard of inspections where infrastructure qualification was/became an issue
- experience implementing the Good Practice Guide and wants to share some of your key learning on this topic

A Since the IT Infrastructure SIG was reformed and following the publication of the Good Practice Guide, the approach to IT Infrastructure qualification has become more pragmatic.

While this is certainly still an issue that needs to be addressed, most regulatory agencies see this as a relatively low risk area and now recognize that if (to paraphrase GAMP® 5) computerized systems can not represent a higher risk, that the associated processes and products, the associated IT infrastructure is even less of a risk.

Some of the key regulatory inspections in this area (1999 – 2001) which are often quoted focused principally on infrastructure.

Regulatory agencies generally accept that this was not/is not a useful approach. Typically nowadays Infrastructure is only cited as an issue during inspections if the lack of qualification/control is reasonably likely to lead to risk to product quality or patient safety.

For most companies IT Infrastructure is not the hot topic that it was because of this more pragmatic approach to inspections and because most reputable companies have addressed the topic (or have started to).

Having said all of that (and to address your second point) where it does still represent a risk to product quality or patient safety it will be cited during an inspection and not only by the FDA. There are a number of occasions where European inspectors have included IT infrastructure findings as part of their observations.

My experience with using the Good Practice Guide (and I should declare here that I was a member of the SIG) is that it provides a sound and pragmatic approach.

However, some smaller companies have struggled with some of the examples and guidance given because to a significant extent it was written with 'Big Pharma' organizations in mind and many smaller companies struggle to apply the concepts when they only have three people in their IT departments. The concepts are however sound and when applied properly the guidance can be scaled to organizations of any size.

Another area where people seem to struggle is taking a risk-based approach to infrastructure qualification and like GAMP® 4, the Good Practice Guide is probably a little light in that area. This can result in a 'one-size-fits-all' approach to Infrastructure Qualification which is fine for most areas, but is sometimes too much or too little for specific components.

However, the expanded Risk Management section to GAMP® 5 can be applied to the principles of Infrastructure Qualification and my experience is that a risk-based approach can be successfully used to scale qualification and control activities to those areas where the risk likelihood is greater (e.g. when using 'novel' infrastructure or using infrastructure for a purpose not intended by the manufacturer) or where the probability of detection is low (e.g. where there is no resilience and no in-built diagnostics or performance monitoring).

Technology moves on and many people are struggling with how to apply the principles to technology not addressed in detail in the Good Practice Guide, i.e., looking towards virtualization (e.g. VMWare) and Service Oriented Architecture/Middleware. Although not addressed in detail in the Good Practice Guide the 'hierarchical' layer and component model can be extended to additional dimensions and allows a pragmatic approach to be developed for the appropriate qualification of newer technology not explicitly addressed in the Good Practice Guide.

To summarize, the pragmatism inherent within the Good Practice Guide has helped to define a sensible approach to Infrastructure Qualification and has gone a long way to making this less of a hot topic. Although they need thinking about in some circumstances the principles of the Good Practice Guide are still sound.

A Thank you for this very comprehensive statement! I am aware about the concerns of smaller organizations complaining that the GPG is only achievable for large (and rich) companies. I do not really agree with this concern because the GPG is not prescriptive regarding the number and the complexity of required activities.

GPG objectives are to define a framework and to provide recommendation regarding how to establish compliant IT infrastructures and how to maintain the controlled state of them. We should consider two main drivers for keeping IT infrastructure under control:

- Impact on the Patient's health
- Impact on the business capability (which can also impact the Patient's health)

Having reliable IT infrastructure for GCP reasons is – in my humble opinion – a not negotiable requirement. Having reliable IT infrastructure is part of Good Business Practice and is also part of the SOx scope.

The implementation of PAT is often very challenging for the IT infrastructure; various systems (process control as well as multiple information systems) have to be interconnected and they must exchange numerous information in real time. The deployment of chromatography data systems requires also a reliable IT infrastructure, allowing laboratory equipments to communicate accurately with servers. The deployment of electronic lab-journals, the use of PKI-based electronic signatures, request reliable and secure IT infrastructure.

All these facts plead for maintaining with rigor IT infrastructure under control. All these facts are at least just as important as "pure" regulatory requirements.

In my experience as CSV and e-compliance auditor, I met once a small

company (around 200 employees) with a very well structured and reliable IT support. Everything (every configuration item) was documented and maintained under change control. Each activity was documented in log-book. The reason for this exemplary behavior was the size of the team providing IT support: 3 people big.

These three persons had to provide support regarding the network and server infrastructure for both office as well as production areas. They had to ensure the external connectivity of the company (internet, e-mail, web) and the company worked 24/7.

Because somebody could become sick during the colleague's vacation, it was vital for this IT team to make all relevant information available to the rest of the team in an accurate and consistent manner: full cooperation without any "kingdom!"

The quality of the documentation, the rigor of activities (including change control and business continuity planning) were the main drivers for this organization; not the fear of a GxP inspector!!! Even if regulatory requirements are important in our industry, we have to think again in terms of common sense. The question is not what the Quality costs are!

Furthermore, the question is: How expensive is it to not have sufficient Quality (to not have reliable IT infrastructure) in place?

Please consider the Good Practice Guide about IT Infrastructure and GAMP® 5 as a support for doing the right thing at the right time, because it is good for the business!

Good Control Laboratory Practices (GCLP) COP

Scanning Electron Microscope

Q I'm researching the regulatory requirements for Scanning Electron Microscopes under GLP. So far, I've only found text suggesting that Microscopes can not be validated or tested for Robustness. Can any one offer insights or opinions on the use of Scanning Electron Microscopes in the Lab?

A There is an article in the *Journal of Measurement Science and Technology,* Vol. 17, pp. 2613-2622, (2006), titled, Metrology on Scanning Electronic Microscope: Theoretical Developments and Experimental Validation (though I have not seen that). You may refer to this paper for some information you are seeking.

Heating, Ventilation, and Air Conditioning (HVAC) COP

HEPA Filter Integrity Test Failure

Q Ceiling HEPA filters are tested for integrity annually. If filter fails integrity test, what is done with all product processed from the last failure till to-day. On testing particulate matter the test passed.

A Your question shows the need for continuous monitoring. The only action can be: to sequester the material produced since the last good reading. If the last good reading was three months ago then all the product produced since that date is suspect and needs to be QCed and tested. If most of that product has been shipped, then only a recall is possible and not probable. If the product was passed by QC before shipment, then no foul; no damage.

The issue is the following: You need real-time, near-real time, or high frequency monitoring to help determine the health of the environment at all times. High frequency monitoring can help determine issues long before specification excursions.

A I recommend to look into the release product SOP and QA/QC batch criteria or document related to that, there should be a contingency plan for this kind of event, if there is none then the Quality system needs to be reviewed and a plan needs to be in place (e.g. release criteria and critical parameters to release product SOP needs to be in place). If the HEPA filter integrity test is a criteria to release product, then you should follow the release product SOP. However if it is, consider just an additional test, then a system has to be implemented to avoid this situation to happen again.

The situation that I see in here is that the HEPA filter integrity test SOP was not followed or was followed but the SOP is not clear on how to report to the different departments that the test didn't pass and that all production activities needed to be cancelled due to the test failure. First the Deviation Report needs to be addressed then the quality system needs to be evaluated and let QA/QC analyze the data if PARTICLE COUNT AND THE MICROBIAL LEVEL ARE OK DURING YOUR PRODUCTION TIMEFRAME THEN YOUR PRODUCT IS OK and your deviation will address all of these investigational facts.

The main function of the HEPA is filtration and microbial level control. So, if those two parameters are within the acceptance limit your deviation report must indicate that.

A You say the room particle counts were OK, I assume the particle counts under the Grade A hoods were OK. So there's likely no risk to product. Here's why:

A pinhole leak in a terminal filter will NOT cause a measurable rise in room particles, as the activities of the people in the room can cause more variability in room air particles than the few particles per minute leaking thru a pinhole. With a pinhole, you MIGHT see a rise in AT REST particle counts, but likely not enough to cause anyone to notice. Did the at-rest counts increase?

If the terminal HEPA filter is the SECOND HEPA filter (i.e., there's a primary HEPA filter in the air handler) there could be essentially NO particles passing thru the pinhole.

We have contended that it's of no value to pinhole (integrity) test ceiling terminal filters for Grade C and B rooms, as the presence of a pinhole has negligible effect on the room's airborne counts. You'd need a good sized hole, especially if the HEPA is downstream of a primary HEPA. However, it is of utmost importance to integrity test the HEPA filters in a Grade A hood, as the

pinhole MAY be directly over a critical site.

Bottom line – were the particle counts near product exposure still "normal?"

A In your last post you mention: "We have contended that it's of no value to pinhole (integrity) test ceiling terminal filters for Grade C and B rooms." Is this documented somewhere and is it generally accepted? If no integrity test is performed, how is filter replacement scheduled? By pressure drop?

A Unfortunately, there has been no concession by the regulators regarding integrity testing vs. overall efficiency testing of terminal (ceiling) filters. The key factor is bacteria retention, a pinhole in a filter will pass a bit more bacteria than one that has been integrity scanned to 99.99% (which also passes some bacteria, less than 0.01% of them). (But remember, even more bacteria come from the operators, so the few bacteria passed may not change room counts).

However, there is a lesser expectation for testing rigor and even testing frequency for Grade C rooms, and I think we even say that in the latest draft of the ISPE Sterile Manufacturing Facilities Baseline® Guide, which I don't have nearby right now (and it hasn't been through final FDA review). There are a number of "reality checks" that we need to run by FDA, that go beyond the content of the Sterile Baseline® Guide, and this is one of them. Perhaps the fastest way to get an answer is to pose a question at the June 2008 Washington Conference during the FDA Q&A session.

Regardless of the results of integrity tests, I'd suggest replacing TERMINAL filters (and filters in air handlers) based on pressure drop. You can usually repair terminal and AHU filters (to a predetermined limit, no more than a few percent of face area) and pressure drop will go up a little (due to reduced face area and thus higher velocity). Once the DP is about twice the original DP the filter is full. Check the actual DP factor with the filter manufacturer. Dirty HEPA filters filter better than clean ones, but they use energy. Often replacement frequency will be driven by life cycle cost analysis.

For filters in Grade A (Unidirectional flow) hoods, the above discussion does not apply. Those filters are part of the process equipment, and pinholes and repairs can be a major problem.

A The nature of the HEPA failure needs to be understood in relation to the manufacturing activities carried out in the area. Are the ceiling HEPAs in the Grade B area (EU area classification) or the Grade A area. I have seen over the years a small numbers of HEPA failures which have not impacted upon the routine environmental data for both viable and non-viable particles for the relevant area. All data was well within the EU specifications even when a Grade A area HEPA was involved in the failure. You should also consider when the last media fill was done in the area in relation to the date of the HEPA failure. The HEPA failure needs to be addressed as part of the deviation system and included in the investigation will be the potential impact on product filled since the last test passed. It is highly unlikely that a HEPA failure will lead to the area classification failing the environmental standards required for the product manufacture and hence there is no risk to the products previously manufactured since the last pass result. The only justification for a potential recall of products would be if the failure involved a LAF HEPA or tunnel HEPA and the failure was a gross one which did compromise the environmental standards of the area. One that comes to mind would be the major damage of the filter media, i.e., a hole!

Investigational Products (IP) COP

Certificates of Analysis

Q I am attempting to assess the need for C of A's with every shipment of drug to centres and distribution sites alike. Does anyone have a comprehensive list of custom versus regulatory requirements?

A Good question! In my personal opinion, it is more a matter of habits. Site pharmacists were used to receiving CoA, so documents describing the "chemical and biologics" attributes of drugs, now, after the Directive/QP implementation, the majority of release certificates have the format of "statements" or "disclaimers" and this is generating questions and concerns; that's why the request to also have the drug CoAs.

A Our experience is that we supply a "Quality Statement" with shipments in the EU. In the US, we only supply the statement when requested. We do not generate a CofA for packaged supplies.

Packaging COP

Packaging Defects Classification

Q I am working to classify the Packaging defects as Critical, major and minor in aluminum, PVC, Polietilen bottles, individual boxes, mainly for inspection. Anyone has done some similar work and has some classification of defects or any orientation?

A First, most all companies use the MIl-STD-105 to determine sampling plans. This is a valuable tool to use. As far as classifying defects it is really a quality issue. If a package has a defect that would be a detriment to the product (Hole in blister, defective childproof cap, missing print, or illegible print) these would normally be major defects. Minor defects are usually cosmetic defects that would not affect the product. These could be dented boxes, blisters, smeared print (still readable) or other defects caused by poor material or equipment caused. It really depends on your quality standards. Some companies consider all of the above unacceptable and would reject them. The major defects would most likely call for a 100% inspection of the lot but the minor defects would not call for this. Hope this helps.

A Thank you for your comments, actually we are using the mil-std 105 (ANZI) as sampling plan, however, what I want to do is quantify the defects and level found on each inspection, I mean define an AQL for critical, major and minor defects. In your experience, what are the most common AQL defined for a critical, major or minor defects?

A Well again it depends on the defect. The AQL is defined as 1.0% for critical defects and 2.5% for minor defects. Major might be in the 1.5% area. For six sigma calculations, the common is 3.4 defects per (one) million opportunities (DPMO) so this is much tighter. This is a goal some companies are using. I have not done this for awhile but you really should set these goals with the Quality department. A 1.0% AQL might not be acceptable for a wrong lot number/bar code or other product quality defect. A wrong lot number should never be found and if it is then the entire batch should be stopped and 100% re-inspected. A wrong tablet count might be OK if it still meets label claims. Some cos. fill a little over in a tablet bottle. A missing print is still critical but might not warrant a 100% inspection unless you would find a second one. Hope this helps.

A One thing that I have done in the past is take the individual components that come together that make the final package (i.e., bottle, closure, label, carton, case, etc), and consider what could actually go wrong with each one of those components during packaging. Incoming inspection had its own inspection process which (right or wrong) we used as justification not to inspect for those defects as part of the packaging AQL.

Take for instance label. Defects that could occur to the label include: Missing (i.e., not on the bottle), damage that causes information not to be legible, presence of material behind label (separating material of known and unknown origin), wrinkled, skewed placement, air pockets behind, damage that presents a poor appearance, etc.

Once we identified all these potential defects, we then considered what the impact of each of those defects would be to the consumers (safety, use, relations with), and to regulatory bodies (meets or doesn't meet regulations). Each one of these defects was then classified in these categories to determine which level it would fit under. This developed into the critical, major and minor defects that we used with the AQL levels for inspection.

A I would agree that you have to understand the interaction of each component in all your packs to ensure that you have the correct classification. It can be too easy to misclassify and either risk failure or increase unit costs.

Process Analytical Technology (PAT) COP

Analysis of Data

Q The major challenge involved in any analysis is generation, integration and organization of data. Usually data are stored in big warehouses but rarely retrieved. This is the common situation in (bio)-pharmaceutical industry. Multivariate methods are ideal for analysis. Any other methods available for Analysis of Variables (ANOVA)? What is the Industry practice?

A Have you tried "parallel coordinates." I have used XMDV tool (you can go to their web pages and see the application). It is a very useful tool to evaluate thousands of data!

A We have used the product from Curvaceous Software for the last five or so years and found it excellent, especially for explaining complex interactions to plant personnel. The fact that no scaling or pre-processing of data is required and parameters can be shown at their native scale makes it much easier to communicate than a multivariate PCA model.

A You might want to consult an article I wrote on Exponentially Weighted Process Statistics and SPC published in *Pharmaceutical Engineering* in March/April 2007. This is an excellent article on data especially with high frequency.

A In regards to multivariate data analysis, especially for spectroscopic based data, I have always found The Unscrambler, by Camo as being very useful.

A Another excellent data mining and modeling set of tools comes from Pavilion Technologies, who was recently purchased by Rockwell Automation. They have solid data evaluation tools that incorporate multivariate analysis and modeling. I would check out their tools as well. Very effective.

Process/Product Development (PPD) COP

Product Transfer

Q There are several cases for product transfer and manufacturing and development work together like the transfer from development to manufacturing (obvious!) or the transfer from old to a new process system; usually product transfer from site to site, mainly in the cases of outsourcing, does not include the development team. Is there any real need for that when process does not change? I would say yes since they are the owners (in some way) of process and product design and any modification should be handled by them before green light is granted. Any comments?

A We struggle with who owns what in transfers all the time. We have established a system with a Master Transfer Plan, where each time we approve a RACI (Responsible, Accountable/Approver, Contributor, Informed). That seems to help. I agree that Development should be involved to some degree since they may have intimate knowledge of the process that would help the team understand special nuances in the transfer program.

A This seems to be a topic many struggle with! I liked the response

given in that having the RACI defined can greatly aid as a communication tool across a tech transfer team. The details of RACI may also depend on the size of your organization, complexity of the tech transfer project, availability of resources, and timeline. Roles may also change with the progression of the project.

Specific to this question, if the development team has produced a process that is well characterized, and is DOCUMENTED, there may be a way to make modifications without including an intensive commitment from dev, freeing them to work on the next big thing! Otherwise, subject-matter experts need to be involved when making changes, and without the tools to transfer the subject-matter expertise, you may have to commit your dev team to later phase projects.

A Thanks, good points! Let me put this question together with ICH Q8, Q9 and Q10 plus ICH Q8 Annex (draft) and outsourcing activities. The Design Space is a multivariate relation involving materials, methods, machines, measures, the environment and the people, then, when a product is moved out of the company at least the following is different: environment and people. I am just thinking that the complexity to manage the transfer could be very high unless some basics are accepted, therefore the question could be, what are those basics?

Project Management (PM) COP

POLL Results – Why Do Projects Still Fail

A So the results are in:

1 - 50% of vote – poor planning
2 - 25% of vote – lack of control
2 - 25% of vote – no management of the business changes needed to support the project

None of you identified the following as causes:

- inappropriate selection of project manager
- no benefits management
- lack of teamwork and poor team culture
- no link between the project and the business

Thanks for voting.

A On larger projects that take more than 1 year of Pre-Construction change in Stake Holders, failure to revisit and confirm expectations can lead to failure. Inadequate time to specify speciality equipment, accessories, utility requirements, compliance with local codes and integration with the architectural theme can force last minute changes, add costs and delay the project. It is important to have upper management support allocating sufficient resources to the project with clear understanding of decision making authority.

A I agree that longer duration projects do have some specific challenges around both stakeholder management and control of delivery (project objectives and associated business benefits). Getting key processes in place (like decision making authority) at the start of the project will reap benefits particularly for those projects lasting a few years!

Sterile Products Processing (SPP) COP

Biofilm Removal

Q Could anyone please help me regarding the method for removal of biofilm appearing in WFI water tank as well piping? What would be the right chemicals to be used for removal of same?

A Chlorine bleach is harsh but effective. It may not be appropriate in your system at all. You must ensure the liquid contact parts, etc. are compatible with Cl bleach and it is all removed.

Sustainable Facilities COP

Energy Policy/Carbon Reduction Plans/Aims

Q Can anyone comment on the status of their company's corporate energy policy/plans to reduce carbon emissions or attempt to become carbon neutral and the logistics of this challenge from a cultural and financial viewpoint? Also, is anyone looking at the viability/possibility of a carbon neutral laboratory/manufacturing plant or even campus/ site?

Respond to this question by joining this newly developed COP. Questions and answers are welcome under the section "Community Discussions," on the Sustainable Facilities COP site.