Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2010, Vol. 30 No. 4
www.ISPE.org

This case study demonstrates how Quality by Design transcends API synthesis through to the final drug product.

Quality by Design using an Integrated Active Pharmaceutical Ingredient – Drug Product Approach to Development

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Introduction

Quality by Design (QbD) is gaining wide acceptance within the industry to help pharmaceutical manufacturing move into the 21st century with enhanced process understanding and process capability. While elements of QbD have been implemented in various companies for many years, it is unlikely that pharmaceutical companies were implementing it in a holistic manner as described in ICH Q8(R1), Q9, and Q10, prior to 2005. The major ingredient that has been lacking is a comprehensive understanding of risks and the management of risks in a formal manner. The ICH guidances provide the framework for industry and regulators to establish QbD programs that will enhance the robustness of pharmaceutical manufacturing processes. The varenicline project was one of the initial filings that the FDA accepted into the QbD pilot program.[1] The regulatory filing for varenicline was one of the first regulatory filings that utilized a QbD approach for both the API and Drug Product. The benefits of this enhanced robustness are shown in Table A. The primary aim of a QbD approach is to assure product quality (safety and efficacy). However, many of the benefits listed can be associated with potential lower development and production costs for the industry. Regulators will benefit by having fewer low risk regulatory supplements to review.

ICH Q9 is a guideline for applying Quality Risk Management (QRM) to the pharmaceutical industry and regulatory authorities. QRM involves three sequential phases: risk assessment, risk control, and risk review. While both formal and informal approaches of QRM are considered acceptable, a formal QRM is preferred when dealing with more complex situations like pharmaceutical manufacturing. The number of parameters that will impact the product and process performance can be large, due to the large number of unit operations and materials involved in the manufacturing process. Risk assessment is the process used to prioritize parameters and attributes most likely to impact the product quality. When functional relationships exist (Y = f(X1, X2, …)), the risk of impact on the process may be high and the risks must be understood. The risk assessment approach has been applied to identify risks and set up an experimental approach to understand and control those risks.

Risk Assessment

The focal point of a QbD risk assessment is to be able to link quality measures and process controls to the product quality of the drug delivery system, i.e., safety, efficacy, and performance. A Quality Target Product Profile (QTPP) is an effective tool to help identify the Critical Quality Attributes (CQA) of the manufacturing process that link to product quality. The QTPP for varenicline indicated a need for an immediate release, orally available tablet dosage form of a

Table A. Values associated with QbD approach.

Value to R&D	Value to Manufacturing	Value to Regulator
Transparent assessment of risks	Risk-based decision-making	Risk based regulatory decisions (reviews and inspections)
Prioritization of studies	More robust processes	Enable innovative approaches to process validation
Focus regulatory filing on critical parameters and attributes	More rapid implementation of process improvements post-approval	Reductions of post-approval submissions

low dose stable active. Based upon the QTPP prior knowledge of the varenicline material properties, it was evident that API impurities, tablet potency, and uniformity could be potential critical quality attributes.

The first step in the risk assessment process is to define the manufacturing process scope. This is performed by creating a Process Flow Diagram (PFD) as shown in Figure 1. The PFD in Figure 1 shows only a portion of the API process and all of the tablet manufacturing process. However, this article will restrict its focus to only the portions of the API and tablet manufacturing process that had potential to impact critical quality attributes. In order to perform a comprehensive risk assessment across this complex manufacturing process, it was necessary to break the PFD into smaller, more manageable "Focus Areas." Focus Areas (FA) are typically one to three sequential unit operations grouped together for a risk assessment. A Focus Area in reaction Step 4 of the API will be reviewed to illustrate how a risk assessment can identify key process parameters that controlled an impurity formation. Likewise, Focus Areas that include dispense/blend and roller compact/mill and blend will be used to illustrate how a risk assessment can identify key process parameters that controlled the content uniformity of the blend and compressed tablet. The compressed tablet content uniformity was measured using a stratified tablet content uniformity test.[2] There are three parts to meeting the acceptance criteria of the STCU test that consider tablet potency and uniformity results. During development, the criteria includes:

1. tablet potency %RSD ≤ 6%
2. the location mean being within 90.0 to 110.0% of target potency
3. individual potency values being within 75.0 to 125.0% of target potency

For the risk assessment, a total of 25 (18 API + 7 DP) focus areas were evaluated for the API and tablet process. The three focus areas described in detail in this article are selected as illustrative.

An interesting contrast developed when comparing risk assessments of API and Drug Product (DP) processes. The product quality of the chemically synthesized API processes can be controlled at the end of the various reaction steps via isolation of intermediates of well defined purity. Therefore, the prior process history of intermediates may have minimal impact on the resultant quality of the downstream reaction steps. Therefore, it is relatively rare that process parameters from one reaction step interact with process parameters from another. Thus, for API, the process is ultimately controlled both via understanding of the interactions of the process parameters within reactions followed by confirmation of the control via analytical testing. This simplifies required experimentation, process modeling, and defining design space for APIs.

In contrast, the product quality of the DP process is dependent on many of the upstream unit operations, including crystallization of the API. Therefore, it is common for process parameters from downstream operations to interact with upstream operations. For example, the effectiveness of a downstream blending operation can be dependent on the API particle size and particle size distribution established in the API crystallization step.

One option for risk assessment is a tool called a "Cause and Effect Matrix." As the name implies, a Cause and Effect Matrix relates "causes" (inputs, process parameters, or independent variables) to "effects" (outputs, responses, or dependent variables). The Cause and Effect Matrix was established for both the API and drug product Focus Areas using a team-based risk assessment process, consisting of subject matter experts from both R&D as well as manufacturing.

Within each Focus Area, quality attributes were identified and numerically scored (1 to 10 scale) by the project team based on their potential to impact product quality or process efficiency. The quality

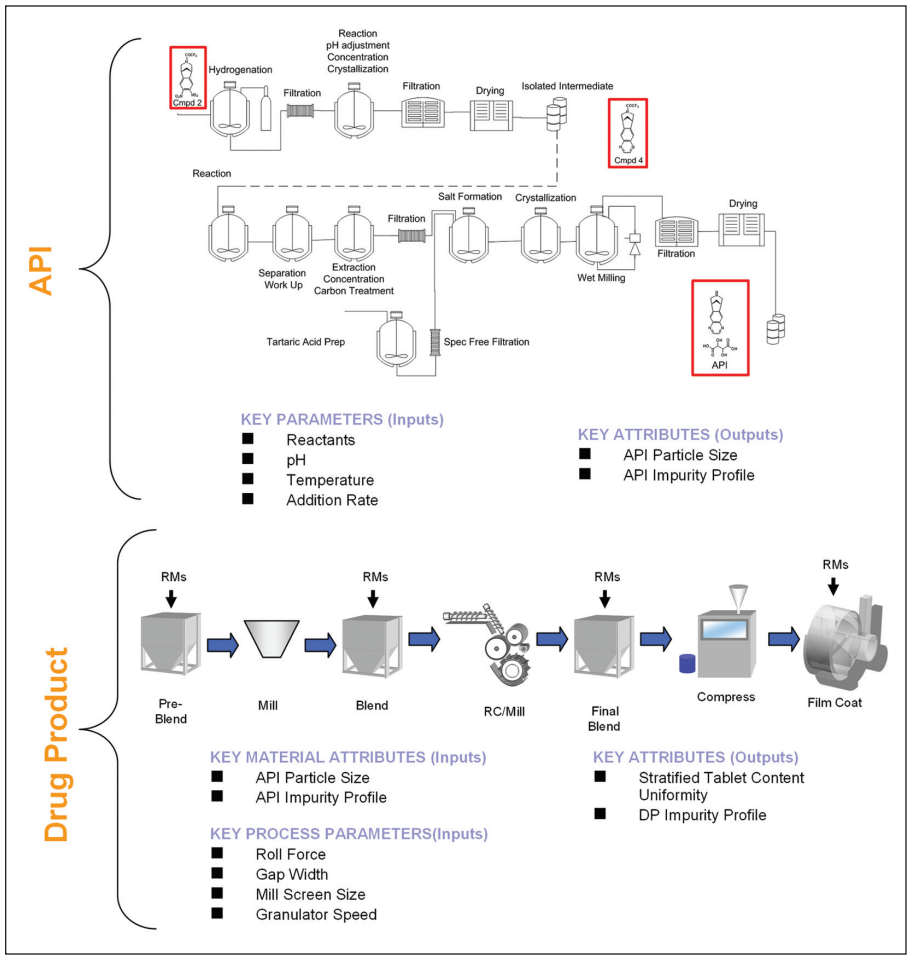


Figure 1. Unit Operation Process Flow Diagram (PFD).

attributes that had the potential for significant impact on the product quality or efficiency were designated as Key Quality Attributes (KQAs). Subsequently, process parameters were identified and numerically ranked (1 to 10 scale) based on their potential to impact the identified quality attributes. A matrix multiplication approach was used to score the relative importance of each process parameter. The process parameters were then sorted from highest importance to lowest. The process parameters that had the potential for significant impact on the established quality attributes were designated as Key Process Parameters (KPPs) and were highlighted with red or yellow to designate the most important to least important. The designation "key" was used to identify those attributes and parameters that would be studied later. *KPP and KQA categories utilized as part of the pilot to determine CPPs and CQAs under the concept that a key parameter might be elevated to critical following further investigation or it may be a parameter, which did not meet the definition of critical, but one which was valuable to track so that additional information was collected. During the wrap-up of the pilot program, the FDA reviewer was accepting of the use of "key" as an intermediate level between non-critical and critical. The ICH guidance did not follow this strategy. As this project is looking at the development of a drug filed in 2005, it is presented here as part of the development of QbD terminology*. A "key" parameter or attribute may eventually be designated as "critical" depending on severity, probability, and detectability of failure.[3]

Quality attributes (Y) were brainstormed and ranked according to the scale below for their potential to impact the product quality:

10 → known or expect a direct impact on safety and/or efficacy of product
7 → unsure or expect impact on product safety, efficacy, or process efficiency (e.g., safety, cost, process performance indicators)
5 → unlikely impact to product quality or process efficiency
1 → no impact to product quality or process efficiency

Likewise process parameters (X) were brainstormed and the potential to impact the quality attributes were ranked according to the scale shown below:

10 → known or expect a strong relationship based on data in hand or experience
9 → don't know, but expect a strong relationship
5 → medium relationship or not sure
1 → known that there is not a relationship

The Cause and Effect Matrices were established by the API and DP development teams. An API-DP bridging sub-team ensured the critical and key API quality attributes were assessed for their impact on drug product attributes. This integrated team identified API impurity profile and API particle size as potential critical quality attributes.

Risk Assessment – API Reaction

Every synthesis requires quality control of the impurities generated. Historially, this quality control has been achieved through the testing of the product and establishing acceptance criterion for the characteristics and purity of the intermediates and API. QbD is a paradigm where the process is controlled through understanding of the reaction parameters, which give rise to the impurity formation, thus it is possible to select the processing parameters to minimize the formation of impurities as much as possible. Testing against the acceptance criterion becomes a mechanism to confirm the performance of the process rather than a "control" for the process. A detailed overview of the control strategy for one of the impurities is provided here to illustrate the QbD approach.

The decision to commit to a QbD approach was made after process development and scale-up work had already started. The initial risk assessment utilized the prior knowledge that had been gained through earlier development and scale-up of the manufacturing process, including a mechanistic understanding of the chemistry, chemical literature, and process scale-up experience. Focused discussion conducted by the development team resulted in prioritized experimental plans to support process understanding. Process understanding began with trials at lab and pilot plant scale. One of the process steps which repeatedly produced product of variable quality was the conversion of Compound 3 to 4, via a cyclization reaction using aqueous glyoxal. The original discovery synthetic route[4,5] utilizing a glyoxal sodium bisulfate addition compound was capricious. Although several process variations were investigated, this transformation remained problematic until additional studies were conducted providing process understanding and control of the impurity formation.

During the synthesis of the desired quinoxaline ring system, an impurity with a benzimidazole ring system was observed. This is displayed in Figure 2. *Figure 2 showing the chemistry scheme is meant to supplement the top line of Figure 1 displaying the Unit operation Process Flow Diagram, showing the intermediate from the reduction and the by-product formed*. In early development, it was thought that Compound 5 would be a major impurity observed in the commercial synthesis.

An early Design of Experiments (DoE) study focused on maximization of the yield showed that formation of impurity Compound 5 was dependent upon glyoxal addition rate as well as glyoxal solution concentration. Fast addition of glyoxal to the reaction produced higher levels of Compound 5. The pH of the reaction was affected by two factors: the starting material

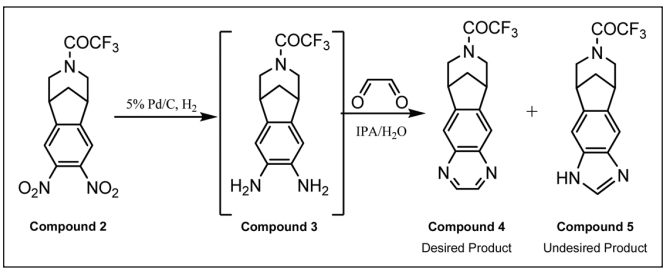
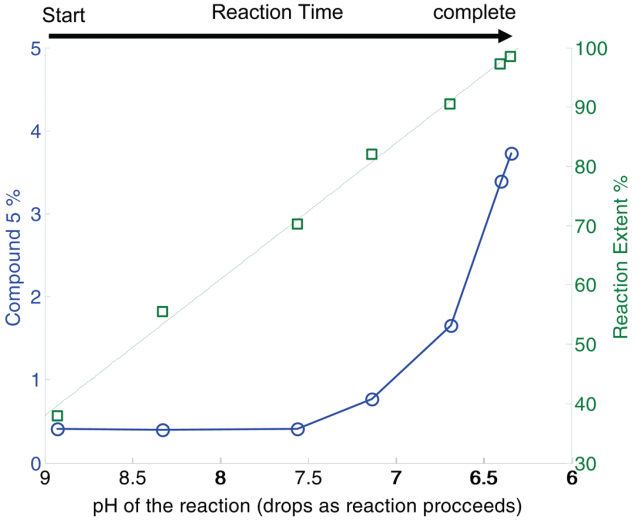


Figure 2. Chemistry scheme of desired reaction, including structure of undesired Compound 5.



The right scale (Green) shows the extent of formation of the desired product (Compound 4) as the reaction progresses. The left scale (blue) shows the amount of the undesired impurity formed. The bottom scale displays the real time monitoring of the reaction for pH. The results indicate that as the pH dropped, the formation of Compound 5 increased rapidly.

Figure 3. Plot of reaction monitoring.

is a di-aniline (basic) and glyoxal is typically pH 2.5 to 4.5. Thus, as the di-aniline is consumed and more glyoxal is added, the pH drops. Control was initially achieved by maintaining slow addition of the glyoxal, which allowed the reaction to self buffer and provided sufficient time for mixing to prevent low pH regions. Yet, the control of the desired cyclization reaction remained problematic. Other factors considered to control the formation of Compound 5 were the pH variation from different lots of glyoxal and the excess glyoxal used.

Preliminary One Factor At A Time (OFAAT) laboratory experiments are sometimes good preludes to DoE studies. An interesting lead was developed when laboratory experiments were conducted adjusting the reaction pH to extremes, i.e., very low or very high. The results from these stress condition experiments clearly pointed to pH being an important variable for further study. Understanding this behavior utilizing the proper PAT technique can provide significant insights. Running the reaction under standard conditions and monitoring the level of Compound 5 and pH revealed an interesting observation (Figure 3). In the initial stages of the reaction, while the pH remained high, only small amounts of Compound 5 were formed and the reaction produced the desired Compound 4. As the reaction progressed and the pH dropped (below 7.5), the rate of formation of Compound 5 increased (at this stage only a small amount of di-amine is present – the reaction is more than 80% complete). Although glyoxal was added very fast, only a small amount of Compound 5 was formed, initially indicating that local pH (mixing) was not the primary factor controlling the impurity, but rather bulk pH variation during the reaction. Armed with this information the team focused on buffering strategies for this reaction system. It was quickly discovered that adding a small amount of sodium bicarbonate can maintain the bulk pH above 8 throughout the reaction time and controlled the level of Compound 5.

Table B contains a distilled view of the Cause and Effect (C&E) matrix for the API reaction Step 4 Focus Area (parameters with very low rankings are not shown). Although Compounds 3, 4, and 5 were ranked in Table B, Compound 5 is of prime focus as it can be a major impurity observed in the synthesis. The development effort also sought to maximize the formation of the desired product, Compound 4. *Due to the QbD initiative being advanced as the development of this chemistry was already underway; Table B was generated after many of the experiments were completed; however, it is still instructive to consider how it can be used to prioritize future experiments*. Experiments can be prioritized based upon the scoring, and the highest priorities are shown in red, while the mid-priorities are shown in yellow.

The Cause and Effect matrix does not include variables, such as equipment configuration, equipment materials of construction, and the like (although for other processes these

Key Attribute	**Y**	**Y**	**Y**	**Score**	**Exp't Strategy**
Rank	**10**	**5**	**7**		
Parameter	**Compound 3**	**Compound 5**	**Compound 4**		
API Reaction Step 4					
Raw Material Quality (40% Aq. glyoxal)	10	10	10	220	OFAAT**
Quality Water	1	10	10	130	FMEA+
Addition Time	1	10	10	130	DoE
Glyoxal Solution Concentration	1	10	10	130	DoE
Order of Addition	1	10	10	130	OFAAT
pH	1	10	10	130	Reaction Monitoring
Reaction Temperature	1	9	9	118	DoE
Reaction Time	1	9	9	118	DoE
Sodium Bicarbonate*	5	5	5	110	OFAAT and DoE
Stoichiometry (Glyoxal equivalents)	5	5	5	110	DoE
Mixing	1	5	5	70	Effect

*The "5" rating was given based upon that sodium bicarbonate is always added to the reaction (0.7-7.0% limits) after the process was revised. If the range studied had included no sodium bicarbonate, the rating would have been a "10" due to the dramatic impact without pH control.
**One Factor At A Time
+FMEA – Failure Mode Effects Analysis

Table B. Cause and Effect Matrix – API Reaction Step 4.

may rise in importance to be key process parameters).

As seen from Table B, several parameters had a higher risk of affecting the impurity levels. Based upon the finding that the formation of Compound 5 showed significant pH dependence (Figure 3), several of the factors originally identified in Table B became less important.

The second and third examples of varenicline Focus Areas were investigated in the drug product and include the dispense/blend and roller compact/mill/blend processes. The formulation work showed a dependence upon the API particle size, thus demonstrating the importance of studying the API-DP process interrelationship.

Risk Assessment – Dispense/Pre-Blend and Roller Compact/Mill/Blend

The risk assessment for key portions of the drug product manufacturing process is summarized in Table C. The key attributes that were identified as having a high potential to impact safety and efficacy were impurities, and blend and tablet content uniformity, respectively. The prior knowledge used by team members in this risk assessment came mostly from an understanding of how material science properties of the API and excipients impact the processing of the blends, granulations, and tablets. Based solely on impact to in vivo performance, the API particle size would be considered as a non-critical material attribute since the API is classified as high solubility and high permeability (BCS Class I). However, based on the impact to the critical quality attribute of stratified tablet content uniformity considered during the initial risk assessment, the API particle size was deemed a critical material attribute.

The drug product formulation was designed to enhance carrier-mediated mixing by selecting small particle size API and large particle diluents prior to granulation.[6] Although dry granulation processing reduced this difference in particle sizes, any ungranulated API particles in the final blend would be susceptible to fluidization segregation during transfer processes between blending and tableting. Therefore, the potential for segregation was monitored throughout development for any impact on the final blend and tablet potency and content uniformity. Early development studies suggested the granulations exhibited a high potential for fluidization segregation.[7] Dry granulation optimization efforts reduced this segregation potential to a moderate category. Therefore, the API particle size was considered as a critical material attribute during the drug product team risk assessment and commercial technology transfer studies.

In the risk assessment, anticipated changes in commercial manufacturing at larger scale were being considered and categorized as having a high likelihood of impacting blend content uniformity and potentially tablet content uniformity. These changes included:

1. increasing the blender fill volume
2. order of addition of API to the blender (adding on top instead of sandwiching between excipients) as simple changes that improved process efficiency

These fill volume and order of addition process changes were investigated through a design of experiments study and a one factor at a time study, respectively, to streamline the acceptance of these anticipated changes based on the QbD regulatory filing. Roller compaction and granulator milling parameters also were studied in a DoE. Most of the key process parameters identified in Table C were studied in experiments summarized below.

Experimental

As a result of the risk assessment analysis, a series of experiments were planned that focus on obtaining an understand-

Key Attribute	Y	Y	Y	Score	Exp't Strategy
Rank	7	7	7		
Parameter	Blend Content Uniformity	Stratified Tablet Content Uniformity	Impurity Profile		
Dispense and Pre-Blend = Focus Area #1					
API Particle Size	10	5	1	112	OFAAT**
Agglomeration of API	10	5	1	112	OFAAT
Container Loading (% fill)	10	5	1	112	DoE
Order of API Addition	10	5	1	112	DoE/FMEA
Impurity Levels in Excipients	1	1	10	84	OFAAT
API Impurity Profile	1	1	10	84	OFAAT
API Milling Procedure	5	1	5	77	OFAAT
Blend Time	5	1	1	49	DoE
Sampling Procedure	1	1	1	21	FMEA
RC/Mill and Blend = Focus Area #5					
Roll Force	10	10	1	147	DoE
Screen Size	10	5	1	112	DoE
Gap Width	10	5	1	112	DoE
Roll Speed	5	1	1	49	DoE
Granulator Speed	5	1	1	49	DoE
**OFAAT = One Factor At A Time +Failure Mode Effects Analysis					

Table C. Cause and Effect Matrix – dispense and pre-blend, and roller compact/mill and blend.

ing of the functional relationships between the key quality attributes and the key process parameters. The designs of these experiments were set up to establish proven acceptable ranges or boundary limits for the processes to operate, i.e., design space. Based upon the risk assessment analysis, the following major experiments were identified that would help to define the functional relationships.

API Reaction Step 4 DoE – to determine which reaction conditions affected the formation of the key impurity.

API Particle Size Modeling – to study impact of particle size on tablet potency and uniformity.

Impact of API Crystallization Process on Particle Size – to determine what conditions affected the API particle size.

Drug Product Blending OFAAT and DoE Studies – to study which pre-blending parameters affected blend potency and uniformity.

Roller Compacting/Milling – to study which drug product manufacturing parameters affected the blend uniformity and tablet uniformity.

API Reaction Step 4 DoE

Based upon the prior knowledge gathered from the DoE and OFAAT studies described above, five key process parameters were expected to impact formation of Compound 5. Several studies were conducted on the quality of the glyoxal, which is supplied commercially as a 40% aqueous solution. It was found that the quality of lots varied by supplier, and that the material changed, giving a precipitate when held longer than six months (a sign that the glyoxal is degrading into trimers and oligiomers). Overall, the quality of the glyoxal was controlled by establishing acceptance criterion for this purchased material and by defining an acceptable holding time. Five of the key process parameters (glyoxal equivalents, glyoxal concentration, sodium bicarbonate, addition time, and reaction temperature) were combined into one Design of Experiments study as shown in Table D. The DoE used for this study was a 5 factor, 2-level, 1/2 fraction (2^{5-1}). In addition to the 16 factorial experiments, the experimental design included three replicates of the centerpoint for testing curvature and reproducibility, and three replicates of the standard conditions for testing reproducibility for a total of 22 experiments. The process ranges of the design are shown in Table D. The impact of these parameters on the quality attributes of API Compound 5 impurity level were investigated.

Variable	Low	Hi
Glyoxal equivalents	1.05	1.3
Glyoxal Concentration (%wt)	5	20
Sodium Bicarbonate ($NaHCO_3$% mol)	0.7	7
Addition Time (min.)	10	120
Temperature (°C)	0	25

Table D. Variable ranges for API Reaction Step 4 DoE experiments.

API Particle Size Modeling

Since API particle size was identified as a critical material attribute for drug product, it was important to understand its functional relationship to the critical quality attribute in drug product, specifically tablet stratified content uniformity. Predictive models are well established that provide a mathematical relationship between API particle size and content uniformity in terms of meeting the tablet potency criteria.[8] The model simulates the entire number, size, and mass of drug particles expected to be found in a batch of solid dosage forms based on the drug particle size distribution input. The prediction algorithm used involves evenly distributing the drug particles across one million unit doses. This model was used to establish the API particle size to ensure drug product met tablet potency and content uniformity acceptance criteria. Although soft agglomerates of API were detected in the pre-blend, the subsequent milling process step effectively destroyed the loose agglomerates and assures blend and tablet content uniformity. Therefore, the theoretical model for API particle size is relevant for the primary particles that are dispersed within the blend following the de-lumping (mill) step.

Impact of API Crystallization Process on Particle Size

The crystallization process of an API can have a significant impact on many attributes of the final API, including polymorphic form, particle size, impurity levels, and yield. A statistical Design of Experiments (DoE) study was completed to evaluate the impact of process parameters of the final crystallization of varenicline tartrate. Particle size and impurity profile are the most likely responses to directly impact product quality and efficacy. While yield is a response that has more relevance to specific business benefit, it also provides a measure for the control of the overall process.

Before beginning a statistically designed experiment on the crystallization, subject matter experts involved in the chemical and crystallization development of the varenicline synthetic process evaluated the salt formation and crystallization process and determined the most important (key) process variables that could influence key product attributes, such as particle size, yield, and impurity profile. A total of eight parameters were identified for evaluation in the laboratory scale/screening DoE. The experimental design conducted on the API crystallization process for particle size understanding consisted of a 2^{8-4} = 16-run fractional factorial with two center points for a total of 18 experiments. The parameters chosen for the design included water content, reaction temperature, L-tartaric acid stoichiometry, initial L-tartaric acid stir time, initial L-tartaric acid concentration, varenicline free base addition rate, agitation speed, and addition point location. The impact of these crystallization parameters on the process yield and particle size measurements was investigated. Table E is a list of each factor used in the study and their corresponding ranges.

A decision was made prior to experimentation to focus the screening DoE study on the crystallization component of the process only and to not include the downstream unit operations. These downstream unit operations included the particle size

Variable	Low	Hi
Water Content	0	6
Reaction Temp (°C)	0	30
L-tartaric Stoichiometry	0.95	1.50
Initial Stir Time (hr)	0.5	8
Reaction Concentration (methanol mL/g)	10	30
Free Base Add Rate (g/min)	3	12
Agitation Speed (rpm)	200	750
Addition Location	Below	Above

Table E. Variable ranges for API crystallization DoE experiments.

reduction/de-agglomeration operations (mechanical milling or high shear wet milling) used to achieve the final particle size through de-agglomeration. *Nanoindentation studies (mechanical analysis of the ductility of the crystalline API demonstrated that varenicline tartrate had a very high plasticity. As a result, mechanical milling of varenicline tartrate will result in de-agglomeration, but primary particle size reduction is very limited*. Due to this decision, standard particle size analysis methods, such as light scattering (Malvern) were of marginal use because the output material for the DoE did not undergo the standard de-agglomeration to form the final primary crystalline particles. At the time this DoE was run, Scanning Electron Microcopy (SEM) were used to determine particle size as a light scattering method was not available. *Particle size was determined by scanning electron microscopy by measuring the length of approximately 50 individual primary particles making up the crystalline agglomerates. An approximate particle size was determined by the average of these particle lengths*.

Due to the difference between laboratory scale and production scale operations, the studies to control particle size were conducted as an iterative process. The initial studies were used to tune the scale-up process. These were followed by refining laboratory studies, which were then tested again on scale-up. The control of both primary particle size and aggregates formation were evaluated as part of these studies. In this case, these particle assemblages are rigidly bound particles, referred to herein as aggregates as known by Gerstner.[9] Following the screening study, additional OFAAT studies were completed to hone the process. These included further investigations of

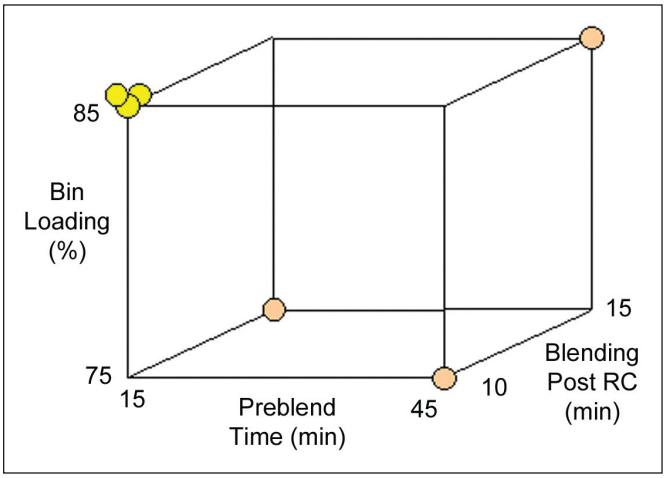


Figure 4. Fractional factorial design of experiments for blending conducted at commercial scale.

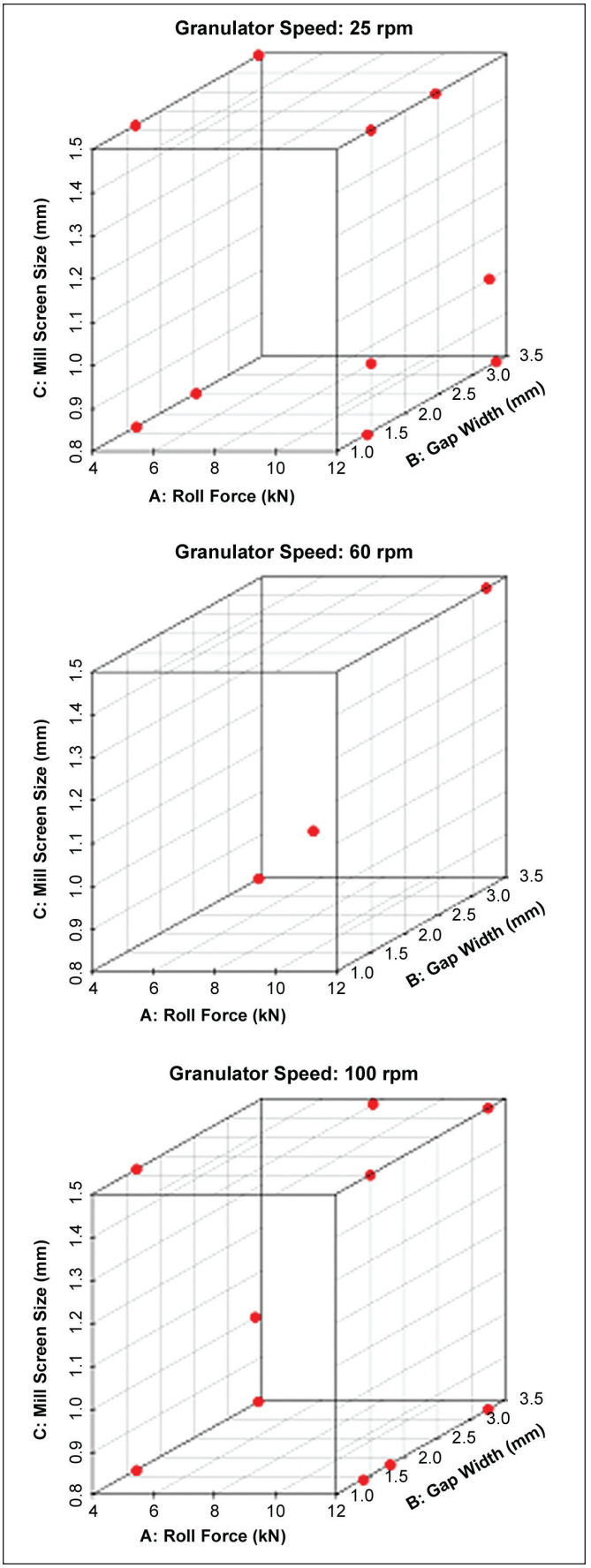


Figure 5. Statistical DoE to evaluate impact of roller compaction parameters.

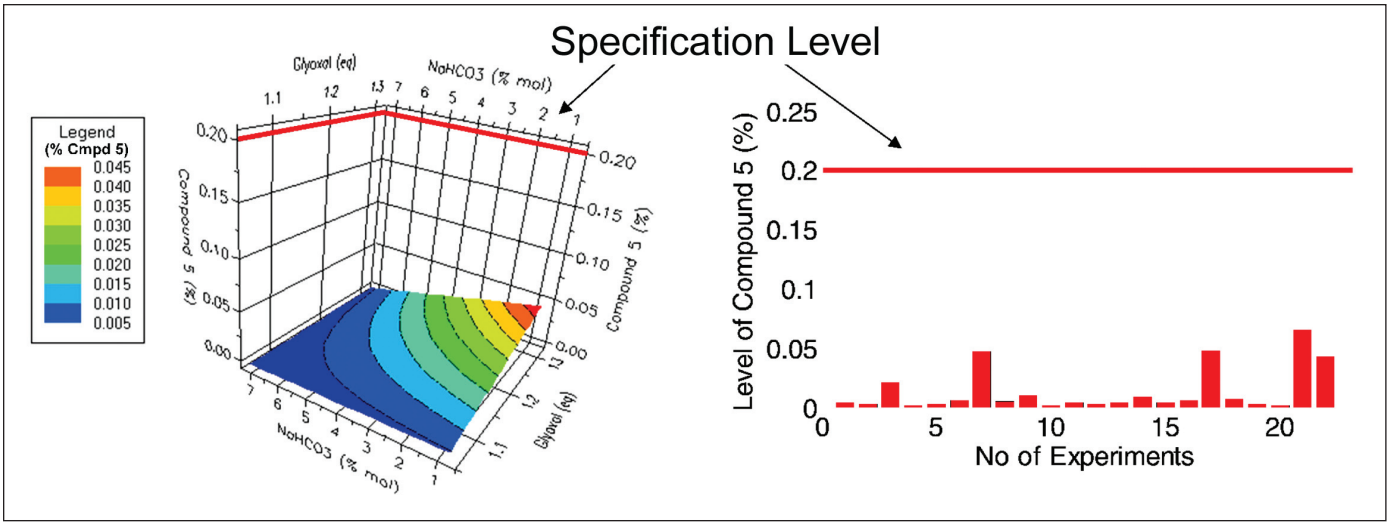


Figure 6. Contour plot of compound 5 formation as a function of glyoxal charge and base.

stirrer speed, addition time, crystallization temperature, and stirrer configuration.

Drug Product Blending OFAAT and DoE Studies

Several studies were conducted on the initial pre-blend process that incorporated a milling step to ameliorate API agglomerates formed during the pre-blending operation to define preferred process ranges. In this case, these particle assemblages are loosely bound particles that are easily dispersed, referred to as soft agglomerates.[10] An OFAAT study was run to evaluate the effect of pre-blending time and the delumping step on blend uniformity. Pre-blend times of 15, 30, and 45 minutes were studied prior to the delumping step.

A design of experiments study was later conducted at the commercial site to further evaluate the impact of the blending conditions on the final tablet content uniformity. This study was performed as a 1/2 fractional factorial design on three process parameters, including pre-blending time (15 to 45 minutes), blending time post-roller compaction (10 to 15 minutes), and the bin loading percentage fill (75 to 85%), as depicted in Figure 4. These final blends were tableted using a centrifugal-feed system on the press with what was later determined to be very low residual blend remaining after press shut-down of approximately 0.3 kg.

Roller Compacting/Milling

Statistically designed experiments (Figure 5) were performed to evaluate the impact of roller compaction and milling process parameters on tablet potency and content uniformity. This DoE was performed using a D-optimal response surface design[11] with four factors: Roll Force (RF), Gap Width (GW), mill Screen Size (SS), and Granulator Speed (GS). These final blends were tableted using a gravity-feed system on the press, with common residual blend remaining after press shut-down of approximately 1 kg.

Results and Discussion

Results of API Reaction Step 4 on Impurities

The DoE study showed that the key process parameters that significantly ($p < 0.05$) affect Compound 5 formation were glyoxal equivalents (A), % sodium bicarbonate (B), and the AB interaction. The contour plot in Figure 6 demonstrates that as the level of sodium bicarbonate increased and the glyoxal equivalents decreased, Compound 5 impurity could be minimized. Further, the buffering with sodium bicarbonate was found to minimize the formation of Compound 5, even at the lowest level studied, 0.007 mole percent.[12] In the final buffered system, the lack of a trend revealed that the addition of base eliminated much of the variability in the process, and thus minimized the undesired reaction.

Although a small amount of base and a large amount of glyoxal increased Compound 5, the level stays well below the acceptance criterion levels for all experimental conditions.

The previous experiments on API described above in the Risk Assessment section showed that pH needed to be controlled to minimize the formation of Compound 5. The subsequent DoE was designed to qualify the proven acceptable range when including sodium bicarbonate as a buffer in the process. With the pH controlled by the presence of sodium bicarbonate, the level of Compound 5 was controlled to well within the desired level. As can be seen in Figure 6, the response surface stays below the 0.05% level over the range studied. Looking on the experimental points on the bar graph, the values are well below the acceptance criterion of 0.2%. This represented a major improvement from the 1 to 8% levels seen in runs where the pH had not been controlled.

The results on the DoE demonstrate that for the buffered system, the addition rate (thus mixing) does not play a significant role in controlling the formation of Compound 5. The outcome of the DoE where buffering was studied, suggests that pH is the most important factor for this step. If a small amount of bicarbonate is added, none of the other factors matter. Because the amount of bicarbonate is small, controlling the grade of the water can be an alternative (as shown in the C&E matrix). *There is evidence that on earlier lots, prior to the discovery of the importance of buffering, where the buffering effect of calcium salts in the potable water, may have been enough to control the impurity formation*. Prior to

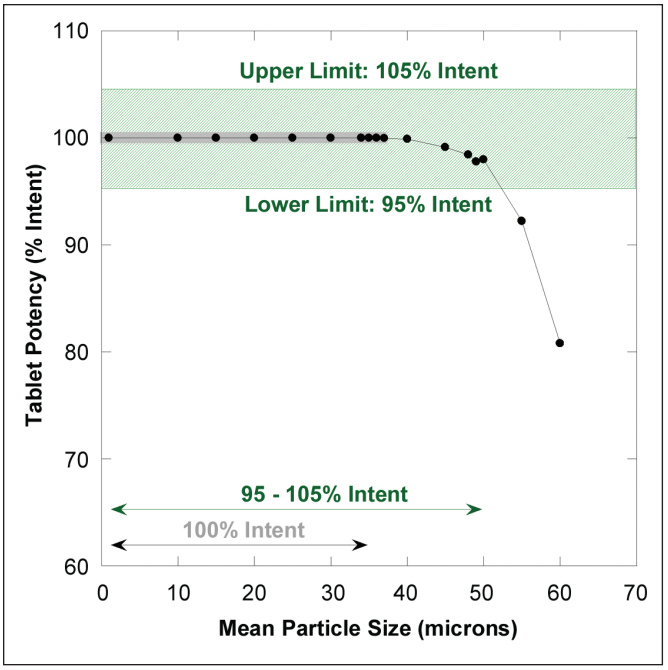


Figure 7. Effect of mean API particle size on tablet potency using a theoretical model for low dose solid dosage forms.

the understanding of the importance of pH on the formation of Compound 5, the critical factors to process control included quality of water used, concentration of the glyoxal, and the rate of glyoxal addition. However, by understanding the reaction mechanism of the formation of this impurity, a robust control strategy was developed by setting the appropriate process parameters, i.e., inclusion of bicarbonate addition.

Results of API Particle Size Modeling

The predicted relationship between API particle size and tablet content uniformity, represented in terms of meeting the tablet potency criteria, is shown in Figure 7.

The model predicted that > 95% of the tablets would meet the European mean tablet potency lower limit of 95 to 105% for mean API particle sizes up to 50 microns (shown by green hatched region). However, during early development of this product, the most conservative prediction in which > 99% of the tablets were predicted to meet 100% potency (shown in gray shaded region) was used to guide the initial mean API particle size target of 35 microns. Subsequent studies were directed at understanding crystallization conditions that would produce API within this range.

Impact of API Crystallization Process on Particle Size

Statistical analysis of the scanning electron microcopy data from the screening DoE revealed that two parameters had a significant influence on the primary particle size. These parameters were reaction temperature and reaction concentration. Larger primary particle size was observed as the reaction temperature was increased and the concentration of the process was decreased. The contour plot in Figure 8 shows the effect of the reaction temperature and reaction concentration on the primary particle size. Figure 9 shows two scanning electron microscope images of the crystalline agglomerates collected during the screening design. Content uniformity and visual observation supported that these agglomerates were broken up in the subsequent milling steps.

As a part of the screening design, the impurity profile levels in the final API were evaluated. It was shown that all conditions evaluated within the parameter space in the screening design gave varenicline tartrate API meeting the desired impurity profile. The impact of the process parameters on the yield of the process also was determined. While there was a small variation in the yields for the individual runs in the screening design, the yields were all within the desired range for the process. The L-tartaric acid stoichiometry was shown to have a small impact on yield with excess L-tartaric acid levels having a deleterious effect, due to the increased solubility of varenicline tartrate in methanol in the presence of excess L-tartaric acid.

It is important to note that screening designs as performed above are meant to ascertain the important parameters and parameter interactions and are not meant to be used for optimization. Optimization designs and other iterative approaches are generally used for process optimization. A series of follow-on studies performed at laboratory and production scale collected data on many process parameters, relative to the particle size quality attribute. These studies provided further evidence that the parameters of reaction temperature and reaction concentration had the most significant impact on primary particle size. In contrast to the screening design, additional pilot studies showed that the addition rate of the free base had an impact on particle size with faster addition rates resulting in slightly smaller particle size. These "learnings" were incorporated into the final API process design.

As the process was implemented at manufacturing scale, minor modifications to the reaction temperature were implemented to reduce the primary particle size. Since all process conditions gave aggregated crystalline clusters, a high shear wet milling operation prior to isolation that enabled breakage of the aggregates also was implemented.

In summary, evaluation of the process using a screening

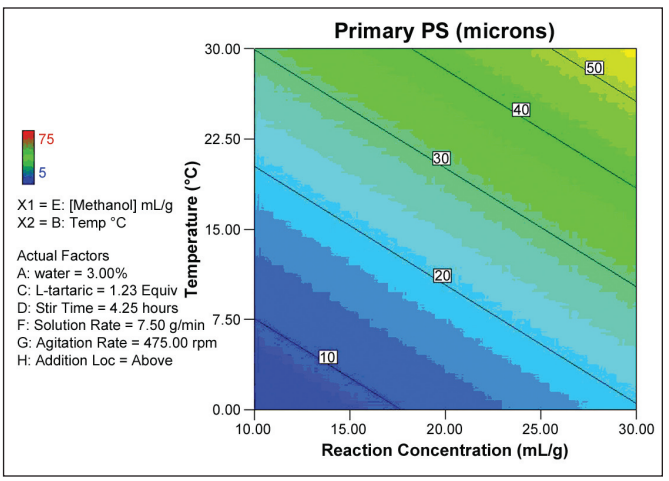


Figure 8. Contour plot of Varenicline Tartrate primary particle size as a function of reaction temperature and reaction concentration.

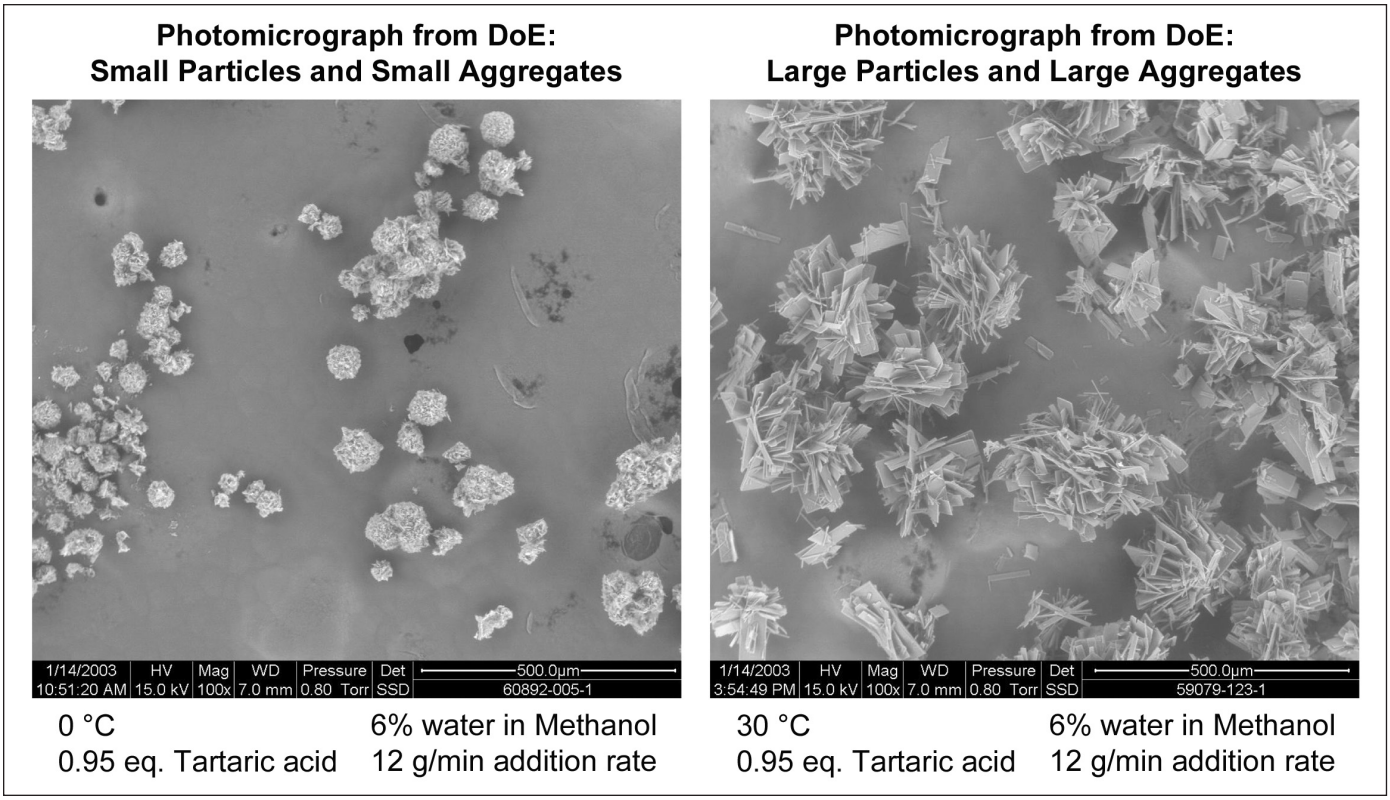


Figure 9. Photomicrographs from DoE.

DoE coupled with OFAAT and process iterations using scale-up runs showed that primary particle and aggregate size can be altered by adjusting addition rate, reaction concentration, and reaction temperature. The experimental results showed that the primary particle size is principally controlled by the crystallization process. Based upon the results of laboratory and scale up studies, a process was developed that consistently delivered a particle size range (D[4,3] of primary particles) of 15 to 25 µm.

Results of Drug Product Blending OFAAT and DoE Studies

The effect of API particle size on stratified tablet content uniformity appeared as a slight trend upward, as shown in Figure 10. This trend was not statistically significant, and the resulting %RSD values were all within the content uniformity acceptance criteria for that CQA (< 6% RSD). The commercial batch exhibiting an %RSD value > 5% was concerning because of the proximity to the acceptance criteria of 6%, but more importantly, because the other part of the stratified tablet content uniformity criteria on the mean stratified tablet potency of 90 to 110% failed (see Lot E in Figure 12). Thus particle size of the API remained a critical material attribute for the formulation of the drug product. The cause and solution to this higher variability at commercial scale is described in the "Impact of Blending DoE on Tablet Content Uniformity" section.

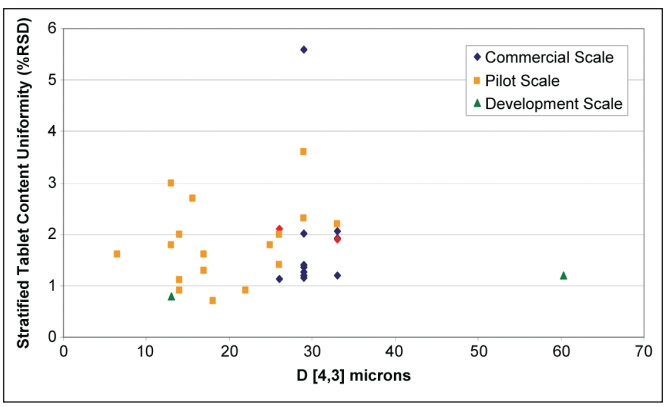
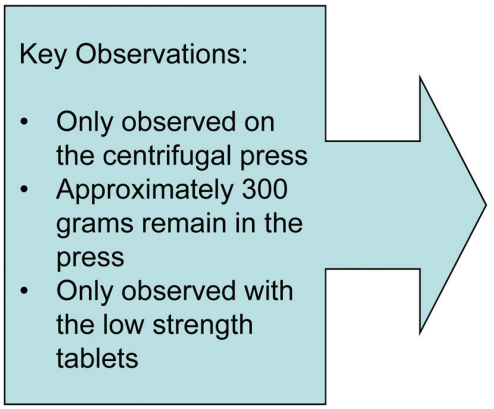


Figure 10. Effect of API particle size on stratified tablet content uniformity for laboratory to production scale.

The first pre-blend study explored the impact of blending time prior to roll compaction. Visible observations of 1 to 2 mm soft-agglomerates in the pre-blend were noted during sampling on the first large scale trial that utilized commercial API process. The agglomerates from the pre-blend step were destroyed in the subsequent milling step instituted on that first batch, which is demonstrated by the results in Table F with blend potency values of 97.0 to 100.1% and uniformity of 0.9 to 2.4% for the 15 to 45 minutes pre-blending time study. The pre-blend (prior to milling) potency results are below 95% for 15 to 30 minutes pre-blending time, which provides evidence of agglomerates not being sampled in the pre-blend (low potency). However, after milling, the potency and uniformity are consistent with the final granulated blend (bottom row in Table F). The final granulated blend uniformity results from the OFAAT study, as shown in Table F, demonstrated that milling to delump the API agglomerates ensured final blend potency and uniformity were on target over the entire



Possible Causes	Evidence Needed To Confirm Hypothesis	Data Supported Hypothesis?
Non-uniform blend prior to compression	Blend uniformity problems	No
Segregation induced during transfer to tablet press	Expected a spike in potency at end of run	No
Segregation induced by low hydrostatic pressure at the centrifugal feed	Super-potent tablets near the end of the run rapidly followed by sub-potent tablets at the end of the run	Yes

Figure 11. Kepner-Tregoe analysis.

range of pre-blend times from 15 to 45 minutes. This work provided the justification for the milling to be an integral step in the drug product process to assure product quality.

The results from the statistical analyses for blending DoE trials at the commercial site are tabulated in terms of their p-values (Table G). The statistical analysis revealed that these process parameters had no significant affect on final blend uniformity or stratified tablet content uniformity (p-values > 0.10). These findings further supported the justification for the mill/delump operation to follow the pre-blend step as a means to eliminate API agglomeration during pre-blending step. The main conclusions for the blending studies are:

1. API agglomerates formed during tumble blending are resolved by inserting a de-lump step prior to lube
2. p values of > 0.05 indicated there was no significant impact of the input variables (blend times and blender fill volume) on the final blend and tablet uniformity
3. the proven acceptable range for blending times are 15 to 45 minutes for pre-blend, and 10 to 15 minutes for final blend
4. acceptable blend uniformity was obtained for bin charges ranging between 75 to 85%

Results of Roller Compacting/Milling DoE

A statistical evaluation of the data from the roller compaction/milling DoE study, listed in Table H, revealed that Roll Force (RF), Gap Width (GW), and mill Screen Size (SS) impact mean tablet potency and % RSD (tablet content uniformity). Roll force had a strong effect on stratified tablet potency ($p < 0.0001$). An increase in RF correlated to increased tablet potency. Actual response values for stratified tablet potency ranged from 96.8 to 99.2% (Table I). Higher potency values suggest less segregation during subsequent processing.

The final regression model describing the functional relationships between tablet potency (%) and tablet content uniformity with RF (kN), GW (mm), and SS (mm) are listed in Equations (1) and (2), respectively.

$$\text{Mean Tablet Potency} = 98.1 + 0.6\ RF \quad \textbf{(1)}$$

Blending Stage	Pre-Blend Time 15 minutes		Pre-Blend Time 30 minutes		Pre-Blend Time 45 minutes	
	Average Potency (% LC)	RSD (%)	Average Potency (% LC)	RSD (%)	Average Potency (% LC)	RSD (%)
Pre-Blend	89.0	2.4	93.0	2.4	98.7	3.4
Milling (Delumping) Step						
Blend After Milling/ Lubrication (2 minutes)	97.0	1.0	99.0	0.9	100.1	2.4
Roller Compaction/Milling Step						
Final Blend (3 minutes)	99.0	0.8	99.0	0.9	99.0	1.8

Table F. Pre-blend OFAAT study to justify range of parameters and mill step.

Variable	% RSD of Final Blend	% Intent of Final Blend	% RSD of Stratified Tablet Cores	% Intent of Stratified Tablet Cores
Pre-Blend Time (minutes)	0.11	0.69	0.58	0.16
Blend Time after Roller Compaction (minutes)	0.78	0.69	0.51	0.62
Bin Loading (%)	0.60	0.10	0.24	0.62
% Intent refers to % Intended Potency				

Table G. p-Values for blending DoE study at commercial scale.

	Parameters				Quality Attributes	
Run Order	Roll Force, RF (kN)	Target [Actual] Gap Width, GW (mm)	Mill Screen Size, SS (mm)	Granulator Speed, GS (rpm)	Mean Tablet Potency (% Intent)	Tablet Uniformity (%RSD of Potency)
1	12	1.7 [1.80]	0.8	100	99.2	0.6
2	4	3.5 [3.45]	0.8	100	97.5	0.8
3	12	3.5 [3.35]	0.8	25	98.9	0.4
4	4	1.7 [1.65]	0.8	25	98.2	0.8
5	12	3.5 [3.25]	0.8	100	98.7	0.3
6	4	3.5 [3.45]	1.5	25	97.5	0.7
7	4	1.7 [1.65]	1.5	100	97.6	1.5
8	12	1.7 [1.50]	1.5	25	98.9	1.0
9	12	3.5 [3.25]	1.5	100	99.0	0.5
10	12	3.5 [3.25]	1.0	25	98.5	0.5
11	8	2.6 [2.45]	1.0	50	98.7	0.8
12	4	3.5 [3.40]	1.0	100	97.7	0.7
13	8	3.5 [3.35]	1.5	100	97.9	0.8
14	12	3.5 [3.20]	1.5	50	98.5	1.0
15	12	1.7 [1.50]	1.5	100	98.7	0.6
16	4	1.7 [1.63]	1.5	25	96.8	0.8
17	12	2.6 [2.45]	1.5	25	98.1	0.6
18	12	1.7 [1.45]	0.8	25	98.7	0.6
19	4	3.5 [3.45]	0.8	50	97.8	0.6
20	8	3.5 [3.30]	0.8	25	98.4	0.7
21	4	1.7 [1.65]	0.8	100	97.3	0.8
22	4	2.6 [2.52]	0.8	25	96.8	0.8
23	12	1.7 [1.40]	0.8	100	97.8	0.6

Table H. Summary of results for roller compaction/milling DoE.

$$\text{Log(Table Potency RSD)} = -0.15 - 0.08\,RF - 0.06\,GW + 0.06\,SS \quad (2)$$

RF appeared to have an effect on tablet content uniformity ($p = 0.0025$). There was an indication that two other process variables, GW ($p = 0.0308$) and SS ($p = 0.0180$), affected tablet content uniformity, as well. The model indicates that smaller SS, higher RF, or larger GW improved tablet content uniformity independently of each other. Actual response values for the % RSD of the stratified tablet potency ranged from 0.3 to 1.5%, easily meeting the acceptance criteria of ≤ 6% for development and 5% for routine commercial batches. Although statistically significant affects, the results demonstrate that there is low risk to quality when operating the press with an automatic shut-off of approximately 1.5 kg blend remaining in hopper.

Higher RF during dry granulation produced tablets with improved uniformity throughout the run, as measured by stratified tablet samples taken during compression and assayed for potency. However, all compaction and milling conditions explored in this investigation produced drug product that met the target acceptance criteria for stratified tablet content uniformity. Therefore, the proven acceptable range for the roller compaction and milling operating parameters were established at 4 to 12 kN RF, 1.7 to 3.5 mm GW, 0.8 to 1.5 mm SS, and 25 to 100 rpm granulator speed. The normal operating conditions for RC and milling parameters were set at 7kN RF, 2.6 mm GW, and 1.0 mm SS, respectively.

Impact of Blending on Tablet Content Uniformity

Stratified Tablet Content Uniformity (STCU) was identified during the risk assessment to be an important quality attribute for detecting unacceptable tablet potency and content uniformity. Common causes of such an issue include poor uniformity blends charged to the press or segregation of blends during transfer from blender to press hopper. During technology transfer from the pilot scale to the commercial site, a change in operating principle for the tablet press occurred. Therefore, samples were collected during the compression

Response (intercept)	RF Coefficient (p-value)	GW Coefficient (p-value)	SS Coefficient (p-value)	GS Coefficient (p-value)	RF × GW Coefficient (p-value)	RF × SS Coefficient (p-value)	SS^2 Coefficient (p-value)	Overall (p-value)	R^2 for Prediction
Mean Tablet Potency (98.1)	0.6 (< 0.0001)	---	---	---	---	---	---	< 0.0001	0.5878
Log (Tablet Potency RSD) (-0.15)	-0.08 (0.0025)	-0.06 (0.0308)	0.06 (0.0180)	---	---	---	---	0.0020	0.2920

Table I. Summary of results of the statistical analyses for the roller compaction/milling DoE study.

trials with greater number of samples during start-up and shut-down operations. The results were assessed against the tablet potency and uniformity criteria.[13]

The STCU test results were instrumental in detecting a spike in the tablet potency during shut-down when approximately 300 grams of blend was remaining in the press, as shown by the mean tablet potency data and acceptance criteria in Figure 12. At this point, a mechanically induced segregation of the blend occurred, due to the lack of head pressure on the blend being fed to the tablet dies. As a result, an automatic press shut-off was implemented to eliminate the risk of high potency tablets entering a batch. The press shut-down was set to divert all tablets to waste after the press hopper low-level indicator alarm, which occurred at approximately 1.5 kg of blend remaining. Acceptable control of the process was accomplished through the stratified sampling of in-process tablet cores throughout the compression run. Control of these process parameters, as demonstrated by the results of testing of stratified samples of tablet cores, has resulted in the production of tablets that consistently exceed quality standards for content uniformity (Figure 13). These batches also satisfied the other two acceptance criteria for the stratified tablet content uniformity.

During the blending trials conducted at the commercial site, STCU was the critical quality attribute that identified the edge of failure for compression of the granulation on a centrifugal feed press. Team-based problem solving tools were utilized to identify the root cause of this failure so that appropriate controls could be implemented to solve the issue.

The problem solving tool used by the team to identify the most probable cause of the issue was the potential problem analysis by Kepner-Tregoe (K-T).[14] Three potential causes were identified and assessed for supporting evidence, and the potential cause exhibiting the greatest supporting evidence being deemed the cause of the issue as shown in Figure 11. In this case, the team identified three distinctions of the issue, including only 300 grams remaining in the press, only incidences occurring in the centrifugal feed press, and only for the lowest dosage strength tablet. Three potential causes consistent with the issue and distinctive features identified by the team were:

1. non-uniform blend prior to docking the blender onto the press
2. segregation induced by press operation
3. segregation induced by centrifugal feed of final blend in absence of hydrostatic pressure

A K-T analysis performed led to the only plausible explanation: The loss of hydrostatic pressure led to centrifugal induced segregation of the blend and poor tablet content uniformity.

1. The non-uniform blend prior to docking on the press would have been detectable by blend content uniformity issues or super- or sub-potency of blend in sample of top layer of blender. These were not the case since blend content uniformity results ranged between 1.2 to 3.0% RSD, and a special blend sample from 1/4 inch below top surface being 100.9% intent. Therefore, this was not likely the cause.
2. The segregation induced by press operation would have evidence in the form of a trend of super-potent tablets at the end (actually detected a spike in potency, but was not preceded by a trend); or super-potent blend remaining in the press at the end of the run (actually sample and test results indicated 70% intent); or press shutdown during routine operation could cause discontinuity in core tablet potency (not revealed in subsequent studies). Therefore, this was not likely the cause of the potency spike.
3. Segregation induced by centrifugal feed of final blend in absence of hydrostatic pressure would have evidence of uniform blend prior to docking on the press (yes), uniform blend throughout compression with or without shut-down (yes), lack of material on the rotor (correct, as no blend remained on rotor); rapid on-set of super-potent tablets at the end of compression, due to lack of hydrostatic pressure on blend in rotor (yes at 120%); and finally, the remaining blend in the press channels would be sub-potent (yes at 70%). This also was supported by the calculation of blend to fill dies and channels feeding dies amounting to approximately 360 grams of blend compared to the 300 grams recovered. For the press speeds and number of dies, this meant there was less than 60 seconds of operation before

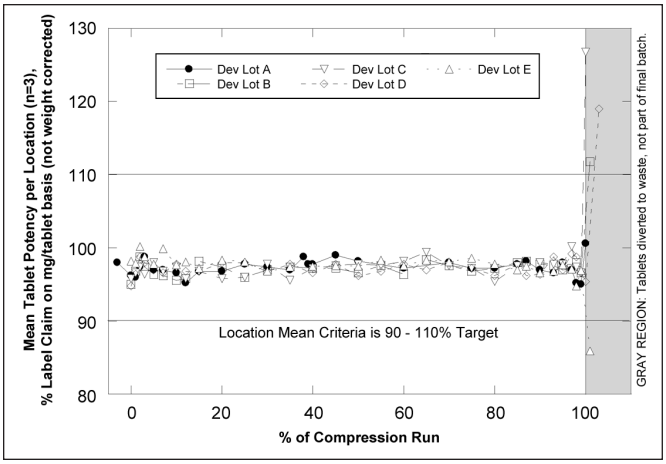


Figure 12. Impact of blending DoE studies on stratified tablet content uniformity as a function of compression runtime.

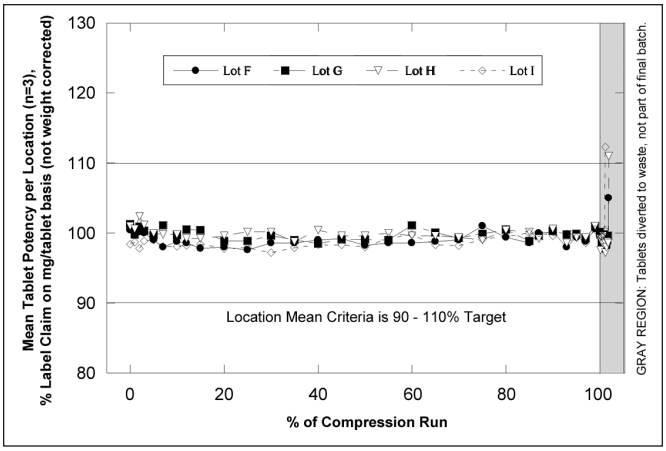


Figure 13. Stratified tablet content uniformity as a function of compression runtime with press shut-down control implemented.

the press were completely depleted of all blend. All the evidence supported the cause being segregation induced by the loss of hydrostatic pressure on the blend in which the press was essentially run dry.

Conclusions

A holistic approach to Quality by Design was pursued for the design and development of the solid oral drug product varenicline tartrate (Chantix®/Champix®). This approach lends itself to a closer integration of the Active Pharmaceutical Ingredient (API) with drug product as the scientific team sought to develop a fundamental understanding of the product. Application of risk assessment tools, such as process flow diagrams and cause and effect matrices provided a systematic approach to identify risks associated with critical process parameters, material and quality attributes. The risk assessment focused the scientific debate, design of experiment studies and process modeling to enable process understanding that transcended API and drug product. The critical quality attributes for API included impurity levels (exemplified above by control of Compound 5) and API particle size, whereas the critical quality attribute for drug product was the stratified tablet content uniformity. The drug product purity profile remained classified as a key quality attribute because of the quality assurance provided by the API process understanding and control.

Based upon the improved understanding of the process achieved by the QbD approach, the API Step 4 reaction process robustness was increased by addition of a small amount of sodium bicarbonate to prevent the pH from dropping during the reaction, thus minimizing the formation of the undesired Compound 5 and maximizing the formation of the desired Compound 4.

The API particle size process understanding was complicated by having to monitor both the size of the aggregates and the size of the primary particles. Control of primary particle size was achieved through crystallization temperature with the normal operating range of 15 to 25°C. The final particle size acceptance criterion were determined to be the volume mean diameter of not more than 35 microns. Agglomerates were controlled with a milling operation after the pre-blend step. Based upon these studies and the experience gained in scale-up trials, the commercial API crystallization temperature and addition rate were adjusted to ensure the particle size remained below 35 microns and was targeted at 20±5 microns for routine manufacture.

The drug product process robustness for high potency tablets at the end of compression was assured by tablet press shut-off control instituted to prevent segregation when the press was essentially empty of blend.

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Acknowledgments

The authors wish to extend their gratitude to the following people for their valuable contributions: Bill Arikpo, Bob Ball, Dot Beaulieu, John Berridge, Dan Blackwood, Deborah Booth-Schindler, Steven Brenek, Karen Bronk, Kelly Canter, Anthony Carella, Alanya Engtrakul, Andreas Fleisher, Rashmi Gadkari, Thomas Garcia, Sal Garcia-Munoz, Tim Graul, Christina Grillo, Alton Johnson, Phil Johnson, Fasheng Li, Matt

Mullarney, Ralph Moessner, Sara Moses, Roger Nosal, Dan O'Connell, Eanna O'Maitiu, Amy Orce, Angel Otano, Kirsten Reinheimmer, Eveline Reininger, Terry Sinay, Chris Sinko, Jim Spavins, Greg Steeno, Rob Timpano, Kim Vukovinsky, Gregory Withbroe, Marcella Whelan, and Kim Zoka.

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Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2010, Vol. 30 No. 4
www.ISPE.org

Virtualization – Compliance and Control

by Ulrik Hjulmand-Lassen

This article presents the advantages and risks associated with the use of virtualization techniques in regulated areas and provides a list of quality focus issues to review, as a prerequisite to avoid the most likely pitfalls.

Introduction

Background

As budgets become tighter, data centers run out of space, and Green IT becomes a hot topic, management increase pressure on IT teams to find solutions on how to accommodate more software applications in less space using fewer resources. The solution, as it appears in the media, is virtualization as pointed out by Wildangier and Jensen in *Pharmaceutical Engineering*, Vol. 27, 2007.[1]

By using server virtualization techniques, life sciences organizations can gain several advantages, apart from the widely promoted ability to consolidate several underutilized servers on larger host(s). By introducing Virtualized Environments, it is possible for servers to become more specialized in function, as the cost of separating small or less intensively used applications onto separate Virtual Machines is significantly less.

This simplifies the server build and setup and allows staff to focus on key issues, such as the specific operating system functionalities and security settings, such as services and open ports. Managed correctly, this reduces the complexity of the individual Virtual Machine, enables security settings to be more appropriately defined, and reduces the physical server-count compared to the traditional hardware bound situation.

Before the use of virtualization, the installation of multiple applications on a single hardware server brought potential security and interoperability issues, meaning either that sharing hardware had to be avoided or preceded by significant risk assessment, impact assessment, and regression analysis.

Virtualization Advantages

In regulated industries, a best practice is to maintain at least three server landscapes per application, usually as development, validation, and production systems. With virtualization, these environments are both cheaper to establish and have the potential to become much more similar than in the physical world, when less limited by physical or monetary constraints. Application servers running as virtual machines in a virtual environment also offer numerous management, maintenance, and availability features that are difficult to obtain otherwise. Some virtualization products allow clusters of virtual hosts to be established making it pos-

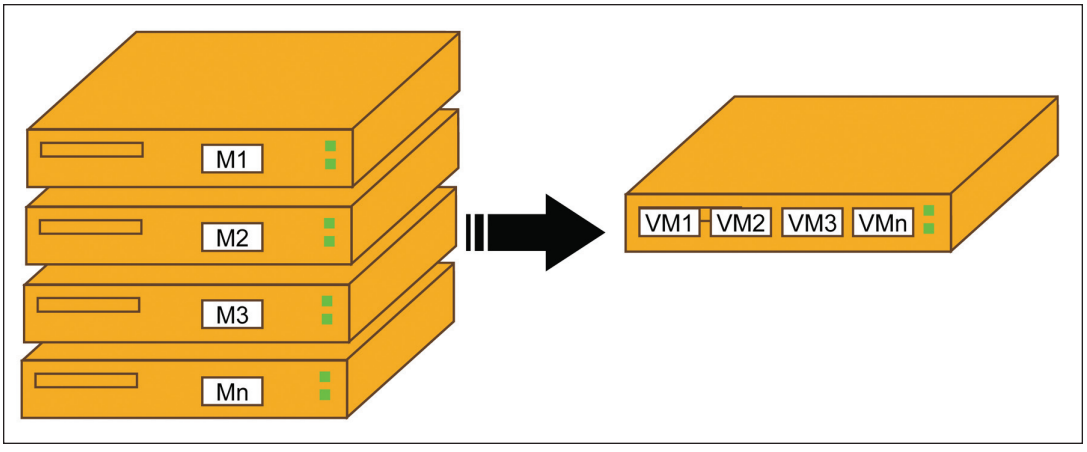

Figure 1. Virtualization allows the consolidation of underutilized physical servers by creating logically independent operating environments within a single server (or cluster of servers).

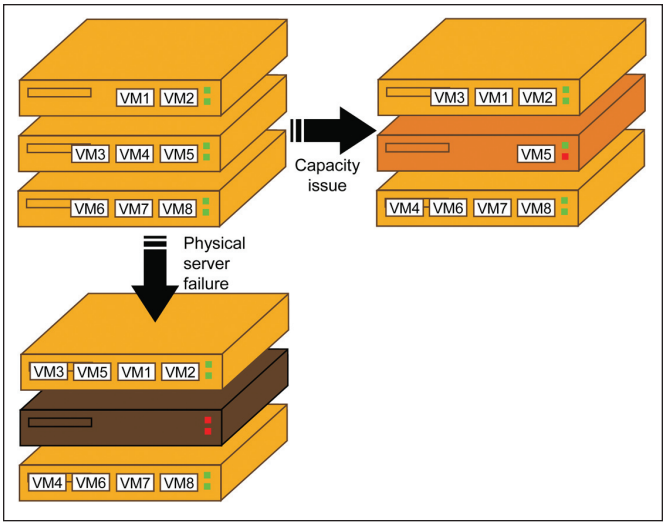

Figure 2. A properly configured VM cluster allows seemless failover of some of the virtual servers to other physical servers when capacity limits are reached, or all of them in case of a complete failure of the host.

sible to move (migrate) a running server between physical servers (either manually or automatically) without interruption. This enables maintenance and hardware replacement to be conducted in an entirely new way, allows resources to be dynamically allocated when needed, and provides greater availability and business continuity.

These are significant advantages compared to traditional operations where discrete resources, such as processors, memory, storage, etc., had to be added only when a server shut down and restart was authorized by business operations. The newest generation of virtualization technology, such as vSphere® from VMware®, offers mirrored CPU functionality at a very low performance penalty with complete transparency to the software application and its operating system.

Many systems often will have a much longer lifetime than anticipated by vendors when compared to ordinary business use partly due to the cost of bringing them into operation in regulated environments. This creates the dilemma that hardware wear and tear restricts the hardware lifetime, while software is kept running on an increasingly expensive platform, as the hardware becomes more and more expensive to maintain if supported at all.

The encapsulation of virtual servers in logic environments makes it possible to keep older configurations running much longer (if allowed by security policies) as the dependency between driver availability/compatibility and the underlying hardware is reduced or eliminated in many configurations. This allows life sciences companies to continue to operate mission critical software applications long beyond the life of the original hardware. Virtualization will, in many cases, offer a platform that can be maintained for a much longer period of time, without forcing validated applications to be changed because of the hardware abstraction.

Perfect – or too Good to be True?

The big question is whether all of these benefits come by themselves or (if not) what does it take to obtain them without compromising security policies, threatening business continuity, or sacrificing the level of control required by applications used for regulated purposes? It also is useful to identify prerequisites for success, any new tasks or risks, and whether it is possible to introduce measurements or parameters that enable virtualized environments to be measured, compared, or audited against set requirements.

Regulated companies need to consider the extent to which virtualization means increased complexity and whether special quality assurance or quality control activities are required. For example, does virtualization challenge existing procedures and processes like security and configuration management, and to what extent will the technology require new competencies to be acquired or hired?

Maintaining Compliance

Because the technology is relatively new, built-in support for generating configuration management baseline reports of settings or privileged user accounts to support periodic review is often unavailable. Under these circumstances, using this technology to support key business and regulated functionality requires users to conduct complex manual review processes or search a number of third-party tools that offer solutions to address some of the inherent risks.

Added Complexity in a New Environment

The need for administration, software licenses, and training can considerably delay and/or decrease actual cost reductions when compared to the savings suggested by vendors. This means that virtualization should not have cost saving as the only objective and where cost savings are a key objective, realistic return on investment calculations should bear in mind the cost of compliance in a complex environment.

It is worth noting that consolidating servers into a virtualized environment moves maintenance tasks from hardware to software, as many hardware boxes are removed and virtualization only adds a few servers. Also new server technology is added, either as: 1. some virtualization products bring a variant of Linux or 2. introduction of a relatively immature virtualization platform from other vendors, where you have to evaluate whether the security patch policy and maintenance schedules match the requirements of your business.

The virtualized environments will by nature reduce the number of hardware boxes, but in the end, a few additional servers and workstations also must be added to allow for maintenance and access administration. Backup/restore routines also will need to be adjusted to address the whole environment. As the server capacity needed for the infrastructure and administration will be much less than the gain of the consolidation, it is mostly the manual processes that needs attention, but it also must be considered that the multiple previously individual servers now have the potential to become unavailable at the same time. Properly set up, the virtualized environment is much more robust to hardware failures in general, but a risk exists that unanticipated interaction[5] between separate virtual machines may allow a low

risk application on one virtual machine to cause a high risk application on the same host to fail.

While virtualization brings benefits, the added complexity can complicate tasks, such as risk assessment, impact assessment, and regression analysis.

Additional Issues

If virtualization is introduced in an uncontrolled manner (i.e., without appropriate risk assessment, establishing or updating procedures) or by poorly trained staff, it has a potential major impact on the stability of existing datacenters and their operations, as almost everything and every process will be affected. Also the cooling capacity of datacenters have to be revisited, as much more efficient use of the installed hardware can lead to thermal overload despite no servers have been added.

Virtualization initially offers increased up-time, faster server deployment, and requires less resources, but the prerequisites and operation of these and many other attributes of virtualization can be interpreted differently by stakeholders (business, vendor, quality groups, and datacenter staff, etc.). If not stated explicitly, dedicated procedures and staff are needed to establish objectives and to define and follow a structured process. Virtual environments are so integrated and complex that expertise from several traditional specialist areas (i.e., network, storage, firewall, security, and servers) are needed, but often supplied by a new group with focus on the virtualization product.

Existing technology and processes can claim to be unaffected by the introduction of virtualization, but as outside expectations and the need for technical qualifications changes, it is very likely that everything else needs to adjust. For example, one of the major advantages of virtualization (migration of a virtual machine from one host to the other (and back) for maintenance purposes) can seem uncomplicated for system users, but license conditions from vendors can call for planning and license migration and compliance of the system can be challenged by the flexibility of moving Virtual Machines if host number two is different, at another location, or operated by another (differently trained or less formally controlled GMP or 21 CFR part 11 aware) group of personnel. The forensic study and intrusion tracking of attacked servers also can be obstructed if logging and time server synchronization is different between the hosts, increasing risk likelihood. With careful planning and risk assessment, these issues are relatively uncomplicated to handle prospectively, but they can potentially have a major impact if neglected.

Given this added complexity and the introduction of new risks and issues, a major goal in this process should be to establish a way to control the flexibility of virtualization without taking away the flexibility itself.

Specific Uses of Virtualization

Almost every infrastructure element is becoming available in a virtual variant in a significant number of competing or complementary variants and proprietary naming-schemes:

- Virtual Storage
- Virtual Switch
- Virtual LAN (VLAN)
- Virtual Firewall
- Application Virtualization
- Virtual Desktop (VDI)

Many technologies aid us to isolate applications from each other, keep data in data-centers, and improve centralized administration, but no known solutions (or combinations of these) can promise lower complexity, vendor independence, fewer licenses, or lower cost at the same time.

As well as the virtualization of servers through the use of virtual machines, it also is worth considering two other specific uses of virtualization, namely Virtual Desktop Infrastructure (VDI) and virtual test environments.

Pros and Cons of Application and Desktop Virtualization

The two major advantages of isolating applications in a VDI and establishing central administration are data-security and application focused client maintenance. In many situations, commercially sensitive or confidential data (e.g., patient, research, or customer related documents) can be better protected if only presented on the workstation when the user opens it rather than being saved on the workstation (that can be stolen) or available in a batch or bulk-copy enabled form.

Maintenance of the client part of corporate applications can become (almost) independent of other applications maintenance and of other client platform maintenance issues, like upgrade of Java, Adobe, or MS-Windows security patches. However, corporate application system administrators also will have to take on an additional task because they will need to specify and maintain the virtualization layer.

As part of introducing any virtualization technology, investigations are needed to ensure that the solution is fit for the intended environment (compatible) and provides appropriate return on investment. For instance, "thick" clients

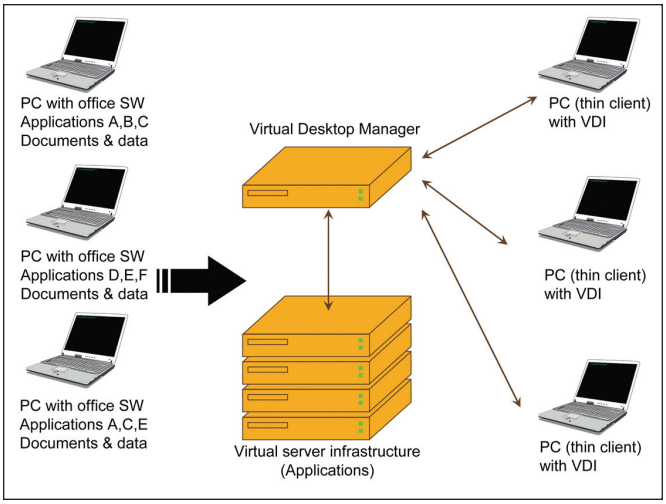

Figure 3. A virtual desktop architecture can simplify compliance issues by centralizing management of validated applications and regulated data.

which traditionally rely on the processing power of the PC or laptop gains application management advantages from desktop or application virtualization, using the power of the central server, but loses on the capacity management side. For example, a graphics-intensive application will typically run more efficiently locally. Likewise, some browser based applications may benefit less from application virtualization, while the most used and most important element: the Internet Explorer® browser itself is an integral part of the desktop that (at the time of writing) is very difficult to encapsulate because of the close integration with the client operating system. All solutions need careful network capacity planning as well.

Centralized solutions obviously require users to be on-line (on the corporate network or internet), but as corporate applications are usually centralized in a non-virtual environment, this should not pose a problem. However, if users also require off-line post processing or similar activities, these specific requirements also must be considered, i.e., which tools and data must be available when disconnected from the corporate network. This requires the use of emerging application synchronization solutions (where the otherwise centralized virtualized applications are cached locally for offline use) and this proves to be a solution with the best from both worlds without introducing any new security issues or other problems.

An important part of desktop and application virtualization of the client is isolation and encapsulation, but the impact on the workflow can be high, as the integration or connection between applications can be difficult (or impossible) to retain, potentially preventing users from exchanging shortcuts to documents in the document management system or copying and pasting tables from LIMS to Excel for reporting, without new procedures or new technical solutions. Efforts to make data more secure also can make work-processes more cumbersome and this impact also needs to be considered.

Licensing aspects, capacity needs, security, and performance aspects also have to be considered. The cost of licensing may favor VDI if a concurrent licensing scheme is favorable depending on business needs, and this is simply one of several criteria that have to be evaluated as part of a decision whether to go to VDI as VDI itself also requires licenses. The central servers must have capacity for all of the concurrent clients, lost (or "overtaken") connections should not allow for intruders to get wrongful access and worst case capacity planning becomes more complicated if the processor power is centralized.

Virtual Test-Environments

Another advantageous use of virtualization is the possibility to create entire development or test environments as duplicates of existing physical or virtual systems. Complete server environments and client/server scenarios can be quickly cloned at reasonable cost to support development and test instances, without having to interrupt production systems or purchase dedicated hardware.

In each case, it is necessary to evaluate the extent to which the "copy" (clone) is sufficiently identical to the production instance and which virtualized environments are suitable for hosting formal verification test cases. The duplicate environment, the tools used for server cloning, and the potential impact of the cloning on the production environment should all be evaluated and qualified, but the process should in most cases be very similar to usual backup/restore test scenarios.

Virtualization Quality Planning

When server virtualization is adopted, it inherently affects the service level attributes and hazard profile of systems and applications migrated to the virtual platform. Some service level attributes of virtualized systems are usually significantly improved (e.g., maintainability, reduced power consumption, portability, and availability) just by establishing the associated working procedures and this may change risk likelihood and detectability.

However, the nature and complexity of the technology means that a number of new risks need to be addressed in the quality and planning phase for appropriate mitigation. This includes new risks that need to be considered, such as various failure modes for the virtualization software, the potential for interaction between different virtual machines, the potential for applications to perform in unexpected ways when running under a virtualized environment, human risks because of the increased complexity of the architecture, and whether or not vendors will support applications running in a virtualized environment.

The specification, implementation, and/or test of purely physical attributes (e.g., access security, power, temperature, and cooling) are attributable directly to the host which needs to be qualified just once. Virtual machines can trace fulfillment of related requirements to the attributes and qualification of the virtual environment, meaning these tasks need not be considered for the individual virtual machine.

Qualification, Compliance, and Control

Based on the GAMP Infrastructure Control and Compliance Good Practice Guide (GPG)[4] philosophy, the infrastructure platforms and components may be qualified independent of the validation of the dependant systems, as long as the infrastructure is properly specified, verified, controlled, and maintained and as long as the infrastructure is not designed to fulfill specific user requirements (as could be the case with some middleware). In the case of virtualization, the added complexity of the architecture adds to the complexity of the platform and component model and means that these are not trivial conditions. The qualification of the virtualized environment and virtual machines should be conducted in such a way as to leverage the strengths of the architecture, while effectively mitigating the specific risks.

Therefore, planning should start with clear identification of what and how systems/applications/processes are within the scope of the virtualized environment. The upper bounds for potential risk impact can be set and the effort to qualify the virtualized environment and mitigate risks decided. It also is necessary to consider which of the effects of virtualization need to be included in system requirement specifications to assure an effective and reproducible business process (e.g., availability, performance etc).

In some cases, virtualized environments will be used to group together applications with a similar risk impact and to qualify and control the environments (or virtual machines) accordingly. This implies that controls must be introduced to avoid scope creep or misalignment because of poorly controlled operation and maintenance procedures and also to prevent high risk impact applications from being installed in a virtualized environment that is only qualified and controlled to support low risk applications.

Virtualization Strategy

The planning process continues with the identification of service level goals affected by virtualization. These will range from the intended goals (virtualization is supposedly introduced with a purpose) to the less desirable weaknesses that calls for further risk mitigation actions, either by design or procedural controls (see risks section below). As part of the planning of what to virtualize with most benefits and in what (risk) groupings, what not to virtualize also should be investigated because excessive impact on the surrounding virtualized environment or potential impact on the application is possible.

Real time process control systems, for example, should be analyzed thoroughly and only virtualized in close cooperation with the vendor, as fixed execution schedules or timing/synchronization mechanisms could call for special attention or impose design limits with undesirable impact on the co-hosted systems, which makes it relevant to consider if it is feasible to virtualize. Likewise, business criticality, regulatory, or confidentiality requirements for a single system can affect the policies for the whole environment, which makes it undesirable to introduce virtualization in a mixed criticality environment.

The system with the highest potential impact defines the criticality level for the entire environment.

Security in Virtualization or Virtual Security

When compared to a dedicated hardware server, there is an inherent difference between the efforts needed to demonstrate adequate control and security of a virtual machine and its data, requiring policies, procedural controls, and an appropriately specified and controlled environment. Most significantly, the "attack surface" (the potential points of software vulnerability considering the entry points and associated code a malicious user could exploit) for the individual application grows with virtualization because of the complexities and reduced physical separation between networking layers, virtual machines, and application data.

When virtualization is introduced for non-critical purposes, it is still relevant to consider network separation policies and maintenance procedures to minimize the risk of vulnerabilities within the virtualized environment (i.e., virtual machines and applications) being used as entry points for attacks into more critical systems because of lack of segregation within the environment. Where vulnerabilities in the virtualized environment are not addressed and the separation of networks is insufficient, access to more critical applications and data may be enabled. This is a key issue as the usual network design responsibilities to some extent are shifted from the networking experts to the virtualization group, because of the embedded networking capabilities of virtualized environments. This requires an exchange of best practices and on-going cooperation between the groups.

An approach is to qualify and control all virtualized environments assuming the potential installation of high risk impact applications. This has the advantage of allowing the full flexibility of virtualization to be realized from day one and reducing the burden of operational risk assessment, because any application can run in any virtual machine in any virtualized environment. It also means that all virtualized environments can leverage the same policies, processes, and controls, which reduces the risk of human error. From a cost perspective, the initial qualification and control overhead may be greater, but this is easily offset because everything is qualified and controlled to the highest standard, thus alleviating the complication of managing multiple clusters or networks to different standards. In reality, this should be little more that well documented good IT practices as described in the GAMP Good Practice Guide.[4] However, it does need planning, support, and operation by subject matter experts from the outset if unacceptable risks to high impact applications are to be avoided.

After establishing boundaries for the use of the virtualized environment and its contents, the service level goals should be set to reflect the most significant common denominator of the servers being virtualized (or servers potentially impacted by the virtualized environment) and the criticality of the supported business processes. While service levels like disk capacity and processor capacity may be specified at the level of the application or virtual machine, service levels for hardware availability and physical security must be determined at the common virtualization layer, and they must meet the requirements of the most stringent application.

Risk Assessments of Virtualized Environments

As discussed above, there are additional risks to be considered in a virtualized environment. Some of these risks are the same and must be considered for all items of infrastructure, but the complexity of the virtualized environment means that additional failure mode must be considered and that risk likelihood and detectability must be reconsidered.

Other risks are unique to the virtualized environment and will require specific risk assessments to be conducted, at least prior to the introduction of virtualization if not for every build and installation.

Table A provides an overview of the risks, potential causes introduced or exacerbated in connection with virtualization, along with ideas for their mitigation. It should be considered to what extent it is relevant to select and include them in local risk management processes and where focus should be placed on the technological, procedural, or behavioral level depending on a risk evaluation of the given environment.

It can, for instance, be argued that in some organizations,

many risks are easily mitigated by the use of trained staff working in a mature environment, whereas other organizations might need to define and qualify the processes to assure continuous (and compliant) operation. The decision should be based on an analysis of the given environment, but implementation of the suggested quality focus issues below should reduce the risk to an acceptable level.

Although the chance of virtualized IT infrastructure inspection by a health authority is somewhat low, there have been several examples in the last decade where it has drawn the attention of Health Authorities. It also should be pointed out that infrastructure controls are the focus of laws and regulations outside GxP, such as the US Sarbanes-Oxley Act, and the recommendations in this article are applicable to compliance to these as well.

Identification of Quality Focus Issues for the Virtualized Environment

Fulfillment of all issues with a quality focus (included in the checklist) is seen as a prerequisite for the successful implementation of server virtualization although additional control activities may be required because of specific criticality or company procedures.

Audits of a virtualized environment can be based on this list in order to ensure that all issues are addressed properly. As in other areas, the frequency of internal audits or periodic reviews should be based in part on risk, guided by the effective level of risk mitigation determined as part of the audit or review.

The list is created based on the previously suggested potential causes for hazards, knowledge acquired at VMware® training course,[2] interviews with well experienced administrators of virtualized servers in NNIT and LEGO System A/S, combined with studies of VMware® guides,[6] US Department of Defense guidelines, and checklists (created by DISA[3]).

For further details on most of the abovementioned risks and issues, the DISA Security Technical Implementation Guides (STIGs) cover, among other relevant matters, checklists for virtual computing, hardening of particular Operating Systems, and specifically VMware® ESX-server.[3]

Most issues are well known from "classic" computerized environments and the application specific risk impact does not necessarily change with virtualization. However, some risk scenarios that are unique to virtualization can lead to failures affecting a large number of virtual machines, causing a failure of the virtualized environment to have a much

Risk	Causes	Suggested Mitigation
Corrupt data, Lost data, Incorrect data:	Data corruption in one or the other systems because of SAN confusion, missing backups, restoration to the wrong LUN* (all because of LUN confusion), or LAN intrusion, virtual machine breakout or misconfigured dualized/failover resources. Root cause examples: poor backup/restore procedures, poorly trained operators, incomplete design or configuration management, missing LUN masking/zoning, unmitigated host vulnerability, insufficient (implementation of) LAN security policies or missing separation of security zones. *LUN: Logical Unit Number, the key (pointer) to data allocation/addressing in Storage Area Networks (SANs)	• Thorough planning, documentation, and verification of the virtual infrastructure. • Configuration Management Data Base (CMDB) tailored to manage the dynamic nature of virtual environments and support the needs for logical naming schemes and connections, including LUNs, LUN masking, zones, and VLANs. • Backup/restore planned, documented, and verified. • Virtualization software properly patched and upgraded including Virtual Machine Tools and managing consoles.
Unauthorized access to data:	Successful LAN intrusion on migrating virtual machine or illegal (or stolen) copy of virtual machine data. Root cause examples: missing logical and physical security.	• Virtualization software properly patched and upgraded, including Virtual Machine Tools and managing consoles. • VLAN or physical separation of all different security classes of communications
Production disruption because of platform malfunction, poor performance, denial of service attack, or inadequate cooling capacity:	Poor performance or failure to operate for otherwise unknown reasons, configuration failures leading to delays or inability to implement changes, virtual machine breakout or Denial of Service attack on host, or insufficient host capacity for peak demands. Servers overheating. Root cause examples: application not fit for chosen virtualization type, patches lost by uncontrolled snapshot rollback, virtualization functionalities (migration and HA/server restart) unfit for application, poor resource management or configuration management routines not adapted to virtualized environment. Data center cooling capacity not built for all servers being used much more efficiently.	• Risk analysis and mitigation • Verification of critical functionalities and services • Maintenance of the hosts • CMDB suited for the purpose • Close cooperation with vendors • Detailed analysis of effect of virtualization on utilities (e.g., cooling) and adjustment as needed.
Human error, leading to any of the above	The increased complexity of the virtualized environment can increase the likelihood of human error.	• Training • Adequate quality management system
No fulfillment of "license to operate" conditions, fines, or damaged public image.	Noncompliance with internal-, regulatory-, or license-requirements. Root cause examples: lacking configuration control of virtual environment, missing tools or procedures for configuration and compliance review, unintended violation of License Agreements during virtualization or migration of servers.	• CMDB suited for the purpose • Close cooperation with vendors • Verify baseline review processes as part of platform qualification • Negotiate (or renegotiate) license agreements with virtualization in mind
Lack of application vendor support for virtual environments	In some cases, applications vendors may choose not to support applications that were not designed to operate in a virtualized environment and this may represent a risk to business continuity, where a fault is not acknowledged or corrected by the vendor.	• Thorough testing of virtualized solution • Maintenance of native physical reference environment for test or troubleshooting • Additional resources to provide second and/or third line support

Table A. Risks related to the potential impact of virtualization on business processes.

more significant business impact than the failure of a single hardware server.

In building virtualized environments, additional failure modes are created and known failure modes change risk likelihood or risk detectability and a focus on these issues is a prerequisite when replacing the physical platform with a virtual one. Issues 4 to 11 in the sidebar are directly related to aspects introduced or significantly changed by the nature of virtualization, as the complex and transient nature of virtualization allows for new modes of failure or attack, misunderstandings, lack of control, or for malicious individuals to compromise, copy, or break down virtualized systems either invisibly, massively, or by incremental changes if not controlled properly.

Suggested Approach to Controlling a Virtual Infrastructure

Governance and Control

As with all other platforms, the virtual platform needs to be specified and installed in a defined and controlled way. There also should be risk-based demonstration that it fulfills the business requirements (intended use, defined as service levels). Depending upon these requirements, this may entail relatively simple verification (Installation Qualification) and/or some level of functional testing.

A technology subject matter expert should be appointed to govern the company's expectations for the use of the virtual infrastructure technology. In this way, the general policies, principles, installation guidelines, vulnerability management, patch management, fundamental qualification, and templates for SOPs can be issued and controlled centrally. This will reduce the level of work for local platform administrators responsible for the implementation, resource allocation, administration, operation, and maintenance and ensure more uniform solutions, which can be kept under aligned control using the centrally defined compliance tools and procedures.

Paced by Knowhow

The organization should decide on the appropriate level of testing, qualification, and other risk controls dependant on the criticality of the supported applications, the maturity and size of maintenance and support organization, and the organization's previous knowledge of both vendor and their virtualization products.

However, it can be a challenge to find qualified staff with knowledge of virtualization solutions and until these people are on-board, it also is a challenge to determine the appropriate risk controls for the supported processes, especially if the virtualization strategy is not yet finalized.

A safe approach is to restrict the "operating range" for the criticality of virtualized servers and avoid more critical (or complex) applications from being virtualized without revised risk assessments, hereby initially limiting the use of virtualization to low risk applications. Virtualization can be introduced in a step-by-step manner as knowledge and experience are gradually accumulated. The virtualization of more critical applications can then be paced as the ability of the managing personnel and the maturity and robustness of the maintenance procedures increases. However, this does require more in the way of on-going risk assessment and there may be an increased risk of human error if different levels of control and compliance are operated in the same organization.

Build as a Solid Platform

Central management of tested approved software versions, approved hardware lists, security policies, and generic requirements for the virtualization platform will offer local business units a qualified concept to build. This will allow local business units to focus on application specific testing on qualified virtualized platforms. If, for instance, an application is required to run 24/7 without exception with a given performance and without a single point of failure, the virtual infrastructure will need specific configurations for resource scheduling, availability tools, and failover network settings to support this. The support for availability requirements like this is a major virtualization driver, as close to 100% availability and inexpensive failover options are integral elements of virtual infrastructures, offered at much lower cost that traditional hardware solutions.

When compared to the smaller number of easier-to-review settings for physical servers, the logical nature of virtualized solutions means that performance, capacity, continuity, and security features of the virtualization software requires more detailed design, extensive configuration, and thorough testing before confidence is established to ensure that all resource pointers and duplicated connections work correctly. Qualification tests to challenge failure scenarios and demonstrate fulfillment of these service level requirements must be considered when developing initial designs and controls.

Leverage Standardized Designs

All installations of virtual machines should be based on detailed designs derived from local (application specific) requirements. However, many major virtualization solutions lack default factory settings because of the flexibility of use. Centrally crafted specifications and templates with suggestions, decision trees, and operating ranges allow local implementations to leverage a set of standard designs and reduce the need for local testing to a minimum.

And/Or Test Locally

Where environments are based upon standardized designs, individual local testing can seem superfluous and difficult to manage, but the decision on how much local testing to conduct must be based on a consideration of whether the use of the virtualized environment is well known and controlled or not, as the prerequisites and necessary settings are neither trivial nor easily reviewed. It is important to note that virtualization offers fewer (if any) possibilities for physical inspection and review of connections between servers and storage or servers and the network. The logical nature of the setup increases the likelihood of simple spelling errors or upper/lower case mistakes in the logical setup. This can cause communications

paths to break, storage units to be overwritten, or backups to fail. This requires rigid naming schemes, detailed designs, and thorough configuration management.

Even where standard backup/restore, dynamic failover, etc., services are used there will usually be a need for testing tailored configurations and "dynamic" functionalities like failover and redundancies on an application specific basis.

Where the applications software vendor does not support virtualization, it also may be necessary to conduct more rigorous testing of the basic functioning of the application within the virtualized environment, which may involve testing functionality that can normally be assumed to work in a standard hardware environment like the ability to use network printers or to be connected to remote users outside the firewall across a Virtual Private Network (VPN) – also during live migration. Well planned tests can be designed to incorporate these verification activities, but it takes careful risk-based planning to determine the scope and rigor of such tests.

Maintaining Compliance

During the operations phase the addition or decommissioning of virtual machines, performance monitoring and capacity planning, on-going maintenance, and the administration and use of privileged access rights should be executed according to written procedures. These should be specific to the virtualized environment and periodic reviews should be performed to demonstrate continuous control of the environment.

Their complex and highly configured nature means that virtualized environments can be considered less robust with respect to the likelihood of human error, which leaves a lot of room for misspellings and logical errors. As there are relatively

Quality Focus Checklist for the Virtualized Environment

1. Is ownership of the technology and applications (the hardware, virtualization software, virtual machines, and application modules) established and assigned to System Owners and Business Process Owners?
2. Do all platforms and components have an appropriately trained or experienced responsible subject matter expert?
3. Are roles and responsibilities for System Owners, Business Process Owners, and subject matter experts described, including the responsibility for assuring policies, resources, and delegation of duties in place?
4. Have all privileged users been assigned sufficient and specific access rights to perform their duties using their own individual account and have they been trained in operational procedures and potential consequences of operational errors or misuse?
5. Are tasks and responsibilities in relation to the virtual infrastructure clearly distributed to subject matter units (i.e., between storage-, network- and virtualization-experts)?
6. Is an approved strategy for the virtualization of hosts and clusters in place, which balances quality (service level) goals against economic incentives?
7. Are the specification, creation, and qualification of virtual machines controlled by approved guidelines, which also describe required specifications, naming schemes, usage domains etc.?
8. Are the special considerations in relation to real time systems (e.g., timing and resource needs) addressed in the virtualization strategy?
9. Does qualification of all virtualized applications include risk assessment (and mitigation, where relevant) of specific virtualization risks, i.e., the consequences of being implemented in an environment with variability in available resources?
10. Is vendor support assured or is the lack of support appropriately mitigated?
11. Are all virtual machines identified, owned, and documented and only decommissioned in a controlled way according to defined plans?
12. Does the migration of virtual machines take place in a controlled manner, is this logged, executed only over appropriately secure lines and is the physical location of each application known at all times?
13. Is it assured that systems with varying criticality, sensitivity, and requirements for control are grouped, clustered, and managed by hosts, personnel, and procedures with the system with the largest potential impact defining the criticality level for the group?
14. Is the Configuration Management Data Base tailored to manage the dynamic nature of virtual environments and support the needs for logical naming schemes and connections?
15. Are all virtualization platforms and components under Configuration Management and monitored by automated compliance checkers or regularly reviewed for compliance?
16. Are all operation, maintenance, and hotfix, patch, and upgrade of virtualized environments and virtual machines (live as well as dormant and templates) planned or documented and executed according to controlled procedures?
17. Has documented verification of configuration baselines, backup/restore processes, and operating procedures taken place and is the intended use of hosts and required functionality (and un-needed functionality) by virtualized applications documented?
18. Are security policies in place that are specific to virtualized environments, describing separation of networks, contingency planning, requirements for time synchronization, remote event logging, event trending, operating system hardening,[3,6] and where installation of antivirus is mandatory?

few built in tools to support configuration management and since most of the setup is logical, this increases the difficulty of conducting reviews by traditional or automated methods and appropriate methods of conducting periodic reviews must be developed.

Continuously Improved and Matured

As virtualization on x86 platforms is a relatively new technology for both vendors and their target clients, some companies will find a temporary setback in the maturity of some of their IT process management capabilities as a consequence of virtualization. Introducing and improving actions based on the suggested quality focus issues will address elements of all the six attributes of the COBIT process[7] maturity model (awareness, policies, tools, skills, responsibilities, and goal setting). Over time, this will facilitate the virtualization processes to mature to an optimal level. It also is expected that virtualization products will mature further and address the needs for built in configuration management tools and periodic review.

Summary

Because of the large number of obvious advantages, server virtualization is here to stay, but as complexity is increased and new risks are introduced, organizations should pace the consolidation of servers into virtualized environments at a speed where training, experience, and processes can keep up.

To achieve and maintain a state of control and compliance, this requires the development of good practices in parallel with the increasing availability and use of third party (or built in) tools, as well as more mature virtualized solutions. It is worth remembering that virtualized infrastructure consists mostly of software which fails from time to time because of new vulnerabilities (e.g., arbitrary code vulnerability in VMware®[5] April 2009). Organizations need to exercise due diligence to prevent a situation where all eggs are put in the same basket, without having demonstrated that it can carry the weight!

The very tight dependency on the chosen virtualization solution currently prevents an alternative sourcing option of the fundamental computing platform, so careful supplier and interoperability assessment is essential. This "virtual monopoly" may be broken with the emerging Open Virtualization Format;[9] allowing virtual machines to be moved between environments from major vendors, and allowing contingency plans and vendor dependency policies to again rely on alternative vendors.

In time, virtualization has potential to become a true foundation for utility computing[8] where pools of servers transparently deliver scalable resources for multiple applications in an environment with automated management capabilities.

The benefits of virtualization are certainly worth realizing, and with proper attention on the suggested quality focus issues, experience shows that it is possible to reduce or minimize any new risks, while gaining all the advantages of virtualization in a controlled way.

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Acknowledgements

The author would like to acknowledge valuable comments and input from Randy Perez (Novartis) and David Stokes (Business and Decision (Europe) Ltd.) during the development of this article. The author also would like to thank Anette Westphal (NNIT) and Arne C. Andersen (LEGO System A/S) for valuable knowledge sharing and insight in their use of Virtualization techniques.

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Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2010, Vol. 30 No. 4
www.ISPE.org

This article presents a process transfer case study and the significance of continued project support after the site is licensed.

Process Transfer to Contract Manufacturing Organizations: A Case Study on Process Development Support Past Regulatory Approval

by Amy Webb, David H. Reifsnyder, and Jean Bender

Introduction

Transferring a process to a contract manufacturing site typically follows a lifecycle model as shown in Figure 1. Contract negotiation is focused on the objectives and goals of the partnership. It is typically managed by business and project managers of each organization. Once contract negotiation is complete, the project focuses on the technical aspects of the transfer, including facility fit, process/knowledge/documentation transfer, and validation lots. The identification of any necessary process updates as part of introduction into the site and large equipment purchases are performed as part of facility fit. Following facility fit, there is a large information exchange that culminates to the execution of validation lots. These three phases require a large deal of time and effort and are usually the main focus of the process transfer. The transfer often is considered complete once the site attains regulatory approval. However, the routine manufacturing stage of the project plays an equally important role in process transfer and could be the longest duration of the transfer process lifecycle. An examination into a recent transfer of a commercial antibody purification process to a CMO demonstrates the significance of continued support from both the CMO and client during routine manufacturing at a CMO.

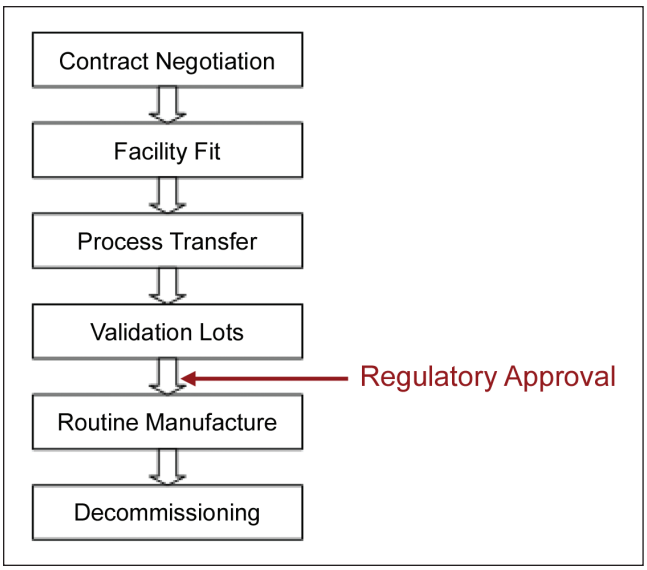


Figure 1. Typical process transfer lifecycle.

Background

Genentech transferred an existing commercial antibody process to a CMO to increase manufacturing capacity. The transfer to the CMO site also required a scale increase relative to the licensed process due to the pre-existing equipment at the CMO. Existing process validation work from the initial licensure was leveraged during the transfer wherever possible.

Both companies had an aggressive timeline for regulatory approval. Figure 2 shows the overall project schedule. Validation lots for regulatory approval at the site occurred roughly one year after the contract was signed. Routine manufacturing was performed on a campaign basis. When Genentech's product was not being manufactured, the facility was in use for the manufacture of other products.

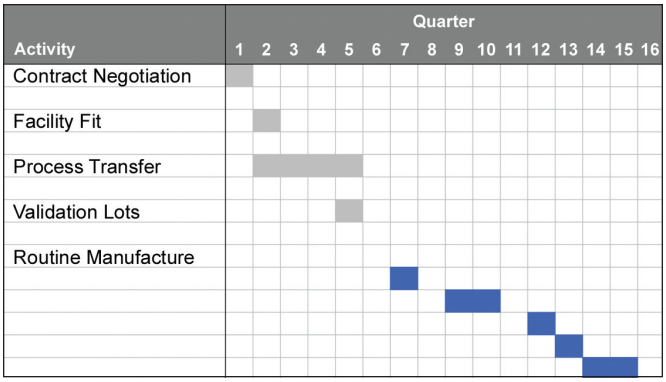


Figure 2. Timeline for the process transfer.

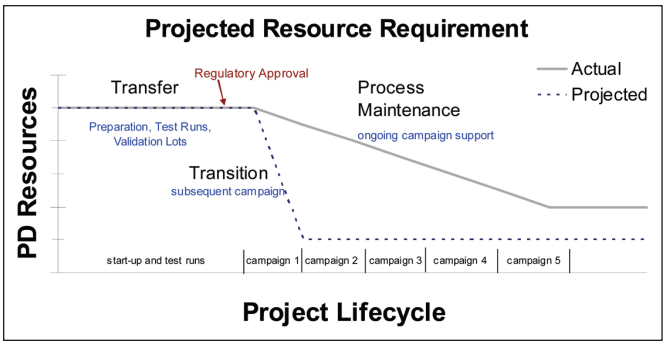


Figure 3. Project resource support during the lifecycle of the process transfer.

Genentech's purification process transfer team included several Process Development (PD) members. During facility fit to validation lots, considerable resources were dedicated to the project with approximately four Genentech purification representatives committed full time to the project. After regulatory approval was obtained, both Genentech and the CMO immediately decreased their process development/manufacturing support staff considerably to one person full time from each site. Upstream cell culture support was similar for both Genentech and the CMO.

Manufacturing support demands proved to be more than expected. Process monitoring, deviation review, change control, and process improvements required additional staff not originally budgeted to support ongoing production. The issues seen during routine manufacturing at the CMO demonstrated the importance of continued process support, and showed the process transfer team that transfer activities do not end at regulatory approval at the site. Figure 3 compares the anticipated Genentech purification PD support for the process transfer lifecycle to the actual required resources. Relating back to timelines shown in Figure 2, the Genentech strategy for supporting the project lifecycle was to augment staff during commissioning and process transfer, and then reduce headcount for the commercial production campaigns.

Case Study Review

Soon after regulatory approval, it became apparent that considerable off-site support would be required to maintain the transferred process. Time dedicated to batch record, change control, and deviation review was significant. Process monitoring proved to be a useful way to ensure the process was operating as originally transferred and intended. However, this exercise was time consuming and resulted in the discovery of multiple issues and process enhancements that needed to be addressed.

Case Study #1: Method Transfer

Due to tank limitations at the CMO site, an affinity chromatography buffer was prepared as a concentrate and diluted on-line prior to the column. Since this was a process change based on facility fit, the project team examined impact by investigating solubility, stability, and specifications for the buffer. The team ensured that the concentrated buffer could be prepared correctly and diluted online to meet the same specification as the neat buffer. Soon after regulatory approval, routine process monitoring noted a difference in the conductivity measurement for the online buffer. Despite the same buffer composition, the CMO consistently obtained lower conductivity readings compared to the historical average at Genentech. Figure 4 shows the historical conductivity values for the equilibration buffer at Genentech and the CMO.

Although still within specification, the lower conductivity values potentially pointed to an issue with robust processing. At the CMO, the buffer concentrate was diluted inline with Water for Injection and measured for conductivity at the chromatography skid. When conductivity was outside of range, the buffer was sent to drain until the specification was met. Since the buffer concentrate conductivity was already at the low end of the specification, the diluted buffer conductivity also was on the low end of the range. Therefore, small fluctuations in conductivity during inline dilution caused the skid to flush the system and increase overall buffer usage. The increase in buffer usage was above the planned projections for the process step. Buffer usage was a specific concern on this process step, because multiple cycles were run on the column for each lot. The maximum amount of protein processed was limited by buffer volume. Therefore, sending large volumes of buffer to drain to meet conductivity specifications negatively impacted the total amount of protein processed.

An assessment of the raw materials and the buffer preparation process did not point to a root cause for the shift in conductivity. Upon review of the method for conductivity meter standardization, the team noted slight differences in how each site accounted for temperature compensation. These differences led to an offset in conductivity measurement as

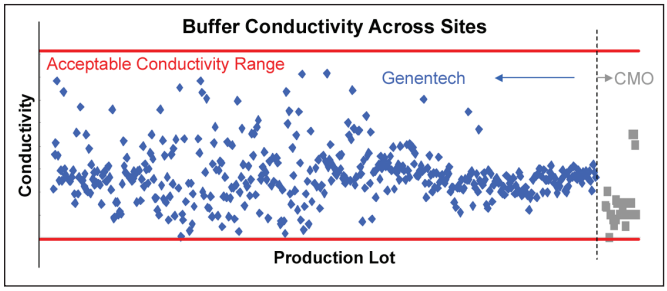


Figure 4. Historical conductivity values at Genentech and the CMO for a chromatography buffer.

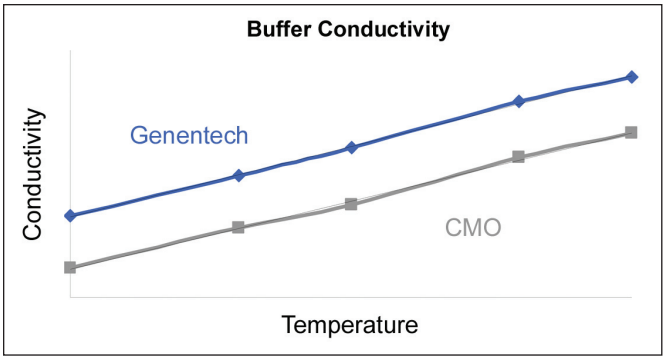


Figure 5. Conductivity correlation of a process buffer measured at Genentech and the CMO.

shown in Figure 5. Small scale studies were performed for all buffers in the process so that specifications were aligned with the measurement method.

Approximately 20 buffers were tested in total, requiring a large time commitment by Genentech PD. Small scale lab support of this project was not originally anticipated and required an additional temporary employee for three months to perform the study. When the study was completed, CMO site-specific conductivity ranges were created. Implementation of the new ranges reset the target specification so that the diluted buffer conductivity value was more centered within the range, leading to less buffer wasted. The total amount of material that could be processed increased on this step.

Case Study #2: Decrease in Process Yield

During the process transfer, Genentech provided historical in-process step yield ranges to the CMO to assess comparability of the processes. Although yields do not affect final product quality, they are used to gauge potential performance differences between sites. Typically, once the CMO has produced a minimum number of runs, the yield ranges are updated based on site specific CMO data.

Through routine process monitoring, the project team observed an approximately 10% decrease in yield on the cation exchange chromatography step as shown in Figure 6.

Column Packing	Upstream Processing	Processing Time
Buffer pH	Resin Variability	Automation
Buffer Conductivity	Load Density	Load Cell
Raw Materials	Equipment Calibrations	Assay

Table A. Partial list of potential root causes examined by CMO and Genentech.

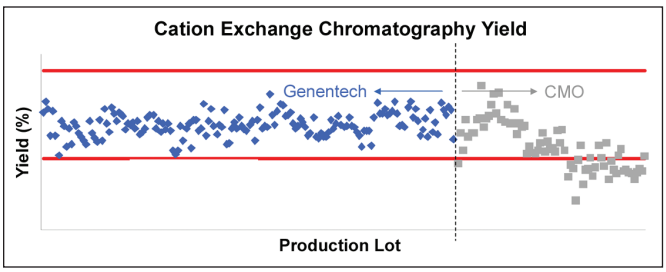


Figure 6. Historical yields on cation exchange column at Genentech and CMO.

Step yields were routinely falling below the historical values used to track step performance, resulting in deviations. These deviations were thoroughly investigated by the CMO.

Despite the low step yields, product quality was not affected and the final product consistently met all specifications. The CMO performed an extensive review of the processing data at the site to address root cause for the decrease in yields. The thorough review of historical data included, but was not limited to, the potential root causes listed in Table A.

The CMO review of the step parameters listed in Table A did not determine a root cause to the decrease in yields and small scale studies were required to further assess the issue. Studies were initiated at Genentech in purification PD to examine the decrease in yield. Small scale studies examined resin lot variability, load lot variability, and column packing variability as potential root causes. Studies performed at Genentech were able to mimic the decrease in yield seen at large scale. Additionally, the studies showed the decrease in yields was associated with a shift in the charge distribution of the load material as shown in Figure 7.

This shift in charge distribution was a result of a change in the amount of acidic and basic variants found in the load material. The change in charge distribution of the load material caused increased binding of the load to the resin. The increased binding resulted in a smaller elution profile, during the product pooling phase. Additionally, the process was

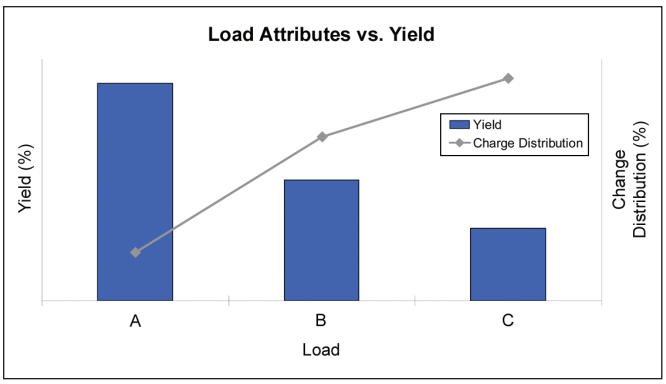


Figure 7. Small scale studies investigating the decrease in cation exchange yields at the CMO. Loads A, B, and C represent load material from the CMO during early, middle, and later lots of routine manufacture.

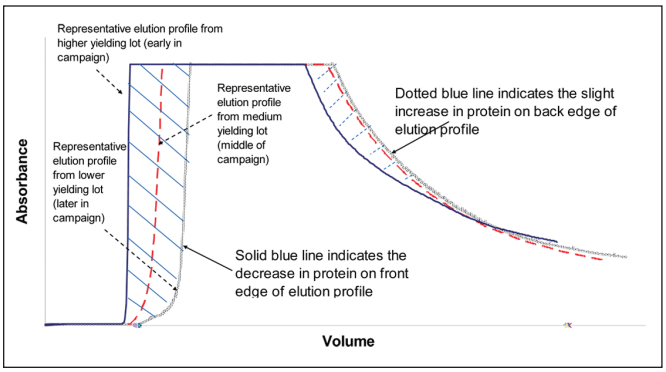


Figure 8. Change in elution profile of the cation exchange column due to the shift in charge distribution of the load. The shift in elution profile negatively effected process yield.

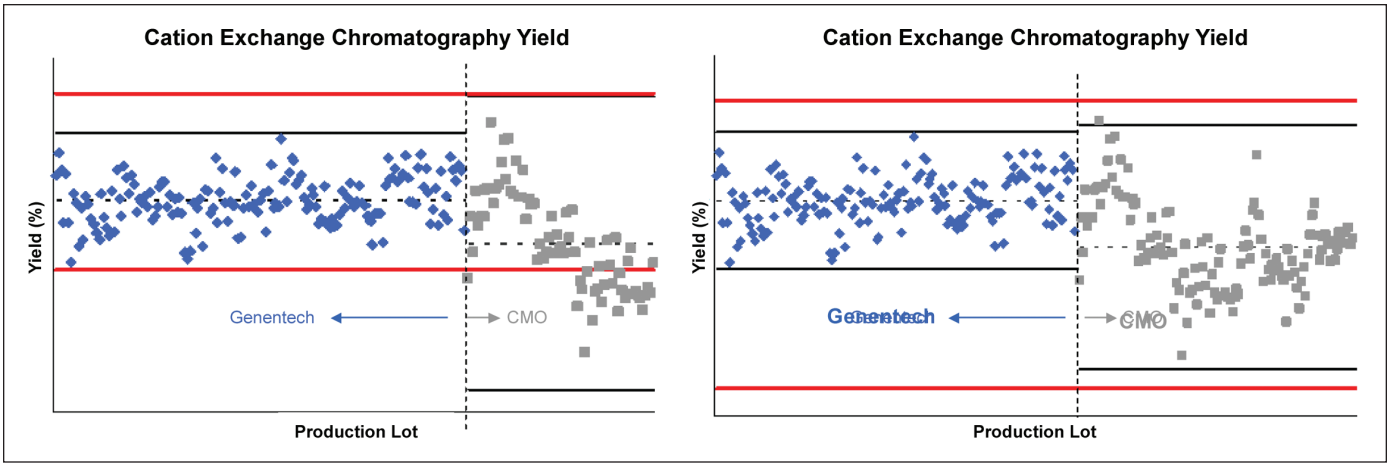


Figure 9. Yield comparison, historical Genentech yield and updated CMO yield.

pooled to a fixed volume, further amplifying the decreased yield effect. Figure 8 shows how the differences in the charge distribution of the load material affected the elution peak profile. An increase in basic variants in the load material created more narrow elution peaks, which ultimately caused a decrease in yield across the column. The solid blue lines in Figure 8 show graphically the reduction in protein yield across the column.

The change in charge distribution of the load material was attributed to cell culture variability. Further analysis within cell culture could not definitely assign a root cause. Ultimately, small scale studies were able to show the cation exchange column was performing as designed and there was no impact to product quality. Since product quality was not compromised and addressing the root cause to increase yields would require substantial changes to the production license, in this case, the team chose to maintain the current process design.

Although product quality was confirmed, the team still needed to address the multiple deviations generated from the step yield falling below the specified range. Process changes to improve the yield, such as a change in pooling strategy or buffer make-up, would have required significant regulatory involvement. Genentech and the CMO agreed to update yield specifications in order to maintain the current licensed state of the process. These updated ranges used historical data from the CMO and reflected the normal manufacturing process variability observed. The updated process yield range for this step coincided with Genentech's typical process transfer activities where yield ranges are updated for all process steps based on historical CMO data. The updated ranges, shown in Figure 9, were wider than the historical GNE range. However, these new ranges reflected the current expectations for the process.

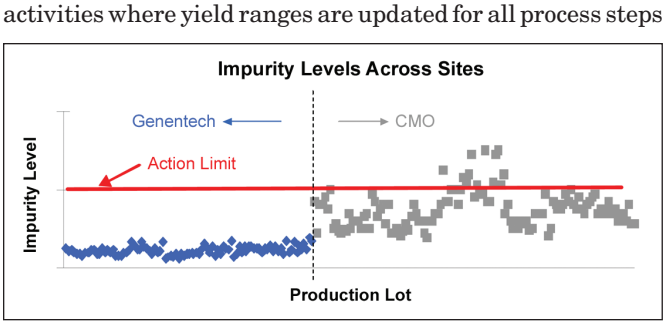


Figure 10. Impurity level comparison at Genentech and the CMO.

Case Study #3: Higher In-process Impurity

Routine process monitoring at the CMO revealed the concentration of a process related impurity trended higher at the CMO. This impurity is measured in an intermediate process pool and has been validated to be removed to less than detectable levels with further downstream processing. Figure 10 shows the impurity values for runs produced at Genentech were lower than those produced at the CMO.

Testing of the final bulk verified removal of the impurity for all lots above the action limit. The CMO examined the out of trend results by performing root cause analysis investigation similar to the step yield investigation described in Case Study #2 - *Table A*. However, review of numerous parameters and step performance did not result in identification of the root cause.

Upon further analysis, the Genentech/CMO team did note a difference in the set-up of the automation recipes between the sites. Although the automation procedures were the same, the CMO loaded these procedures individually (1 process sub-step = 1 recipe) compared to Genentech's single recipe (all process steps combined = 1 recipe). Consequently, the CMO loaded seven recipes correlating to Equilibration, Load, Wash1, Wash2, Wash3, Elution, and Regeneration, when Genentech typically loaded one recipe for all of the steps combined - *Figure 11*. This resulted in a longer residence time for the product in contact with the resin, while the operators manually loaded the first wash recipe after the load recipe was completed.

Genentech designed small scale studies to assess the impact of residence time on impurity levels. In these small scale studies, a hold time was introduced after the load phase to mimic the amount of time the operators manually loaded the wash sub-step. The studies showed that higher levels of impurities were seen with longer residence times - *Figure 12*. In-process impurity levels increased approximately two-fold

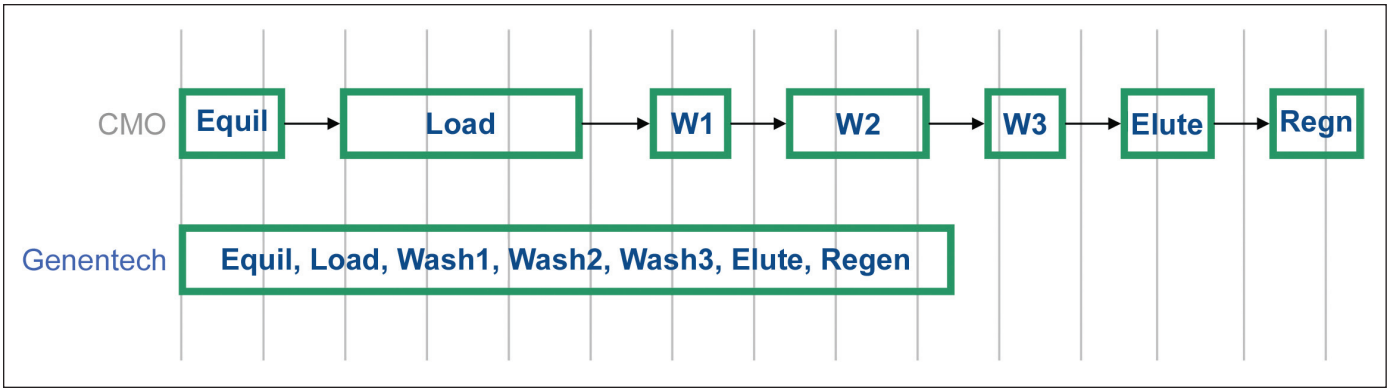


Figure 11. Automation recipe configuration at each site. The block sizes and location are roughly equivalent to process time. The CMO loaded several smaller sub-recipes and Genentech loaded one recipe to complete a given chromatography process.

with an increase in residence time of one hour.

Based on the small scale data, the CMO merged the individual automation recipes into one recipe, which decreased the residence time and also reduced overall processing time for this step by 10%. As a result, lower process impurities were seen during the next campaign.

Lessons Learned

These three case studies provide valuable lessons learned for the technology transfer team. The process transfer was regarded as highly successful to both the CMO and Genentech. The project team was able to transfer a process to a CMO, produce comparable product, and obtain regulatory approval at the site to meet business needs and ensure product to patients.

While meeting this important primary goal, the team addressed other goals including optimizing the manufacturing fit at the CMO. To accomplish this goal, process monitoring was essential for recognizing differences in manufacturing and assessing the available data for potential product impact. In all three cases presented, the optimization took time and resources. Laboratory work or equipment modifications were needed and the team worked to ensure quality product and robust manufacturing, all the while providing material for the market.

Case Study #1 demonstrated the importance of a rigorous assay transfer. In this case, both sites had methods in place to determine conductivity. A thorough review of potential differences in these methods was not performed prior to process transfer. Because the conductivity method correlation occurred after regulatory approval, a significant amount of change control and regulatory documentation was required to implement the revised specification. Current transfer activities now require method assessment at the start of transfer.

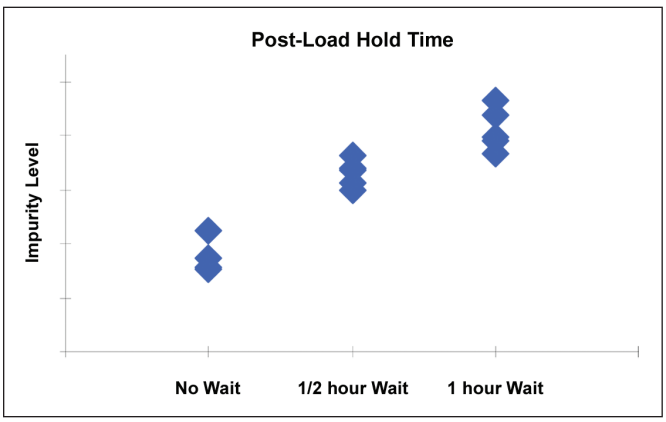


Figure 12. Effect of residence time on in-process impurity.

Case Study #2 illustrated the importance of detecting data trends real-time. Early detection enabled the team to trouble-shoot the problem in multiple ways. First, the team was able to gather and analyze historical data to rule out any changes in processing. Once processing changes had been ruled out, samples were taken to perform small scale studies, which ultimately assessed whether the transferred process was aligned with the original design of the process. Had the team detected the trend later, sample collection to permit further analysis at small scale in both purification and cell culture would not have been possible.

Case Study #3 illustrated the importance subtle differences can play on the overall manufacture of a product. A documentation review of the process steps would have concluded that both sites were performing similarly. However, thorough automation recipe review and on-the-floor support from Genentech enabled the detection of more subtle differences between the sites, particularly the configuration of automation recipes. Discovering this difference in operation not only improved process performance but decreased overall processing time at the CMO.

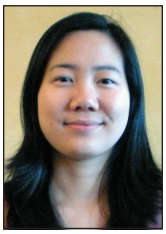
Although the original intent of continued process monitoring was to ensure product quality, the benefits went beyond maintaining the transferred process. The case studies also demonstrate improved process economics. Although additional resources were required to further optimize production, a return on investment is dependent on other factors, including production costs, final product costs, process yields, and product lifecycle. In our case, both businesses benefited from the decrease in manufacturing time and increase in yield.

Summary

The project lifecycle of a successful process transfer does not end with regulatory approval at the site. Continued support from both the transfer site and CMO is required to ensure

the transferred process runs as originally intended. In this case study, continued process support from both the CMO and Genentech was more than originally anticipated. The elevated level of support of the product not only ensured successful manufactured lots, but also provided both companies with important lessons learned for future process transfers.

About the Authors



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Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2010, Vol. 30 No. 4
www.ISPE.org

This article presents three different case study applications of CFD modeling.

Computational Fluid Dynamics as a Tool for Designing Quality into the Pharmaceutical Cleanroom

by John Gafford, Jesse Roberts, and Joe Sullivan

Introduction

Computational Fluid Dynamic (CFD) modeling is a powerful software-based tool that has found recent success in modeling (simulating) airflow patterns in electronics fabrication and pharmaceutical cleanrooms.[1,2,3,4] When used in conjunction with sound engineering design principles, CFD modeling can be an efficient and economic method of fine tuning the design of a pharmaceutical cleanroom long before the all important qualification (validation) effort begins. For the past four years, Alcon Laboratories, Inc. has been using CFD modeling in the design and construction of all new and renovated aseptic filling suites. In this article, three different case study applications of CFD modeling will be presented. The first example will show how CFD modeling was used in completing the final design of a brand new high speed aseptic filling line. The second example will show how CFD modeling was used to improve air flow in a newly renovated cleanroom. Finally, the third example will show how CFD modeling was used to troubleshoot and improve an environmental monitoring problem with an older cleanroom.

CFD is a branch of fluid mechanics that uses numerical methods and algorithms to solve and analyze problems that involve the flow of fluids.[5] In the examples presented in this article, the fluid being analyzed is the air stream within the cleanroom. CFD models can be used by engineers to quickly and accurately model not only airflow, but also contaminants and thermal comfort.[6]

To construct an accurate CFD model, existing room conditions as well as critical design parameters, must be captured to accurately produce the model. Examples of the room conditions include: cleanroom dimensions, placement of supply HEPA's and return air diffusers, heat sources, and equipment obstructions such as the process equipment contained within the cleanroom. Critical design parameters which aid in an accurate CFD model include temperature and volume of air supplied to each supply air diffuser and volume of air at each return diffuser. Sometimes overlooked, return air volume is very important to the accuracy of a CFD model. If the return air volume is not known, the software will determine the flow. This usually leads to inaccurate results seen in the CFD model. The architectural/engineering firm specifies the return air volume, usually with an acceptable range based on the calculated room leakage. In existing cleanrooms, the return air diffuser dampers may move, which will change the airflow in the complete cleanroom.

The CFD model can be constructed using any number of commercially available software programs. The most common method to produce a model involves breaking down the volume of a cleanroom into discreet cells to form a volume mesh or "grid," which is the finite volume technique, and then apply a suitable algorithm to solve the equations of motion for the airflow throughout the grid. For the model to be predictive, it is important that the data being input is correct and accurate.

CFD results, typically representing steady state airflow, can be visualized through various parameters such as temperature, simulated particle tracings, and mean age of air. The accuracy of the results depends upon the validity of the model. If used properly, CFD models provide a valuable means to reduce risks associated with inconsistent or problematic airflow patterns in cleanrooms. As such, CFD becomes an impor-

tant tool for the engineer when designing a pharmaceutical cleanroom.

Smoke tests are benefitted and enhanced by CFD modeling through comparison with the areas of concern in the CFD models. By analyzing these potential problem areas through the model, the smoke test may be expanded to ensure validation and engineering personnel adequately cover areas of the room, which may not have preferred airflow patterns. As an example, a recent model was performed in an ancillary classified room where primary packaging components were being prepared for entry into the filling room. The CFD model that was generated for this exercise helped to identify an optimal area within the room where an operator could be stationed during periods of non-activity, such that the HEPA-filtered air swept across the operator with good, clean air and into the return air diffuser, while keeping the operator comfortable and reducing any contamination risk to the components. The modeling activity determined that the location of the operator prior to the modeling activity created risk to the primary components by causing some unwanted airflow patterns in the area.

Modeling of new and renovated cleanrooms has been beneficial in helping to locate optimal supply and return air duct locations, as well as optimal damper placement. If these conditions are not optimal, the CFD modeling exercise will reveal areas of low or stagnant airflow. In most instances, problematic airflow patterns and stagnant areas within a Grade A/B cleanroom are due to the lack of strategically placed return air diffusers adjacent to the Grade A operational area. By designing in low wall returns in lieu of traditional return air diffusers throughout the room, the increased surface area allows for lower velocities at the return facilitating an improved laminar airflow throughout the operational area.

Adjustment of air volume at the return air diffusers is very critical for proper airflow patterns in the cleanroom. If too much air volume is returning to one side of the room, unwanted airflow patterns occur resulting in air traveling from one side of the room to the other. CFD modeling has been useful in correcting this type of issue in several cases. CFD modeling has been used to correct return air volumes and reduce unwanted airflow patterns in Class B and C corridors, fill rooms, and gown rooms. In all cases, smoke tests were used to confirm the accuracy of the model.

Using CFD modeling for all cleanroom design applications, has significantly improved cleanroom environmental conditions in a proactive manner. This engineering tool has saved time, resources, and cost by the upfront identification of unwanted airflow patterns in the cleanroom and other critical operational areas. Corrective action may be implemented with a high degree of confidence through CFD modeling to optimize airflow patterns prior to construction. The end result is a properly designed and constructed cleanroom and its supporting mechanical system to ensure a controlled environment during operation. To date, CFD modeling has been used in more than 30 different activities to improve the quality of our cleanroom designs.

In this article, three separate applications of CFD modeling will be described. The first example will show how CFD modeling was used in completing the final cleanroom design of a brand new high speed aseptic filling line. The second example will show how CFD modeling was used to improve air flow in a renovated existing cleanroom. Finally, the third example will show how CFD modeling was used to troubleshoot an environmental monitoring problem with an older cleanroom.

All three applications have resulted in increased airflow quality in the cleanrooms. For the new cleanroom design and for the renovation of existing cleanrooms, the ability to model a room prior to construction execution benefits the construction project in the areas of quality, cost, and schedule. The model helps to identify areas of concern and unforeseen deficiencies in the original design. CFD modeling has the potential to reduce project costs by allowing changes to be made before cleanroom walls are constructed or ductwork is fabricated and installed. CFD modeling can aid in design optimization of cleanrooms to improve the room's airflow that may not have been anticipated until well after the room has been constructed and qualification is in progress.

Case Study 1 – New Aseptic Filling Line

Typically, a good engineering practice for an architectural/engineering firm is to specify the air change rate based on the heat loads, process definition, and area classification desired. These design parameters must be met during design phase and must be maintained over time. As an example, Grade A cleanrooms must provide 90 fpm laminar airflow over the criti-

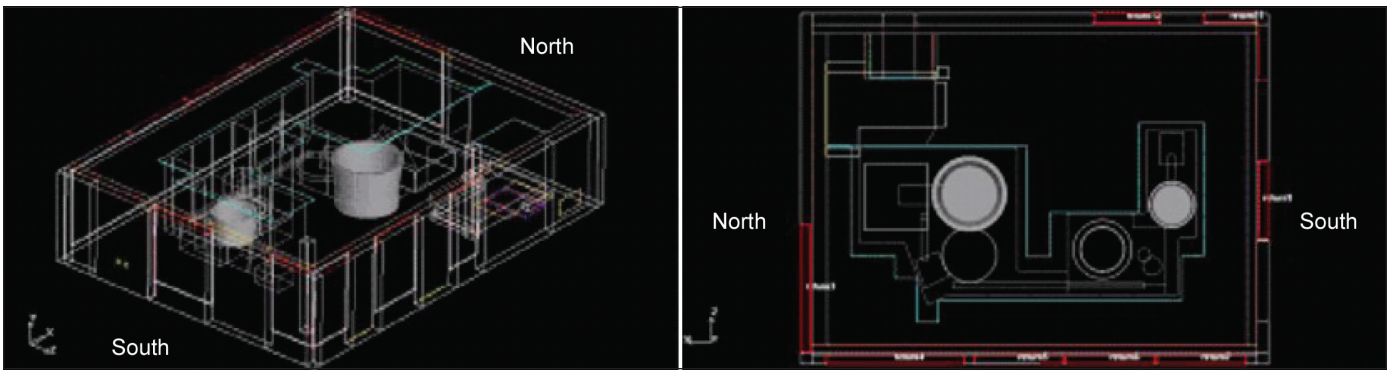

Figure 1. Isometric and ceiling view of original design.

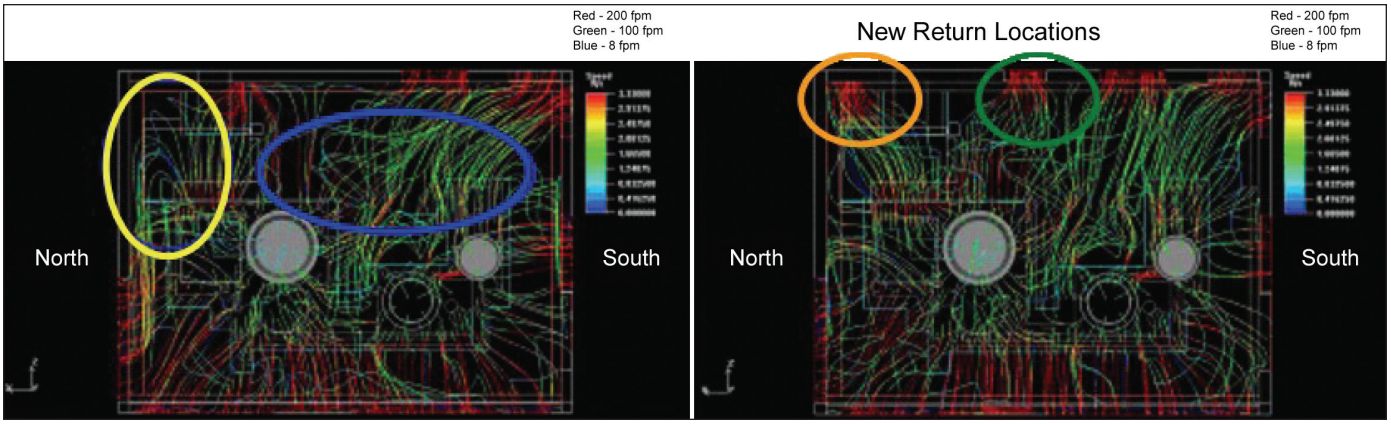

Figure 2. Original and modified design particle trace of Class 100 airflow.

cal operational area. Grade B and C cleanrooms must meet minimum air change rates and an appropriate differential pressures cascade between these rooms must be established and maintained to reduce the risk potential for microbial ingress into the cleanroom. Locations for supply air and return air diffusers throughout the fill suite are vital to reduce stagnant areas and to direct clean air to the appropriate areas in the cleanroom. In the first case study, a CFD model was performed during the early stages of a design of a new high speed aseptic filling line. The preliminary design appeared to meet all requirements for temperature, humidity, air change rate, and differential pressure cascade. The engineering firm designed the locations of the return air diffusers in a logical layout. The supply air was directed through a full ceiling diffuser that allowed for laminar flow over the complete fill room. Figure 1 depicts the CFD model of the fill room with the filling equipment located in the room.

When the model was evaluated, there were several areas of concern that were identified. However, since the modeling was performed prior to any construction, making corrections were simple and cost effective. Three additional models were performed and several changes from the original design were recommended. Return air volumes were first adjusted to eliminate unwanted airflow patterns. When this change proved to be only partially successful, several return air diffusers were added to the fill room. Most of the problematic airflow areas were corrected with the exception of an unwanted airflow pattern at the location of a barometric damper above a component conveyor leading into the fill room. Again, through the graphical representation of this unwanted airflow pattern, the damper was moved to an alternate location in the room and offered the added benefit of eliminating an existing return air diffuser that was going to be difficult to install. In Figure 2, the green circle identifies the new return and the orange circle identifies the new location of the barometric damper.

Figure 2 depicts the plan view of the airflow for the initial and final room design, and the velocity of the airflow is demonstrated by the color range of the particle tracings. The yellow circle identifies a stagnant area within the original design of the room and the blue circle identifies air that is crossing the room in a critical background area. What we were looking for in these results was air flowing from the Grade A area dispersing evenly to the returns and not crossing paths. When comparing the original design on the left panel to the modified design on the right panel, the one on the right shows airflow from the center of the filler flowing outward evenly. After the minor modifications were made as described above, the view in the right panel of Figure 2 shows the unwanted air patterns were eliminated. Figure 2 only shows the plane view, but in the CFD software, all perspectives were analyzed, including viewing from all three axis in the plane view along with the rotational isometric view. This also allowed us to verify that air is not traveling from the floor upward across a critical area.

Case Study 2 – Renovation of an Existing Cleanroom

During a recent renovation of an existing cleanroom, a return air diffuser was added to the one corner of the room to improve airflow and is identified in Figure 3 by the yellow circle. During the actual construction, it was discovered that the proper size of ductwork leading to this return air diffuser could not be installed due to an interference with an existing utility pipe. An alternate duct size was installed and the CFD model was run again to measure the effects of the smaller duct size on return air volume. In the model, air was viewed to be improperly traveling from one side of the room to the other and

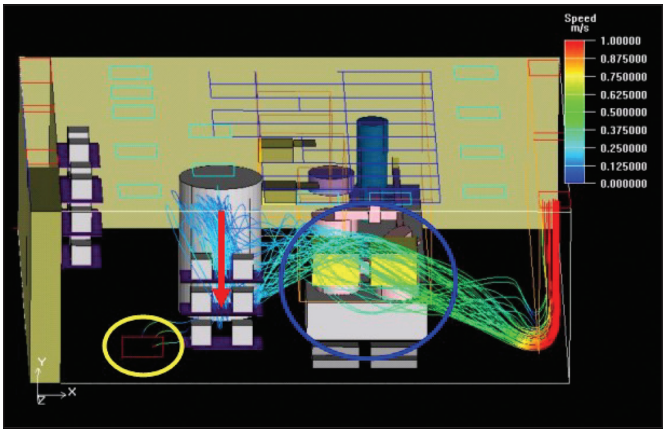

Figure 3. Initial CFD model prior to return air volume adjustments.

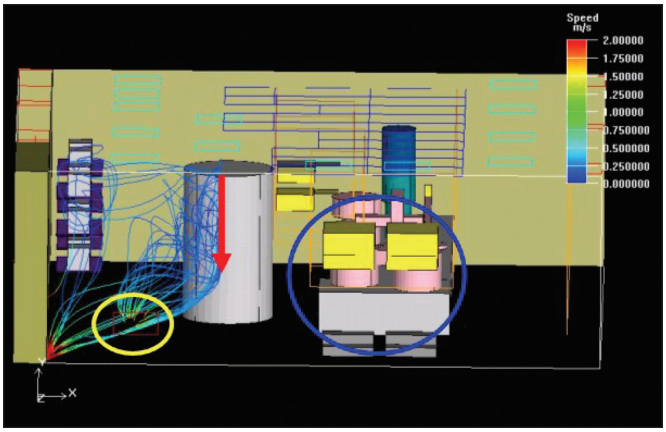

Figure 4. Final CFD model with return air volume adjustments.

crossing a critical area where operators load a bottle hopper. This critical area is identified by the blue circle in Figure 3. As illustrated, air is crossing this area from the opposite side of the room. A smoke test was then performed in and around the area of concern. The red line indicates the location where smoke was introduced into the room. The model shows the pattern of the air flow in Figure 3. The smoke test confirmed the problem seen in the model. With construction completed and with a clear graphical representation of an unwanted airflow pattern, adjusting the return air volumes in the room was the proper course of action needed to re-direct the airflow pattern to eliminate this cross flow. An added step was taken to ensure that velocities in the ductwork were not too high. (Note: the CFD software will model it even if it is not practical). Unfortunately, this is something that the CFD software does not check and must be analyzed by an engineer to ensure that too high of velocities are not present at the return air locations. Figure 3 depicts the cross flow of air before return air volume adjustments. Figure 4 depicts improved airflow patterns with the return air volumes adjusted. The red line in Figure 4 shows where smoke was introduced into the room and as illustrated, the airflow no longer crosses the critical area in Figure 4. These return air adjustments could have been done several times before the improved airflow was accomplished, but with the CFD software, the adjustments were only done once. There were four CFD models performed to achieve the final outcome.

Case Study 3 – Troubleshooting a Problematic Area

In this case study, CFD modeling was used to aid in troubleshooting an environmental monitoring concern. In one existing older aseptic filling room, routine environmental monitoring revealed higher than normal viable levels in the air and in several surfaces in the grade B area of the fill room. A CFD model was initiated to understand what was occurring with airflow patterns in the cleanroom in an effort to see if there was enough air movement in the area. Prior to performing the CFD model, there were other corrective actions initiated in an attempt to remedy the problem. These actions included increasing surface disinfection, as well as conducting additional sampling and aseptic training of the operators working in the area. The CFD model actually revealed that there was insufficient movement of air in the areas where these surface samples were being taken. In addition, routine operator activities in this same area increased the potential for microbial contamination. As a result of the modeling exercise, several changes were made to improve the airflow. These changes consisted of adding one HEPA supply air diffuser, replacing a ceiling mounted return recirculation unit with low wall return air diffusers, and locating a return air diffuser in a strategic location where stagnant air was encountered.

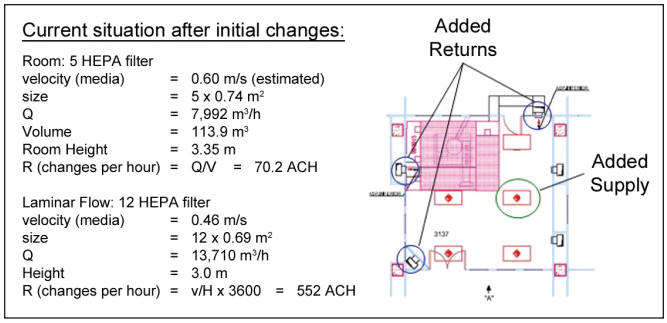

Figure 5. Fill room with corrective actions initiated to improve airflow patterns

Figure 5 depicts airflow volumes and show the initial changes that were made as a result of the modeling exercise. However when performing this initial model, one critically important piece of data was not accounted for, that being the volume of air flowing to each return air diffuser. Airflow to returns may vary greatly depending on the position of dampers in the ductwork and the system that the returns supply.

After the return air volumes were measured in the field, a new CFD model was performed. The mean age of air was evaluated and it was determined that stagnant areas existed in the fill room. Figure 6 depicts stagnant air centered in the room indentified by the red circle, which is where the operator typically works. The model also revealed unwanted airflow patterns throughout the room, due to the high velocity supply air contacting the floor leaving the curtained barrier separating the Grade A critical area from the Grade B surrounding area. Two additional measures were taken; a full ceiling diffuser was added to obtain optimal airflow patterns and some minor curtain configurations were made surrounding the filling

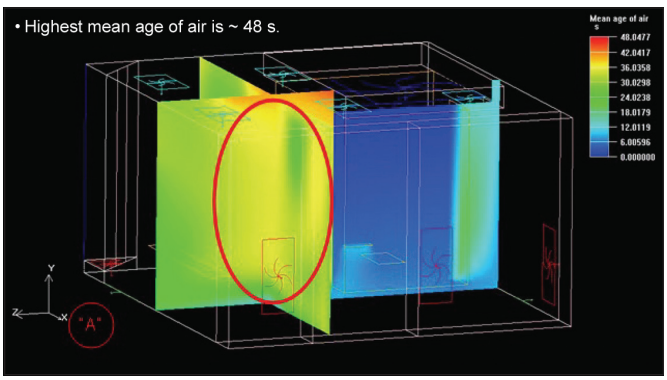

Figure 6. Shows mean age of air for initial changes.

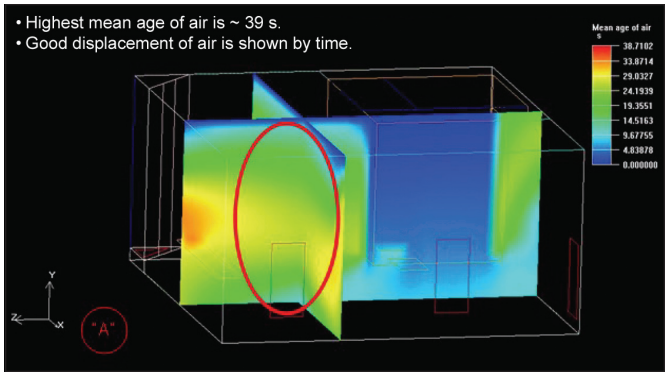

Figure 7. Shows mean age of air for final changes.

machine. In Figure 6, the red circle shows that the mean age of air in this area is approximately 36 seconds. Figure 7 represents the CFD model with the additional measures taken and the red circle identifies the same high traffic area. In Figure 7, the red circle shows that the mean age of air in this area is approximately 20 seconds. In this particular area, an operator was typically stationed performing in process control checks, documentation, etc. Improving the air flow pattern in this area reduced the contamination level for air and surface samples taken in that area.

Table A below shows the environmental monitoring results in the Grade B area of the cleanroom before and after the CFD model and subsequent modifications were made.

As shown in Table A, the modifications made to the cleanroom greatly reduced the growth incident rate observed in air samples (both active and passive samples) collected in the Grade B area. In addition, the relative rate of surface samples collected in the Grade B area that had growth rates above alert levels decreased to zero.

Conclusion

When used in conjunction with sound engineering design and validation principles, CFD modeling can be an invaluable tool for fine tuning the design of a new pharmaceutical cleanroom or for improving the conditions in an older existing cleanroom. If implemented early on in the design of a cleanroom, a CFD modeling program can save significant design time and reduce construction and startup costs. CFD modeling also can be an investigative tool to better understand potential causes for environmental monitoring excursions that may exist in a cleanroom. In addition, when using CFD modeling in a comprehensive manner, it can be an adjunct to aid the implementation of aseptic processing best practices and continuous improvement in pharmaceutical manufacturing facilities worldwide.[7]

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	Environmental Monitoring Results for the seven months Prior to Modifications	Environmental Monitoring through four months after Modifications	Environmental Monitoring Results through 16 months after Modifications	Environmental Monitoring Results through 28 months after Modifications
% Grade B Air Samples with Growth (Active air + Settling Plates)	18.2	15.3	9.4	9.4
% Grade B Surface Samples with growth above Alert levels	3.45	0	0	0

Table A. Environmental monitoring results before and after modifications.

helped lead an effort to design, build, validate, and operate a state-of-the-art manufacturing facility located on Alcon's Ft. Worth, Texas campus. In his current role, Gafford provides technical support for Alcon's manufacturing facilities located worldwide. He specializes in providing technical support in the areas of aseptic processing, compounding, high purity water system design and operation, and technology transfer. He has published several articles on high purity water and he also has been a past presenter at Interphex. He can be contacted by telephone: +1-817-551-8051 or by email: john.gafford@alconlabs.com.

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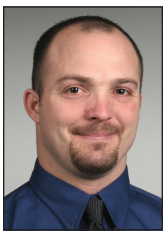

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Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2010, Vol. 30 No. 4
www.ISPE.org

Industry Forces Driving Standardization of the Turnover Package

by Roy F. Greenwald and Bill Schaidle

This article provides an overview of the past and present approaches to formatting of turnover packages for equipment and modular assemblies. It highlights the lack of standardization within the industry and presents an example of an approach that could serve as a starting point for an industry standard.

Introduction

The purchaser of almost any piece of equipment in any industry has certain expectations for the documentation that will be provided along with the procured equipment. This remains true whether purchasing a single piece of equipment, a small skid, or an entire process module. The extent of that documentation can vary greatly, from a simple operations and maintenance manual, to a full set of documentation that may include multiple volumes and reams of pages. Within these, there may be detailed drawings, component information, material certifications, fabrication details, and weld quality documents, and this is by no means a complete list. The pharmaceutical industry (henceforth implied to include biotechnology facilities as well) has been through an evolution in the past 20 years that has led to a virtual explosion in these documentation requirements, especially after the first set of Good Manufacturing Practices regulations were published in 1977.[1]

Presently, almost all equipment purchased for inclusion in a pharmaceutical facility requires the submittal of an accompanying Turnover Package or TOP. Herein lies the problem: the extent and organization of the TOP is not consistent throughout the industry. In fact, it varies from owner to owner, from engineer to engineer, and from vendor to vendor – for the exact same piece of equipment. Yet, the objective of the TOP is the same for all:

- to provide all documentation required by FDA current Good Manufacturing Practices (cGMPs)
- to provide all documentation that the owner may require for installation, commissioning, and validation of the equipment
- to provide all necessary information to operate and maintain the equipment

This lack of uniformity or consistency in the provision of the turnover package documentation for equipment components, equipment skids, or modules adversely affects a project on two of its most critical metrics: cost and schedule. And schedule impact invariably leads to a cost impact. Whether viewed from the owner's, engineer's, or vendor's perspective, project costs increase due to:

- vendor uncertainty as to the exact deliverable requirements
- incomplete or inadequate documentation requiring multiple TOP submittals and review cycles
- reorganization of TOP data to meet each owner's unique requirements
- lack of documentation to prepare commissioning and validation protocols
- equipment startup damage due to inadequate or untimely documentation
- delayed or extended commissioning cycle due to incomplete documentation

Historical Perspective

During the last decade, the industry has responded to the expanding demand for equipment documentation with the creation of a separate specification section often included with the original request for quotation sent to its vendor base. This was variously called the Vendor Data Requirements, Vendor Document Requirements, Drawing and Data Requirements, or other similarly named section (henceforth, it is referred to as the VDR). This specification identified the entire set of document deliverables required from a vendor, including those to be incorporated within the TOP. In previous years, the documentation requirements for a specific equipment component or skid were spread throughout a multitude of specification sections; each addressed specific discipline

Key Attributes	Prior to and During the 1990's	Presently	Future Trends
Source for What Data to Include	Bid specifications	Specifications and Contract Vendor Data Requirements (VDR)	Standardized Matrix
How Data is to Be Organized	Varied	VDR Codes	Tag Numbers
How Data is Transmitted	Paper or CD	Mixed – Paper and DVD	Electronic required; paper at client's option
How Data is Coded (Naming Conventions)	No specific coding	VDR Codes or Vendor-Determined	Unique Numbering
Extent of Quality Checks	Limited to none	Significant	Total

Table A. Evolution of the turnover package.

submittal requirements, such as electrical, mechanical, structural, instrumentation, and automation. This posed a difficult task for the vendor community to determine exactly what information was required under any given contract, especially within typically short bid cycles. The introduction of the VDR provided a single separate document listing all of the information required for the equipment. Without this single document, there were sometimes legitimate claims from the vendor of additional cost and time to produce the needed documentation. Often these came at the end of the project, when the owner and engineer most needed the documents to support ongoing commissioning and validation efforts, and where delays translate directly into costly overruns.

Table A shows how five of the key attributes relative to the TOP have evolved through the 1990s to the present. These key attributes are parameters one must consider when requesting, gathering, storing, and eventually retrieving information. As can be seen from the table, there have been many changes in the span of approximately 15 years. The advent of the VDR has had a major impact in providing more complete TOPs as have the specific ISPE Baseline® Guides[2] although they do not delve into the details of the TOP. Neither the VDR nor the Guides has adequately addressed all of the key attributes listed in the table, as each owner or engineering firm has produced its own VDR form. Without standardization of the VDR between different owners and various engineering firms, vendors have constantly had to revise their TOP deliverables in order to suit each individual contractual need for the same piece of equipment. This has created additional TOP assembly costs, which are naturally passed on to the owner, as well as increased the risk of potential delays and incomplete TOP submittals as documents are reorganized. On some projects, the VDR often imposed more requirements on the vendor than normally required. If this was overlooked or requested belatedly, the vendor incurred added costs to perform a re-compilation of the documentation.

At present, most documentation specifications require vendors to submit both electronic and paper copies of the TOP. The number of paper copies varies greatly from project to project, but not as greatly as the how the documents themselves are required to be organized within the hard copy TOP. From an owner's perspective, having each and every TOP from the various vendors compiled and organized in the same manner serves a legitimate purpose. It allows for quick location of specific data for protocol preparation, commissioning, and validation. From an engineer's perspective, documentation organized to follow the VDR format and naming convention allows for a cost effective review and checking process in order to ensure all required documents have been received. Although some logical connections with this approach are obvious, such as keeping all drawings together or all field instrument documentation together, testing documentation might be found throughout the TOP. From a vendor's perspective, consistently organizing the data in the exact same format from one project to the next produces the highest quality assurance level of the TOP and neatly organized TOP binders. The continual reorganization of data from project to project adds unnecessary risks and costs to both the vendor and owner, as noted previously.

Another factor that varies greatly is the size and sophistication of each owner's team. This has often impacted the type of TOP an owner eventually receives. Some owners are capable of working with vendors early on to incorporate as much of the vendor's standard information as possible to fit within the owner's TOP requirements. However, one of the authors has worked with smaller organizations that were unable or unwilling to commit this necessary time to properly address the TOP. These owners often totally relied on the engineer, or in some cases, the vendors themselves to provide what they believed was needed for maintenance, commissioning, qualification, and validation purposes. The benefit of a standard set of documents to these owners with smaller teams is obvious. Even for the large owner organizations; however, the benefit of having manuals consistent and complete in their content has saved time and money during commissioning and validation. It protects the overall schedule and is why these owners are so involved in formatting the TOP in the first place. As the industry moves toward standardization with the potential to meet the needs of all owners, the cost of customization will no longer warrant its incremental value.

Even more fundamental to the TOP is the process by which the original first-order compilation is accomplished. For instance, if a vendor were providing information on multiple skids placed via a single order, should the vendor provide a single TOP or multiple TOPs? For documents such as welder qualification records, which are applicable to all of the skids, would the documents be duplicated for each skid TOP, adding to the volume of TOPs, or centrally located? Once again, these problems often surfaced at the end of a project if they were not correctly addressed at its initiation. On more complex skids and modules, the time and cost of completely recompiling the TOP are often quite significant.

The electronic TOP copy creates as many problems in organization as the hard copy TOP although they are entirely different in nature. A key concern for electronic files is that they must be readable in a format that will be supported 10 to

20 years in the future. Most owners are willing only to accept either Microsoft® Office-based products or Adobe® PDF files. As a result, the industry as a whole has had difficulty doing anything more than compiling TOPs in the hard copy format and then scanning them into a PDF file. This presents its own set of difficulties because no standardized naming convention or coding requirement for each specific TOP document currently exists. This is a critical area in need of standardization. For instance, although a vendor may provide material test reports on all product-contact components incorporated within a project, the format in which those reports are turned over electronically can vary tremendously. The vendor can provide a single scanned TOP, a TOP scanned by sections (in which case all material test reports may reside in a single PDF), or each report may be individually scanned as a separate PDF. To an owner looking for a single report, the latter approach may appear to be the most desirable – but this is true only if a meaningful naming convention has been adopted for these

STANDARDIZED DOCUMENT REQUIREMENT AND NAMING CONVENTION VDR MATRIX

Data File Name = Component Assigned Tag Number + First Code ID + Second Code ID

TOP SECTION	TOP REQUIREMENT	ELECTRONIC COPY REQUIREMEHT	FIRST CODE ID ↓	SECOND CODE ID → / Company XYZ, Project ABC, AnyCity, AnyState, AnyCountry ↓ Documents	↓ Components →	001 Skid or Module	002 PLC Control Panel	003 Electrical Component	004 Instrument	005 Piping	006 Agitator (tank penetratio)	007 Agitator (magnetic)	008 Vessel (pressure)	009 Heat Exchanger	010 Pump (centrifugal)
					Document Key: A = Always Required: H = Required for Hyglenic Systems Only										
Section 1 - General (System Level Documentation)															
1			A1	List of Tags for System											
1			A2	List of Engineering Specifications Applicable to System											
1	√		A3	List of Drawings Applicable to System											
1			A4	Purchase Orders and Change Orders											
1	√		A5	Warranties											
1	√	√	A6	Piping Line List											
1															
Section 2 - Calculations / Data Sheets															
2	√		C1	Utility Requirements											
2			C2	Allowable Forces and Moments on Nozzles											
2	√		C3	ASME Code Calculations											
2			C4	Completed Data Sheets											
2	√		C5	As-Built Data Sheets											
2	√		C6	Equipment Sizing Calculations											
2															
Section 3 - Drawings															
3			D1	General Arrangement Drawing											
3			D2	Flow Diagram											
3			D3	Piping & Instrumentation Diagram (P & ID)											
3			D4	Control Panel Drawing											
3			D5	Wiring Schematic											
3			D6	Foundation Diagram and Loading Requirement											
3			D7	Mechanical Seal Cross Section											
3															
Section 4 - System, Operational and Validation Documentation															
4			F1	Functional Requirements Specification (FRS)											
4			F2	Detailed Design Specification (DDS)											
4			F3	Pre-FAT Testing and Documentation											
4			F4	Factory Acceptance Test Dossiers and Testing Procedures											
4			F5	Completed FAT Punchlist											
4			F6	Site Acceptance Test Dossiers and Procedures											
4															
Section 5 - Lists and Indicies															
5			L1	Recommended Spare Parts List											
5			L2	Detailed Parts List											
5			L3	Document / Drawing List / Index											
5			L4	Instrument List / Index											
5			L5	List of Special Tools For Maintenance											
5			L6	Alarm & Interlock List											
5			L7	Valve List											
5															
Section 6 - Manuals / Reports															
6			R1	Installation, Operation, Maintenance Manual											
6			R2	Lubrication Manual											
6			R3	ASME Code Data Reports											
6			R4	Hydrotest Data Reports											
6			R5	Certificate of Compliance											
6			R6	Manuals / Reports Mill test certificates with heat Numbers or certificates of Compliance (COC)											
6			R7	Instrument Calibration Sheets											
6															
Section 7 - Miscellaneous															
7			M1	Passivation and Cleaning Procedures											
7			M2	Weld Maps With Welder Identification											
7			M3	Riboflavin Testing Report											
7			M4	Sprayball Listing and Sprayball Flow Data											
7			M5	Electropolishing Procedures											
7			M6	Electropolish Certificates											
7															
Section 8 - Control System Data															
8			V1	Software Development Documentation.											
8			V2	Software Source Codes											
8			V3	Software Test Protocols											
8			V4	Maintenance Manual											
8			V5	Security System Specification											
8			V6	Program Structure											
8			V7	Calibration Procedures											
8															

Figure 1.

files. Despite all of the focus on electronic files, the electronic copy is still usually (although not universally) the back-up rather than the primary file.

In summary, the above-defined industry's response to the ever increasing documentation demands has been very positive and has remedied some of the TOP problems. However, there are still major inconsistencies in the level of documentation required for specific equipment, how the data is organized, how it is named or numbered, and what the approach will be with respect to electronic files. All of these variations add unnecessary costs and delays to each and every project. One of the primary goals of the vendor must be the delivery of a useful and useable product to the end user in the most cost effective method. This is an area that could be well served through the adoption of an industry standard or guideline for TOPs. The balance of this article presents a starting point for the discussion and possibly the eventual adoption of such a standard. It also seems the ISPE or the BioProcessing Equipment (BPE) standards produced by the BPE Committee of ASME could be the logical source to develop and promulgate such a standard.

TOP Improvements and Standardization

As the industry heads toward electronic documentation and archiving, the goal of standardization should be to adequately address the five key attributes noted in Table A. An initial fundamental observation can be made: if information is provided by the vendor in an appropriate electronic database format, the hard copy becomes a secondary concern. Production of the hard copy simply turns into a report writing exercise from the database; it can be produced at any time, in any format, by simply printing the appropriate files. This in itself can reduce costs and project delays as vendors would no longer need to struggle with different TOP organizations. This requires that owners are willing to accept scanned electronic copies as originals, which are now widely used, and seems the most likely progression. Another advantage of such an approach, if properly designed, is that data can be fed directly into plant-wide database maintenance and management programs, such as Maximo.

In order to move to a fully electronic database for TOP documents, the first and foremost requirement is the assignment of a unique document number to each and every data file. This also will facilitate the extraction of desired data from that database (for instance, to generate a hard copy TOP). Figure 1 shows a much abbreviated VDR that also contains a proposed naming convention; this figure is an example and is not intended to be complete. The naming convention has three elements to it. The first is the component tag number, which is usually defined by the engineer or owner during the design stage. This tag number also is the critical reference point the end user will start with when attempting to locate information from a TOP. Note that it is a baseline assumption that each tag number for each element, instrument, or piece of equipment is unique within an owner's entire facility.

The second element of the data file name will be as indicated under the column headed "First Code ID." This code relates to a specific document type as indicated under the column headed "Documents" (for example, D-1 under First Code ID corresponds to "General Arrangement Drawing). Therefore, each distinct document type will have a unique alphanumeric First Code ID. The Alpha portion of the code will categorize the documents into each of the eight groups as shown in Figure 1. In this example, A = General, C = Calculations, D = Drawings, L = Lists, R = Reports, etc. The numeric portion will identify the specific document type within each group. For example, in group D entitled Drawings, 1 = General Arrangement Drawing, 2 = Process Flow Diagram, etc. The key to creating a successful standard is that each document type must have a unique code and multiple document types are not grouped into a single category such as "All Drawings."

The final code element of the file name would be a numeric code as indicated in the row entitled "Second Code ID." This code identifies a unique physical equipment component, such as magnetic agitators, PLC control panels, instruments, piping, and skid frames. Therefore, as an example, a Temperature Indicator with a tag number of 203-TI-308 would have its instrument data sheet named as 203-TI-308-C4-4. Using this convention, an owner could conduct a sort on all Temperature Indicators (TIs), or all data sheets, or all instruments or all documents related to instrument 203-TI-308. This three element file name would be assigned by the vendor, using the project-approved matrix, when the electronic file for this instrument's data sheet is transmitted by the vendor to the engineer and owner. Should an owner wish to compile hard copies of all instruments or hardware related to a particular skid, room, or line, it is a simple process to list these from the piping and instrumentation drawings and print the necessary documents. Alternatively, electronic files can be sorted into whatever folders are convenient or appropriate for the preparation of commissioning and/or validation protocols. As is also indicated in Figure 1, it is possible to indicate via coding in the proper columns whether documents are always to be part of the TOP, or simply submitted for hygienic/product contact components. Thus, via the referenced figures, both the naming convention is specifically defined as well as providing

Air Compressors	Glass Washers	Refrigerators
Air Handlers	Hoists	Reverse Osmosis System
Biowaste Inactivation	Incubators	Scales (bench)
Boilers	Liquid Handling System (LHS)	Scales (floor)
Cartridge Filters	Material Lifts	Spray Balls
Centrifuges (disc-stack)	Motor Control Center	Sterilizers
Chillers	Motors	Tanks (atmospheric)
Chromatography Columns	Pumps (diaphragm)	Transfer Panels
Clean Steam Generators	Pumps (peristaltic)	Ultrafilters
Freezers	Pumps (rotary lobe)	WFI Generators

Table B. Additional top priority equipment for incorporation into document requirements matrix.

the means to organize and compile data through assigned tag numbers.

Taking a more detailed look at the headings in Figure 1, one can see that only a small sample of equipment and systems are indicated for the columns in the upper right-hand side of the figure. A complete standard would contain a listing of all equipment or systems encountered in the typical biopharmaceutical facility. Table B presents a list of other systems that would be candidates for inclusion into a complete Figure 1 matrix. As previously noted, the listing of documents under the column headed "Document Description" is only a partial listing (as is true of all of the groups in Figure 1). The authors have compiled a substantial and more complete listing of these based on various engineering and owners lists, which although not presented here, could serve as a starting point in a standardization effort.

Finally, the format in which data is transmitted can be indicated on Figure 1 as well. The assumption is that presently hard copies are the standard format with scanned documents as an option. However, an engineer or owner may request electronic files by simply indicating such in the appropriate column labeled "Electronic Copy Requirement." It is expected that eventually most, if not all, data will be submitted electronically from project initiation through the submission of the final TOP. However, the format in Figure 1 will allow engineers and owners to move toward electronic files as their own internal processes and procedures permit.

Although one might assume that introducing the management of a detailed matrix into an owner's set of obligations would bring with it additional burdens, any burden is significantly outweighed by its benefits. Recently a real-world application of a matrix-driven TOP management system was employed at a grassroots, biopharmaceutical facility by one of the authors. It involved more than 1,500 separate instruments, equipment items, and/or skids. It had seemed clear at the outset that the scheme to manage the TOPs for this amount of data would require either a data-base management or matrix management approach. The alternative approach, at its simplest level, was that each item might simply have been listed as requiring a TOP with its documentation reviewed as it was provided. However, this does not allow the owner to have input into exactly what he or she would like or require within each TOP. Nor does it optimize the data management and collection processes. The more advanced matrix proposed in this article solved those problems. Without such a complete matrix early in the process, there is an obvious disadvantage; incomplete or unacceptable TOPs are routinely submitted and must go through a review cycle in order to flesh out what is going to be finally required. Even if a simple TOP plan is prepared by the vendor for review, rather than the entire package, a detailed review of that list is still required. In the project cited by the authors, the complete matrix, prepared early in the project, had several quantifiable benefits to the owner:

- The owner was able to format data for consistency and to align with O&M requirements.
- The owner knew exactly where data would reside.
- TOP packages were more complete in the first submission.
- Review cycles for the final TOPs were reduced.

The means to developing such a standard must follow a step-wise logical progression. It would be expected that owners should first determine exactly what documents will be required for any given component or piece of equipment. The vendor community would next review this list to indicate what documentation is currently part of today's standard, and what documentation will require further development. Any documentation whose production is extremely costly should be flagged at this time for follow-up. The owner community can then confirm that the more costly documents are indeed warranted and therefore justify the additional cost of production. When the list has passed through this milestone, the engineering community should then review and provide their recommendations, and eventually serve as the vehicle through which the standard is promulgated throughout the industry.

Conclusions

As owners and engineers strive to streamline commissioning and validation, it is becoming more and more apparent that the Turnover Package plays a key role in this objective. Due to this drive, the quality, timeliness, and amount of information conveyed within each TOP is receiving more focus. Vendors are being pressured to complete their packages in a more compressed timeframe, while at the same time, demands for thoroughness and accuracy are increasing. One means of meeting the objectives of owners and engineers is to standardize the requirements for the packages themselves. Presently, no such standard exists. The authors have presented a format that has been utilized and tested with success on several projects, and although it may not meet all requirements for all situations, it may serve as a starting point. It is our hope that we have at least highlighted a need within the industry and that it may lead to further discussion, and even more beneficially, to possible standardization.

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Acknowledgements

The authors would like to acknowledge the contributions of both Ms. Karla Hancock and Ms. Chau Nguyen of Fluor Corporation, whose input in both developing the detailed matrices related to this work and their application on past projects was instrumental in determining the value of such an approach. In addition, Ms. Deborah Botham of DPS provided valuable

guidance and assistance in the preparation of this article.

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Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2010, Vol. 30 No. 4
www.ISPE.org

Engineering Information Management – Electronic Project Data from Design through Delivery

by Robert Velén, Dennis Naughton, and Rolf Strömgren

This case study explores lessons learned in data delivery from a decade of facility projects between Eli Lilly (facility owner) and Pharmadule (contractor), focusing on their latest project in Ireland. Perspectives from both the facility owner and contractor are provided.

Engineering Information Management

This case study presents a facility project in Ireland between Eli Lilly (the facility owner) and Pharmadule (contractor). This joint project had approximately 20,000 tags and 45 data fields for each tag, for a total of 900,000 data fields. By importing data electronically, rather than retyping it from hard copies, they reduced errors and decreased cost. As a result, both Lilly and Pharmadule saved money.

This case study explores the project from both the owner's and the contractor's perspectives and will share data collection and management lessons learned. The electronic engineering data was developed during design and procurement and used for commissioning, qualification, operations, and maintenance activities.

Project Background

Eli Lilly and Pharmadule have worked together to deliver modular pharmaceutical manufacturing facilities for more than 10 years. Over the course of these projects, data strategies and techniques have been developed and refined that provide efficient, complete information to the project team and end users.

One result of these multiple project deliveries was applying and refining data management strategies in an effort to attain the most complete, best quality data in a cost efficient manner.

Project Framework

Turn Over Package Basics

The Turn Over Package (TOP) is provided to the owner upon completion of a facility and typically contains the following:

- **Project documents.** This may include specification, design, procurement, commissioning and qualification (verification), and vendor documents.
- **Project drawings.** This includes structural, architectural, electrical, instrumentation, P&IDs, HVAC, and isometrics.
- **Project data.** This includes design, procurement, and verification data developed for the project. This has traditionally been supplied to the owner by the contractors as hard copy.

This article will focus on the data package only. Data collection, management, and distribution represent significant resource commitment from both an owner and a contractor perspective. Historically, data has always been supplied to the owner as lists, data sheets, etc. During the past decade or so, data delivery has evolved into structured electronic formats replacing data delivery in "hard copy." This is then imported into the owner's asset management system, saving a lot of time and increasing data quality.

As a general rule, most owners do not focus on the electronic data requirements early in the project, which leads to extra work at the end of the project resulting in discussions about what is supposed to be part of the original price versus a change, which could increase cost.

Data Delivery Process – Success Built on Shared Learning

Over the last decade, the owner and contractor have delivered seven modular projects successfully with detailed data delivery as part of each project. These project deliveries were located in several countries, including the United States,

Puerto Rico, and Ireland.

What has evolved during these projects is a maturity in working with electronic engineering information. Data requirements have been in focus earlier and earlier for each project, resulting in fewer change orders for the owner to consider and a more stable resource planning for the contractor.

Not only has the focus on data requirements come earlier with each project, the level of detail and the whole process of getting all providers to understand and accept the requirements also has increased for each project. Each project has had lessons learned activities, both internally in each company and also together. During these years the information technology also has improved which have made it easier.

The latest project for this owner and contractor represented the best data specification and delivery to date. Early, clear, complete data requirements from the owner were reviewed by the contractor to gain understanding at the beginning of basic engineering. This timing provided the contractor the opportunity to include the data requirements with every purchase order issued to sub-vendors, and apply the requirements to the contractor fabricated systems.

Owner's Drivers

The owner identified several drivers for project Engineering Information Management.

- Facility engineering – During the design activities, requirements and parameters are captured for specification and operations of the facility.
- Product quality – Lilly products meet and maintain the highest standards for quality.
- Procurement – Using design data, procurement activities link specifications to purchase and deliver assets to site.
- Construction quality assurance – Requires project data and documentation to verify fabrication specifications are met.
- Verification – Proper installation is an initial requirement in every project, and the design data is used as a reference.
- Qualification – Documents that the manufacturing equipment performance to specification.
- Process Validation – Provides a high degree of assurance that the process will consistently perform as intended.
- Maintenance packages – Developed during the project. These packages require design and procurement data.
- Operations – Manufacturing pharmaceuticals demands strict compliance with quality and regulatory requirements.

Contractor's Drivers and Experience

Although the contractor has extensive experience supplying paper based and electronic engineering data as part of the TOP, it appears that early clear communication of detailed electronic data requirements by the owner are becoming more common in the pharmaceutical industry as in other industries.

However, employing a data driven design approach enabled the owner to easily add data fields and adjust timing. These minimal configuration changes enabled the contractor to adapt and excel at meeting the new data requirements.

Data Requirements and Collection Strategies

Owner's Perspective

An Engineering Information Management plan is developed by the owner in early basic design and is reviewed and approved by the owner and contractor by the end of basic design. Plan details will include:

- data requirements for field name, list, format, and description of data populated
- data rules for when data should be filled in or left blank
- tag names and prefixes that are in scope for data collection
- clear and concise data specifications document with examples of data population
- review and approval of data specifications by client user representatives
- kick off meeting with primary data providers (module fabricator and A&E) in basic design phase
- communicate importance of client data requirements to design engineers, contractors, and subcontractors, and provide the reasons why specific data is required
- critical for client to witness designer understanding of data requirements
- agree on and document format for data delivery
- define multiple data maturity milestones: Schematic design, procurement, commissioning
- critical for client to witness data transfer upon initial data maturity; for example: tools, systems, transfer flows working together to deliver complete data of high integrity
- data change management workflows are critical for controlled data updates and data integrity
- data metric reviews scheduled on periodic basis to continue dialog between data providers and client

Owner's Data Steward Perspective

Scope of work for the role of owner data steward includes:

- interface with all project data providers data stewards to answer questions and solve issues
- data integrity review by owner prior to data acceptance
- weekly data metrics reporting on data completion and integrity
- verification form generation and management
- data change management workflow owner

Contractor's (Data Provider) Perspective and Application of Data Requirements

The following are two basic tracks for gathering information. They are:

1. for tags that are engineered in-house or are for simple commodities

"…it is vital that the contactor's purchasing department is well aware of the requirements and communicates them before issuing a purchase order."

(e.g., valves) where the contractor specifies the item and is in control of specification and procurement
2. for advanced equipment and assembled skids where a vendor, having most of the knowledge, specifies and procures skid components

For both tracks, it is vital that the contactor's purchasing department is well aware of the requirements and communicates them before issuing a purchase order. In the purchase order for either track, the EIM data requirements should be a line item in the same format as for a physical object.

There should be contractual penalties for failing to supply data and documentation deliverables.

With regard to the vendor track, it is important to make the vendors aware of the requirements very early. For more advanced equipment, it makes a lot of sense to include the owner in vendor discussions. The EIM discussions should continue after purchase order and prior to FAT to ensure that data is ready on time. The major milestone for skidded process equipment data and documentation is the FAT. Upon skid shipment and associated payment milestone, skid vendors are less likely to supply the data and documentation to specification.

Contractor's Data Steward

The role of the data steward was implemented specifically for this project. Because of positive experience with this project, this role has become part of the contractor's standard work package.

The tasks performed in this role were very similar to those performed by the owner's data steward. The difference is that the contractor data steward had to coordinate multiple design disciplines and work with procurement within the company. In this case, the contractor data steward responsibility began with identification of all tags that required data, and ended with the data delivery to the owner.

For the contractor, it was important for the data steward to coordinate with mechanical, electrical, instrument, and process engineering disciplines, as well as project management staff, document control, and purchasing.

Some issues the contractor (as data provider) experienced were:

- timing of data delivery to project milestones
- slow and incomplete answers to specific data questions
- expediting of data requirements
- a process for channelling questions back to the owner for quick response

Weekly meetings were conducted with the owner, as well as internally with the engineering disciplines and outside vendors to ensure data delivery to project milestones.

Data integrity reviews were required prior to data delivery. As model numbers tend to change, for some vendors, there was post-data delivery change management necessary to update model numbers and other data. The contractor's generation of RV forms and execution of commissioning forms was also part of the project scope, driving the data integrity reviews.

Two Sources for the Same Data Set

This project had several contractors and vendors providing data for inclusion in the overall data delivery package. There were times when two contractors would provide data on the same tag. In this case, one of them was doing the engineering, specification, and purchasing, while the other was responsible for the design and commissioning. The rule set by the owner was that "he who buys provides all the information to the owner." This resulted in the contractors' need to share information, which could be quite challenging; in that, the contractors are likely to use different engineering tools.

Term	Definition
A&E	Architectural and Engineering (firm)
AHU	Air Handling Unit
BIM	Building Information Modeling. The process of generating and managing building data during its life cycle, using three-dimensional, real-time, dynamic building modeling software to increase productivity in building design and construction, with building geometry, spatial relationships, geographic information, and quantities and properties of building
CMMS	Computerized Maintenance Management System
Data Steward	This project role, common to all participating companies, is responsible for coordinating and checking data, as well as working with procedures and interacting with the data stewards from other companies. Although the role is similar for both the owner and the contractor, differences are described in the article.
EIM	Engineering Information Management. The data that describes engineering attributes of equipment and instruments tags on schematic mechanical, electrical, and automation drawings.
ERP	Enterprise Resource Planning
FAT	Factory Acceptance Test
HVAC	Heating, Ventilation, Air Conditioning
P&ID	Piping and Instrument Diagram. For HVAC, these are often referred to as AF&ID which means Air Flow and Instrument Diagram.
PDMS	Plant Design Management System. A 3D Computer Aided Design (CAD) software.
TOP	Turn Over Package

Table A. Terms and definitions.

Engineering Information Management Architecture

Data Management System Requirements

Because of the scope and complexity of the data generated in this project, the contractor and the owner needed more powerful data management tools than the ubiquitous spreadsheet.

The owner did not impose requirements on any contractor or vendor to use specific engineering tools. The requirement was simply that the data format for input to the owner was to be a standard comma delimited file. After receiving this file from the contractors and vendors, the data was uploaded into the owner's system by their data steward.

The Contractor's Systems

The contractor used its standard tool setup with minor adjustments in order to handle data fields that were not normally used and meet the owner's rigorous demands.

The integration of tools and techniques into an eclectic methodology for project management works like this:

- Engineering is performed in Comos (using P&ID and some instrumentation information). Comos is also used for final data integration and data export to the owner's system.
- 3D designs are created using Aveva PDMS. Some data (e.g., physical location) is shared with Comos - *see Figure 1*.
- Document management is handled in Software Innovation's ProArc DM suite.
- Article database and integration is conducted in the internally developed package, DePlan.
- Purchasing and production planning is performed in the ERP system Lawson Movex.

All data is stored digitally. Each system is master of a certain type of data (e.g., Comos holds tag names, PDMS holds location data) and all systems communicate with each other. The combined data forms the Building Information Model (BIM). All the exported data is derived from the BIM. Essentially, the contractor has operated using the BIM concept for almost 10 years.

The Owner's Systems

The owner has developed a project database for use on all projects. Data Organization and Release Application (DORA) imports project data from multiple data sources, filters data to format requirements, displays data metric reports, and exports data to project and site users. Key features of DORA include:

- created in a software framework that can be installed on computers running Microsoft Windows operating systems
- programmed using a database computer language designed for managing data in relational database management systems
- uses Citrix which provides remote access software for delivering DORA over a network and the Internet

Gathering all project data into a single database provides data synchronization among multiple disciplines, minimizing the need for data remediation activities - *see Figure 2*.

As the owner does not use 3D design, the full BIM has not been sent to them.

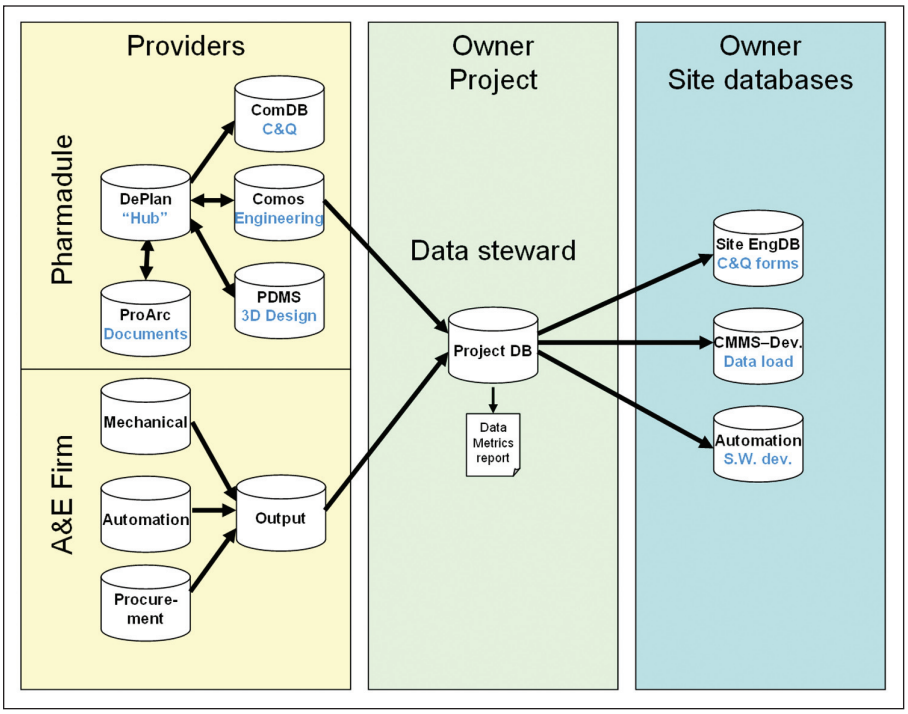

Figure 1. Project database architecture.

Project Implementation

Project Information Management Plan

The owner developed a project information management plan, which included quality planning, during the basic engineering phase of the project. This plan was circulated internally to project team and owner representatives, and externally to engineering firms and fabricators for feedback. Near the end of basic design the project information management plan was approved by the facility owner.

This plan detailed roles and responsibilities of data stewards, quality constraints, work process detailed descriptions, workflow diagrams, data requirements, and mandatory attachments. The contractor developed a similar plan that detailed the work process in the contractor's environment. Both of these plans were brought into alignment, referred to, and followed throughout the project.

Data Requirements

Establishment of data requirements should be the first step in the data collection process. This work should begin

In the Design Data for AHU example we see that design data contains all information that is generated by design disciplines during the development of project drawings and specifications. This data is typically 'mature' at the issue for construction milestone and collection of these data fields at that time should yield complete design from which procurement can begin.

Example DESIGN Data for AHU

Bldg	Tag Name	Item Type	Major Class	Minor Class	System Number	Drawing Number	Tag Service Description	Physical Location
101	AL-AHU4	INST	Life Safety	SS-Smoke Detector	123	101-M06-04-0001	AHU-4 FIRE ALARM	!###
101	CC-AHU4A	EQUP	HVAC	Cooling Coil	123	101-M06-04-0001	Cooling Coil in AHU-4	A-Rm 120, Lvl 2, Col 1F
101	FE-AHU4A	INST	Flow Element	FE-Dif Pressure	123	101-M06-04-0001	AHU-4 SUPPLY AIR	A-Rm 120, Lvl 2, Col 1F
101	FT-AHU4A	INST	Flowmeter	FT-Dif Pressure	123	101-M06-04-0001	AHU-4 SUPPLY AIR	A-Rm 120, Lvl 2, Col 1F
101	HF-AHU4A	EQUP	Filter - HVAC	HEPA Air Terminal	123	101-M06-04-0001	HEPA-flt in AHU-4 sys 123	A-Rm 120, Lvl 2, Col 1F
101	PT-AHU4A	INST	Pressure Transmitter	PT-Gauge No Seals	123	101-M06-04-0001	AHU-4 RETURN DUCT	A-Rm 120, Lvl 2, Col 1G
101	SF-AHU4A	EQUP	HVAC	Centrifugal HVAC Fan	123	101-M06-04-0001	Supply Fan AHU, sys 123	A-Rm 120, Lvl 2, Col 1F
101	TCV-AHU4A	INST	Valve - Mod Cntl	uCV-Globe Valve	123	101-M06-04-0001	PGR Temp Cntl CC-AHU4A	A-Rm 120, Lvl 2, Col 1G
101	TT-AHU4A	INST	Temp Transmitter	TT-RTD	123	101-M06-04-0001	AHU-4 SUPPLY DUCT	A-Rm 124, Lvl 2, Col 1F

In the procurement Data for AHU example we see the information specific to a particular tag. Manufacturer, Model number, and instrument ranges are documented during the procurement activity. We can see that a null character set is applied to several of the data fields, (!##). This character set indicates that this data field is intentionally left blank. A blank data field would indicate that data has not yet been provided.

Example PROCUREMENT Data for AHU

Bldg	Tag Name	Manufacturer Name	Mfg Model Number	Serial Number	Asset Tag	Set Point	Vendor Name	Eqpt Range From	Eqpt Range To	Eqpt UOM
101	AL-AHU4	!##	!##	N/A	N/A	!##	Contractor	!##	!##	!##
101	CC-AHU4A	TOUSSAINT NYSSENNE SA	BRCAG 810 T12 4 F30 E4	8/72189/8	M0011687	!##	Contractor	!##	!##	!##
101	FE-AHU4A	GEBHARDT VENTILATOREN	IMV 13	N/A	N/A	!##	Contractor	!##	!##	!##
101	FT-AHU4A	Furness controls	FCO332-A4-B1-C2,D1-E1	801086	I0011979	!##	Contractor	0	1000	PA
101	HF-AHU4A	CAMFILL FARR	Sofilair H13		M0011689	!##	Contractor	!##	!##	!##
101	PT-AHU4A	Furness controls	FCO332-A4-B1-C2,D1-E1	801082	I0011984	!##	Contractor	-500	0	PA
101	SF-AHU4A	GEBHARDT VENTILATOREN	RER 13-0315 LG/270/G	303136-694032	M0011695	!##	Contractor	!##	!##	!##
101	TCV-AHU4A	Kammer	0350P2	E5397.004	I0011987	!##	Contractor	!##	!##	!##
101	TT-AHU4A	INSTECO LTD	RT-M15-250-100-3-A-KN	1553002	I0011988	!##	Contractor	-5	45	C

Figure 2. Example design and procurement data for AHU.

early, during basic design, and approval targeted for detailed design start. Alignment of process, automation, verification, maintenance, and site engineering data requirements can be challenging so begin early. The data requirements should be part of the project quality plan or referenced by it.

- Document all data requirements by project and site data users prior to detailed design start. This should include data field names, format for data, and examples.
- Develop a data architecture drawing depicting data flows and systems used on the project.
- Map data fields from providers, to project, to owner systems so data destination and custody are clearly identified.
- Establish the approved data requirements with the design and procurement teams so data delivery requirements are included with all contracts and purchase orders issued on the project. As a line item deliverable, data becomes contractual, rather than implied.

Data Collection

Data collection on most projects is not a single event, but a process conducted over time as a design matures. System by system, design is completed and with system design completion, the design data for that system is mature. Several milestones may represent data maturity for any asset.

- Design data is mature at Issue for Construction (IFC), so this is the optimum time to capture that data and start its use by the project team. Prior to IFC, the design development may change. It is inefficient to develop commission documents with immature data that will require rework to make accurate.
- Procurement data is mature at PO release for most tagged instruments and some equipment. Skidded equipment containing multiple tags may not have tag level data available until pre Factory Acceptance Testing.
- Verification data is mature upon receipt of the tagged device. Serial numbers are typically captured at this time. Although physical location is included, it is generally not needed in order to purchase an item.

A new approach in this project was the owners time plan, because as a general rule data should not be turned over at the very end of the project, but during project execution. While this puts an extra strain on the contractor during the peak of engineering and design, there is a huge advantage for the owner. The advantage is that all resources are still in the projects so data that is not complete can more easily be corrected. If this can be properly planned, this will likely be an advantage for the contractor as well.

Data Metrics

Data metric generation and review are critical steps in the project data delivery exercise. Data metrics were viewed at three levels to provide a clear picture of project data delivery.

- *The first level is percent complete for the entire project.* If for example the estimated tag count for a project is 10,000, completing data population to the 50% level on 5000 tags will express a 25% complete data delivery. This high-level view of the data population is an indicator of data population initiation at less than 10%, indicating data delivery from providers and transfer routines are working. At the 50% complete level, design data is near completion and procurement has begun. Nearing the 100% level, procurement and receipt of assets is nearly complete, and construction is well under way.
- *The second level of data metric view looks at all tags within a system.* These system views provide commissioning and maintenance teams a view of complete data at a system level, and verifies that form generation at a system level is ready to begin.
- *The third level of metric view looks at individual tags.* This view is the most granular and enables the project data steward to identify gaps and address this with the providers. By sharing these views

"Through early detection and investigation of data integrity issues with the data providers, the cycle of data change management may be reduced saving project budget."

with data providers, those providers can see exactly what is missing and address issues by providing those data fields. Patterns also become apparent. Some vendors or data providers may be falling behind schedule and require more attention and support.

Data Integrity

Data integrity was defined in the project information management plan with data integrity checks executed early in the project data delivery cycle. Through early detection and investigation of data integrity issues with the data providers, the cycle of data change management may be reduced saving project budget.

Initial data format and integrity are applied at the time of data import by the owner data steward. Data fields with known values are populated into pick lists and new data imports are compared to these pick lists identifying incorrect building names, system identifications, component types, units of measure, and drawing numbers.

Additional data integrity checks are implemented after system data is complete and apply pattern recognition to the data field values and like tags within any dataset. Examples might include set point values populated where not applicable and missing from where required for temperature and pressure switches. Other examples include calibration values and units of measure that do not align with the tag name, and empty data fields indicating no data may require a null character to indicate intentionally blank as blank data fields indicate not yet populated.

Data integrity checks early in the project help the data providers understand the quality level that is expected throughout the project. Once understood by the providers, more care and data integrity diligence will be applied to avoid rework and added project costs.

Tag level data is collected to support commissioning and qualification protocol development, automation development and alignment with process, and maintenance package development during the project delivery. During the operations phase, tag level procurement data support the replacement of instruments and equipment upon failure.

Summary

Many factors contributed to the success of this collaborative project. The following are the main project lessons learned:

- early, clear data requirement definition
- open communication between all parties, including owner, designers, module providers, skid vendors, component vendors, and verification activities
- no requirements for using a specific tool
- importance of using data management tools to manage the large quantity of data for pharmaceutical projects
- commitment to data collection from both owner management and provider management, coupled with process execution diligence
- data transfer at midpoint of detail design to confirm systems and workflows
- weekly metric meetings with data providers during critical periods, weekly communication with providers and continuous project owner support
- early data integrity checks to establish expectations from providers and data users

These factors were key in this project's success in getting accurate data delivered on time for use by both the project team and the owner's operations. For all involved, this project has yielded a new way to approach these issues in future projects.

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4. *ISPE Good Practice Guide: Maintenance*, International Society for Pharmaceutical Engineering (ISPE), May 2009, www.ispe.org.

About the Authors

Robert Velén is Information Systems Manager at Pharmadule AB and was the Project IS Coordinator on the described project. He has responsibility for the IS Department that manages all systems, including CAD, CAE, ERP, etc. His work includes a lot of integration issues. Velén began at Pharmadule seven years ago and has worked at different capacities, mainly in the area of Engineering IT. In his role as Project IS Coordinator, his responsibilities have included coordinating IT related requirements for

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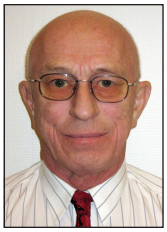

Rolf Strömgren, holds a BSc in chemistry and was the Project Information Management coordinator as well as the Project QA Manager at Pharmadule in the described project. He has some 30 years of experience in QA, QC, and Regulatory Affairs. Strömgren has held various management positions within the pharmaceutical and medical device industry, including three years of green field development in China with Total Parenteral Nutrition. He joined Pharmadule management 10 years ago and he has been actively involved in the development of the Quality and Validation Department, and more recently worked in facility projects as Project Manager or Project QA. He is currently working for Pharmadule on a contractual basis. He can be contacted by telephone: +46(0)705-475251 or by email: rolf.stromgren@gmail.com.

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Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2010, Vol. 30 No. 4
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Risk-MaPP Guide to Provide Scientific, Risk-based Approach to Managing Risk of Cross Contamination

Much-anticipated guide to be released third quarter 2010

As manufacturers are looking to reduce cost and increase efficiency, more multi-product facilities are being utilized either directly by the manufacturers or through partnerships with contract manufacturing organizations. With the use of multi-product facilities, the risk of cross contamination increases.

Recognizing the need for a consistent approach to managing the risk of cross contamination, industry leaders in quality systems, toxicology, manufacturing, process and containment engineering, industrial hygiene set out in close collaboration with regulators worldwide to develop an original, holistic approach to maintain the risk of cross contamination below acceptable limits. By properly managing the risk of cross contamination, manufacturers can reap the benefit of lower cost and higher efficiency while maintaining product quality and operator safety.

The result of this five-year effort is the much anticipated ISPE Baseline Guide® Risk-based Manufacture of Pharmaceutical Products (Risk-MaPP), expected to be available third quarter 2010. Risk-MaPP provides a scientific risk-based approach, based on ICH Q9, to manage the risk of cross contamination in order to achieve and maintain an appropriate balance between product quality and operator safety. This allows the selection of the appropriate risk control strategies to be implemented on a case-by-case basis to maintain operator safety and assure product quality.

ISPE has lined up many opportunities in the form of conferences, webinars, trainings, and additional documents, so that Members and the public can maximize their understanding of this topic and how to use the guide:

- A Live Webinar entitled "Risk-MaPP: What Is It and Why You Need It" will be held on 14 September as an introduction for professionals not yet familiar with, or who seek a better understanding of, the importance of Risk-MaPP. The webinar is a prerequisite to upcoming conference sessions, and should be attended by conference delegates. A recorded version of the webinar will also be available in late September.
- A series of conferences led by the guide authors, will focus on how to determine when multi-product facilities can be used, the use of the logic diagram, where to get health-based data for use in risk assessments, developing cleaning validation limits, case studies, and preparing a Quality Risk Management Plan for cross contamination. Attendees to select conference events will receive a complimentary copy of the guide as soon as it is available. Upcoming conference events featuring Risk-MaPP include:
  - ISPE Brussels Conference: 20-23 September 2010; Brussels, Belgium
  - ISPE Risk-MaPP Conference: 4-5 October 2010; Washington D.C., USA
  - Japan Conference: 21-22 October; Tokyo, Japan
  - Singapore Conference, 25-26 October; Singapore
  - ISPE 2010 Annual Meeting: 7-10 November, Orlando, FL, USA
- An intensive Risk-MaPP training course to be available second quarter 2011.
- An ISPE Risk-MaPP Knowledge Brief and the Risk-MaPP team white paper to the EMEA on the need for updated GMP guidance concerning dedicated facilities provide further information about the subject.

For more information on Risk-MaPP, visit www.ispe.org/Risk-MaPP.

New Knowledge Brief

Knowledge Briefs are concise, summary documents that provide general information on issues, processes, and technologies impacting the contemporary pharmaceutical industry. Although it may contain technical content, Knowledge Briefs are written in terms a non-technical reader can understand and are intended to help industry professionals get up-to-speed quickly on a particular topic. Each brief includes links to additional ISPE resources, such as technical documents, Pharmaceutical Engineering articles, webinars, Communities of Practice, and educational seminars and training courses to provide more specific and detailed information on the subject. Knowledge Briefs are available for immediate download. They are free to ISPE Members, $5 US / €3 to non-Members. The latest Knowledge Brief is:

Ozone Sanitized Pharmaceutical Water Systems: Tank Venting Concerns

by Joe Manfredi

Level: Intermediate

Over the past three decades, for the most part, the system designs and equipment involved in ozone sanitization have been refined and improved significantly so that current installations are both effective and reliable. Yet one specific area, ozone gas venting, has remained primarily unchanged and can still be somewhat problematic. This Knowledge Brief provides an overview of tank venting concerns and discusses design considerations addressing these concerns.

ISPE Brussels Conference to Focus on Risk-based Control Strategies in Pharmaceutical Industries

The ISPE Brussels Conference will take place 20-23 September 2010 at the Sheraton Hotel, Brussels, Belgium. The following is a summary of this year's conference program:

Monday 20 September - Tuesday 21 September

Conference Seminars:

Barrier Isolation Technology Forum: Innovation, Updates, New Case Studies

This seminar presents developing technology and regulatory perspectives for barrier isolation, especially in regard to advanced aseptic processing, Restricted Access Barrier Systems (RABS), and isolators. It will feature a variety of topics including robotics, E-beam sterilization of syringe tubs, measurement of hydrogen peroxide, biological sensitivity to hydrogen peroxide, clinical trial materials produced in an isolator, a biotech facility using isolators, and several contract manufacturing examples using these techniques. Content includes multiple case studies and interactive workshops on topics of global importance.

Dedicated Facilities, Cross Contamination, and the Risk-MaPP Approach

The much anticipated release of ISPE's new Risk-MaPP Baseline® Guide provides a scientific risk-based approach, based on ICH Q9, to manage the risk of cross contamination in order to achieve and maintain an appropriate balance between product quality and operator safety. A series of workshops and case studies led by the Guide authors will focus on use of the logic diagram, how health based limits are developed, setting cleaning validation limits, risk assessments for cross contamination and formulating a Quality Risk Management Plan as part of a Quality System.

GAMP®: Guided Tour of the World of Good Practice Guides

The seminar will focus on GAMP Good Practice. It will provide the delegates with an overview of the guides, together with case studies and workshops. The objective is to help the delegates to identify which particular good practice guide is relevant for their job.

PQLI®: Case Studies in QbD for Biotechnology and Small Molecule Product Realization

Is Quality by Design (QbD) applicable to biotechnology? Yes, and by participating in this two-day Product Quality Lifecycle Implementation® (PQLI®) workshop you will understand and discuss the A-Mab case study, which is the latest thinking in the application of QbD to biotechnology. To complement the biotech approach and for comparison, a second case study developed by a PQLI team (a core component of a forthcoming ISPE Good Practice Guide on Product Realization) will be presented that explains QbD principles for a small molecule drug substance and drug product.

Wednesday 22 September - Thursday 23 September

Conference Seminars:

Containment: The Devil is in the Detail

The devil is in the detail. There is no more appropriate expression in relation to containment. During this two-day seminar, a review of the critical points when planning a new containment facility or modernizing an already existing manufacturing plant will be conducted. Topics covered during the seminar will include: maintenance of containment transfer systems, containment process systems, waste handling, and cross contamination and cleaning. Interfaces to other systems, such as filters and quick couplings such as Tri Clamps round off the program.

The seminar also will include a workshop allowing participants to discuss various topics in small groups. This seminar will provide an overview of powder containment concepts as well as state of the art engineering solutions.

Investigational Products (IP): Lean and Compliant? Applying Efficient Tools to a Regulated Clinical Supply Chain

This seminar will help delegates understand and develop new, lean, and efficient ways along the supply chain for IMPs, while being compliant with clinical trials regulations globally. Using case studies and real examples, the focus will be on sharing experiences from the wide range of companies involved in all supply chain activities for investigational medicinal products.

Through a networking event, interactive workshops, and seminar presentations led by key opinion leaders within the industry, the seminar provides a valuable forum to challenge existing preconceptions, demonstrate usage of new tools and technology, explore alternative approaches and share "best practice" ideas.

Training Courses:

Sterile Drug Manufacturing Facilities: Applying ISPE Baseline® Guide and US FDA Guidance Principles to Design and Operation

This course references ISPE's Sterile Manufacturing Facilities Baseline® Guide and the US FDA's newly published Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. Using the referenced documents, this course will cover regulatory philosophy, aseptic process and equipment considerations, aseptic cleanroom design and operation, differential pressure requirements, airlocks, basic utility systems, European HVAC considerations, basic com-

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

ISPE Participants First to Hear Details of CDER Update on Part 11

Since August of 2003, the industry has had to understand how the US FDA intends to enforce 21 CFR Part 11 as per the Scope and Application Guidance and be in compliance. Therefore, the intention of CDER to take further action as part of the re-examination of Part 11 should not be a surprise, but it will be important to understand their approach.

Attendees of the Seminar E07 GAMP Good Practice Guide: A Risk-Based Approach to Operation of GxP Computerized Systems, 9-10 June 2010, at the ISPE Washington Conference, heard first-hand how the Agency will focus on Part 11 controls during some specific inspections. The presentation was given by George Smith, Project Manager Officer, CDER, US FDA and Sion Wyn, Consultant, Conformity, Ltd., member of core Part 11 team.

As the next step of their re-examination of Part 11, FDA CDER will define inspectional assignments against Part 11 requirements as described in the Part 11 Scope and Application guidance published in August of 2003. This effort will be part of CDER's effort to evaluate industry's compliance and understanding of Part 11 in light of Scope and Application guidance.

CDER intends to use the inspectional findings to help assess how to proceed with regard to the possible modification of Part 11 or other possible options in the re-examination of the regulation. CDER intends to take appropriate action to enforce Part 11 requirements for issues raised during the inspections.

In addition, ISPE held the Live Webinar, "FDA CDER Announces Part 11 Inspectional Assignments," 13 July. The Webinar, also presented by Smith and Wyn, provided the opportunity for participants to understand the very latest progress in FDA's examination of 21 CFR Part 11, prepare for the CDER inspectional assignments, and assess their own organization's level of compliance and readiness.

New on ISPE.org: Comprehensive GMP Resources

ISPE has launched a new section on the Web site called "GMP Resources." It is located on the far left hand column of the site, under the "Products and Services" section and under the "Resource Center" drop down menu. The section includes extensive information and resources on Good Manufacturing Practice (GMP), from the basics to comprehensive training.

Additional ISPE GMP Resources include links to GMP-related Pharmaceutical Engineering articles, books, manuals, Guidance Documents, Community of Practice, Knowledge Briefs, Mini Regulation Handbooks, online courses and Webinars, posters, and training courses and videos.

ISPE Brussels Conference...

Continued from page 2.

missioning and qualification issues, and a brief introduction to barrier isolation technology. In addition, the course will include an exercise in the layout of an aseptic filling facility.

Practical Application of Computerized Systems Compliance: Applying the GAMP® 5 Guide: A Risk-based Approach to Compliant GxP Computerized Systems

This highly interactive workshop gives participants hands-on experience in applying practical techniques and solutions to solve computerized systems compliance challenges. Participants will discuss and analyze case studies, apply newly acquired knowledge to hypothetical case-study systems, and have the opportunity to discuss their own real-life challenges with other participants and an expert trainer. Participants should come prepared to work in groups to devise workable and creative solutions to realistic problems and case study scenarios, facilitated by the instructor.

Complete conference information can be found at:
http://www.ispe.org/cs/2010_brussels_conference/conference_programme

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The Official Magazine of ISPE
July/August 2010, Vol. 30 No. 4
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July/August 2010, Vol. 30 No. 4

Europe

Denmark

Danish Medicines Agency Publishes Report on Compliance with Rules on Good Manufacturing Practice by Manufacturers of Active Pharmaceutical Ingredients[1]

In 2009, the Danish Medicines Agency conducted a survey to examine the extent to which manufacturers of medicinal products comply with their obligation to ensure that the active pharmaceutical ingredients used as raw materials in the manufacture of medicinal products and intermediate products are manufactured in accordance with good manufacturing practice for active pharmaceutical ingredients. As part of the survey, the Agency has carried out inspections at companies in both Denmark and abroad and also has requested that a number of companies submit samples of medicinal products and samples of active pharmaceutical ingredients as well as relevant written documentation for further control.

The survey confirmed the Agency's presumption that Danish manufacturers of medicinal products, by carrying out regular audits of manufacturers of active pharmaceutical ingredients to a wide extent meet the requirement of ensuring that the active pharmaceutical ingredients in question are manufactured in accordance with good manufacturing practice. The survey also identified a number of areas in which the Danish Medicines Agency and the industry can improve the existing control of manufacturers of active pharmaceutical ingredients in the future.

Based on the survey, the Agency will launch additional initiatives and projects to ensure more targeted guidance and control within the area of active pharmaceutical ingredients.

European Union

European Ombudsman Recommends European Medicines Agency Increase Transparency[2]

The European Ombudsman, P. Nikiforos Diamandouros, has asked the European Medicines Agency to reconsider its refusal to give access to documents related to a drug used to treat severe forms of acne. The complainant, an Irish citizen, specifically asked for reports on suspected adverse reactions to the drug, such as reactions giving rise to suicidal tendencies. EMEA refused access, arguing that EU transparency rules do not apply to adverse reaction reports. The Ombudsman did not agree. In his view, the EU transparency rules apply to all documents held by EMEA.

Ten Years of Orphan Medicines Legislation in Europe – European Medicines Agency Reviews Success and Looks Ahead[3]

On 3 and 4 May 2010, the European Medicines Agency held a two day conference to mark the 10th anniversary of the Orphan Regulation in the European Union. The Agency brought together representatives from the European Parliament, the European Commission, international and European regulatory agencies, members of the Committee for Orphan Medicinal Products (COMP), patient groups, health professionals, and the pharmaceutical industry to review the impact of 10 years of orphan medicines legislation and to look ahead at future opportunities and challenges.

Ten years since the orphan legislation came into force in April 2000, the Agency has received more than 1100 applications. Out of these, 720 orphan designations have been granted to date, a success rate of 65%. A total of 62 orphan designated medicines have now been approved for use in the EU, giving treatment options for 53 different rare diseases.

The continued interest in the orphan designation process shown by the pharmaceutical industry indicates that orphan-designated medicines will keep coming to the market at a steady rate offering new treatment options for patients with rare diseases. Over the next few years, the period of market exclusivity (10 years) will expire for the first authorized orphan medicines, opening up the market for older orphan-designated medicines for competition, while new orphan medicines continue to be protected by market exclusivity. The Agency expects that an increasing number of new marketing authorization applications will relate to complex, innovative medicines, such as advanced therapies medicinal products (gene therapy, somatic cell therapy, or tissue engineered products). With the combined expertise of the COMP, CAT, and the Committee for Medicinal Products for Human Use (CHMP) as well as a network of experts from across the EU, the Agency is in a good position to tackle the challenges coming from new scientific developments.

Finland

Fimea will Accept Marketing Authorization Material in E-Format as of 1 June 2010[4]

Fimea has begun accepting marketing authorization material in e-format. The initial-stage solution will facilitate marketing authorization for the pharmaceutical industry. Marketing authorization applicants started to submit their applications to Fimea in electronic eCTD or NeeS format as of 1 June 2010 in such a way that modules 1–3 are also delivered, on account of national archiving requirements, still in hard copy format. During the transition period in the rest of 2010, Fimea will accept marketing authorization applications both in electronic and hard copy format. As of the beginning of 2011, applications will be accepted only in e-format. Even then, it will be necessary to provide the above-mentioned modules 1–3 in hard copy in addition to e-format.

The receipt of e-submissions is part of the re-launched Säihke project aimed at e-enabling all of Fimea's core processes. The project will progress in stages until summer 2013. It will be possible to process marketing authorization applications entirely in e-format by the end of 2012. Fimea published on its Web site more detailed instructions for marketing authorization holders during May, when more experience from pilot testing the reception system will have been obtained. Marketing authorization holders are encouraged to send application documents in e-format to Fimea for pilot testing.

Germany

eSubmission[5]

From 31 March 2010 onward, the Federal Institute for Drugs and Medical Devices will accept nearly paperless electronic-only submissions for new applications for authorization or registration of medicinal product as well as for post authorization procedures (e.g. variations, renewals, PSURs) of those medicinal products which have already been submitted under this new rules after 31 March 2010.

Asia/Pacific

China

Provisions for Pharmaceutical Precursor Chemicals issued[6]

For the purpose of further strengthening the supervision of pharmaceutical precursor chemicals, regulating the production and supply order, and preventing them from flowing into illegal channels, the Provisions for Pharmaceutical Precursor Chemicals, drafted by the State Food and Drug Administration, and issued by the Ministry of Health on 18 March 2010, came into force on 1 May 2010.

Provisions for Pharmaceutical Precursor Chemicals comprises eight chapters and 50 articles, specifying the limits, conditions, procedures, data requirements, and approval time limit for the production, distribution, and purchase licensing of pharmaceutical precursor chemicals; the channels for the purchase and distribution of raw materials and prescribed preparations of pharmaceutical precursor chemicals, and small package ephedrine. The Provisions also regulate the system and condition requirement for the safety management of manufacturers, distributers, and the use of pharmaceutical precursor chemicals, and the supervision of the food and drug regulatory departments.

Japan

Ministry of Health, Labour and Welfare and PMDA Concluded Confidentiality Arrangement with the Health Sciences Authority of Republic of Singapore[7]

The participants intend to cooperate through exchanging more regulatory information including advanced drafts of legislation and/or regulatory guidance documents as well as information related to authorization and supervision of medical products for human use in accordance with their respective national laws and regulations. Since this type of information may include information of a non-public nature, participants have agreed to keep the information exchanged confidential.

This cooperation is intended to advance and improve policy and operational regulatory issues from pre-market to post-market stages in the lifecycle of medicines, medical devices, and cosmetics, enable the participants to acquire reciprocal knowledge and understanding of each other's regulatory requirements and processes, and to ensure the quality, safety, and efficacy of medicines, medical devices, and cosmetics marketed in each country.

North/South America

Canada

Health Canada Publishes Information on How to Stay Connected on Social Media[8]

Health Canada uses a variety of social media tools to share its content and provide access to reliable and timely health information. Information on how to follow Health Canada using an RSS feed, social bookmarking, Twitter, widgets, and YouTube can be found at http://www.hc-sc.gc.ca/home-accueil/sm-ms/index-eng.php.

USA

US FDA Launches FDA-TRACK to Make Information about the Work of FDA's Program Offices Available[9]

FDA-TRACK is a new agency-wide program performance management system that monitors more than 100 FDA program offices through key performance measures. These measures are developed by the program offices across the FDA and reported on a monthly basis. Each quarter, monthly performance data is analyzed and senior managers present this data to FDA senior leadership. The FDA-TRACK Web site enables all interested external and internal visitors to view FDA's performance data at the program office level and gain a better understanding of the breadth of FDA's core responsibilities, as well as see progress on important projects and programs.

US FDA Unveils Draft Proposals on Agency Disclosure Policies for Public Comment[10]

FDA's Transparency Task Force released 21 draft proposals about FDA's disclosure policies. FDA is asking for comments on the proposals for 60 days. After 60 days, FDA will use the input to recommend specific proposals to FDA Commissioner Dr. Margaret Hamburg for implementation. FDA will not necessarily implement each of these ideas. Some of the proposals require extensive resources to implement and some may require changes to regulations or legislation.

USP

New USP Standards for Botanical Ingredients to Help Ensure their Quality for Manufacturers and Consumers[11]

New standards that will help ensure the quality of 11 botanical ingredients used in dietary supplements in the United States and corresponding to traditional medicines in India are being proposed by the US Pharmacopeial Convention (USP). The standards were created within the context of a Memorandum of Understanding (MOU) between USP and the Indian Pharmacopoeia Commission (IPC) in which the two organizations pledged support of cooperative activities, including development of science-based standards of mutual interest. USP is seeking comments from manufacturers and others on the proposed new standards for identity as well as the strength, quality, and purity of these botanical ingredients.

International

PIC/S

Quality Risk Management: Implementation of ICH Q9 in the Pharmaceutical Field – an Example of Methodology from PIC/S[12]

A small, informal Working Group within PIC/S has started to develop

an objective and pragmatic example of methodology of implementation of ICH Q9, directly usable by the widest audience. It is also able to meet the demands of both operators and inspectors and to comply with all regulatory requirements. This example of methodology is not intended to be issued later by PIC/S as a recommendation or as a guideline for industry and/or for GMP inspectors, but it could be used by PIC/S for training purposes.

ICH

ICH Guidance for Industry: Q8, Q9, and Q10 Questions and Answers[13]

Since the Q8, Q9, and Q10 guidances were made final, experiences implementing the guidances in the ICH regions have given rise to requests for clarification. This Question and Answer (Q&A) document is intended to clarify key issues. The guidance reflects the current working procedure of the ICH Quality Implementation Working Group (Q-IWG) for implementing the Q8, Q9, and Q10 guidances.

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