This article discusses the methods and tools employed using Six Sigma to optimize a bulk biopharmaceutical process, providing an increase in overall plant capacity using a structured process improvement approach.

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Applying Six Sigma Principles to a Bulk and Fill/Finish Biopharmaceutical Process

by Bikash Chatterjee, Benir Ruano, and Kenneth Myers

Introduction

Increasing demands by Wall Street to demonstrate continued growth and profitability, along with public pressure to control the rising cost of therapeutics, have driven the pharmaceutical manufacturing industry to take a closer look at optimizing their organizations. Coupled with the escalating cost of manufacturing facilities and process equipment, the biopharmaceutical industry is being pushed to look for innovative ways to increase plant capacity and improve production efficiencies in an effort to delay or avoid the capital investment required to build new or expand existing facilities.

While there is no magic bullet that can transform an organization's effectiveness overnight, there are a number of methods and tools that have been developed that can improve organizational performance. The effective application of these improvement tools and methodologies derived from multiple principles allow organizations to develop successful strategies for business improvement. This article illustrates the application of the Six Sigma[12] methodology in the improvement of a hypothetical biopharmaceutical manufacturing process. The methodologies employed and challenges encountered are based upon actual Six Sigma deployment initiatives.

Business Problem

The business unit had identified a number of improvement opportunities in its manufacturing process at one of its biopharmaceutical bulk and fill/finish manufacturing plants. Poor pro-

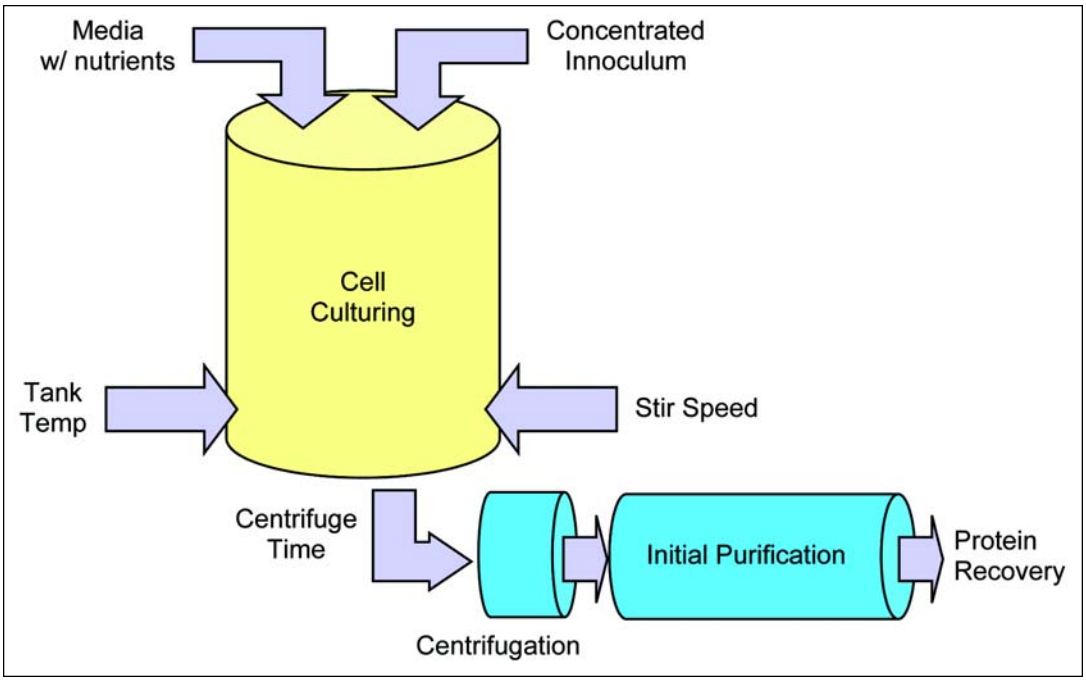

Figure 1. Cell culture and centrifugation process flow.

tein recovery per batch was creating a growing economic loss on a per batch basis. This loss, in turn, caused poor business practices that produced an increasing erosion of plant capacity, resulting in missed shipments and lost revenue to the business unit. The planned addition of a new product introduction in a year coupled with the current process inefficiencies was creating a projected plant capacity shortfall for the coming year. Faced with this shortfall, there were only two alternatives to finding additional capacity: build or optimize the process. Expanding existing facilities could create additional plant capacity, but the time required to expand and qualify the additional capacity would be greater than the forecasted demand time. The decision was made to deploy a team to identify areas to improve within the current operation that could provide the additional throughput needed to meet the forecasted shortfall.

Plant Process Flow

The business unit manufactured a parenteral product. The process flow for manufacturing the product consisted of cell culture production, purification, a fill/finish operation, packaging, and a labeling operation. The focus of the initial improvement effort was in the cell culture scale-up portion of the process specifically the cell culturing and centrifugation steps. A process schematic is shown in Figure 1.

Improvement Team

The business unit had an established improvement program that was responsible for deploying Six Sigma principles throughout the company. The challenge within the organization was identifying and obtaining the needed resources from key areas in the company in order to implement the magnitude of change necessary to meet the capacity shortfall.

A project team was established that consisted of experts from across the business unit. The first task for the team was to identify the Burning Platform. This is a term used to define the business driver for the improvement effort. As we described earlier, the plant was suffering from a capacity shortfall. The team met and identified the following opportunities:

1. At the current manufacturing rate, the poor protein recovery per batch was costing the company approximately $1 million annually in lost product sales.

2. The estimated cost to the business unit, due to the low recovery rate, was approximately 12% of the standing Work-In-Process (WIP) cost and lost revenue due to missed shipments.

3. The instantaneous WIP on the floor was estimated at $3 million.

The team determined that each 2% increase in protein recovery per batch would equate to about a $100,000 reduction in instantaneous WIP across the facility. Additionally, each 2% increase in protein recovery would provide an additional $75,000 in annual revenue to the business. The team decided

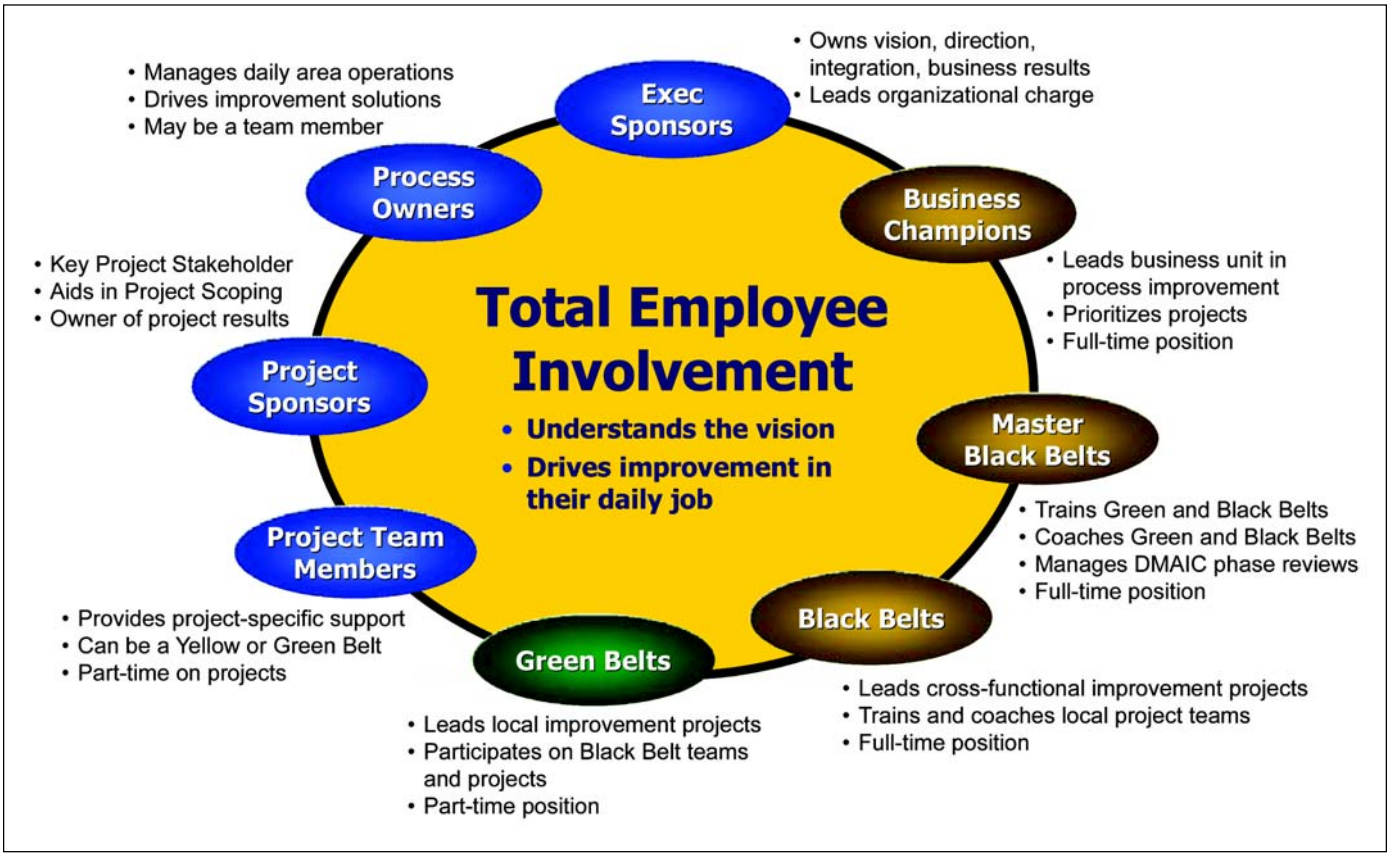

Figure 2. Developing a process focus toward business improvement.

to focus on the protein recovery process first as a means of increasing the effective plant capacity.

Six Sigma Roadmap

The Six Sigma roadmap provides a methodology for improving business processes, increasing customer satisfaction, and elevating the business competitive standing. It establishes guidelines for creating the right organizational support structure to enable business improvement using structured project prioritization as a backbone, and a fact-based, data driven process for making sound business decisions. The first step in the Six Sigma roadmap involves creating the right organizational support structure. Key to this structure is the selection of both dedicated and part-time resources to support the improvement effort. If the proper resources cannot be allocated, it is doubtful that the Six Sigma initiative will yield the desired level of success. The roles and responsibilities of each individual in a Six Sigma deployment effort are shown in Figure 2.

Managing Improvement Projects

The Six Sigma roadmap uses a five-phase project management process to drive improvement: Define, Measure, Analyze, Improve, and Control (DMAIC). Each phase in the DMAIC process is intended to guide the members of an improvement team through the project in a way that provides the right data and best process understanding. The DMAIC project management approach allows the business to make the best possible decisions with the available data and resources. The concept behind the DMAIC process follows:

1. **Define:** Clearly define the problem and relate it to the customers' needs.
2. **Measure:** Measure what is key to the customer and know that the measure is good.
3. **Analyze:** Search for the root causes and identify the most likely causes.
4. **Improve:** Determine the root causes and establish methods to control them.
5. **Control:** Monitor and make sure the problem does not come back.

Within each of the DMAIC phases there is a set of deliverables that must be completed to ensure all project requirements are met. A summary of the deliverables and typical activities for each phase of the DMAIC process is shown in Table A.

Returning to our earlier problem, the team convened to describe the business problem using the criteria above.

Define

In the Define phase, the process improvement team is tasked with completing three deliverables: 1) identify the customer and their Critical to Quality concerns (called CTQs), 2) develop a project charter which identifies the members of the team and scope of the improvement project, and 3) create a high level process map. The process map is used to identify the Process Input Variables and the Process Output Variables the team will focus on to drive improvement. The input variables for the cell culturing process identified by the improvement team were as follows:

1. Media Nutrients
2. Innoculum Concentration
3. Tank Stir Speed
4. Tank Temperature
5. Centrifugation Time

In addition to average protein recovery rate (Y_1), the team decided to improve the between batch recovery variation (Y_2) to ensure future process consistency. In Six Sigma improvement, it is not only important to focus on mean process performance, but also to focus on process variation. In fact, companies like GE, Allied Signal, and Dupont have achieved their greatest improvement results by reducing variation in all processes across the value chain. The observed protein recovery process had an initial recovery yield of 60 mg/l with a between batch variation of greater than 50 mg/l. Working with management, the improvement goal for this project was

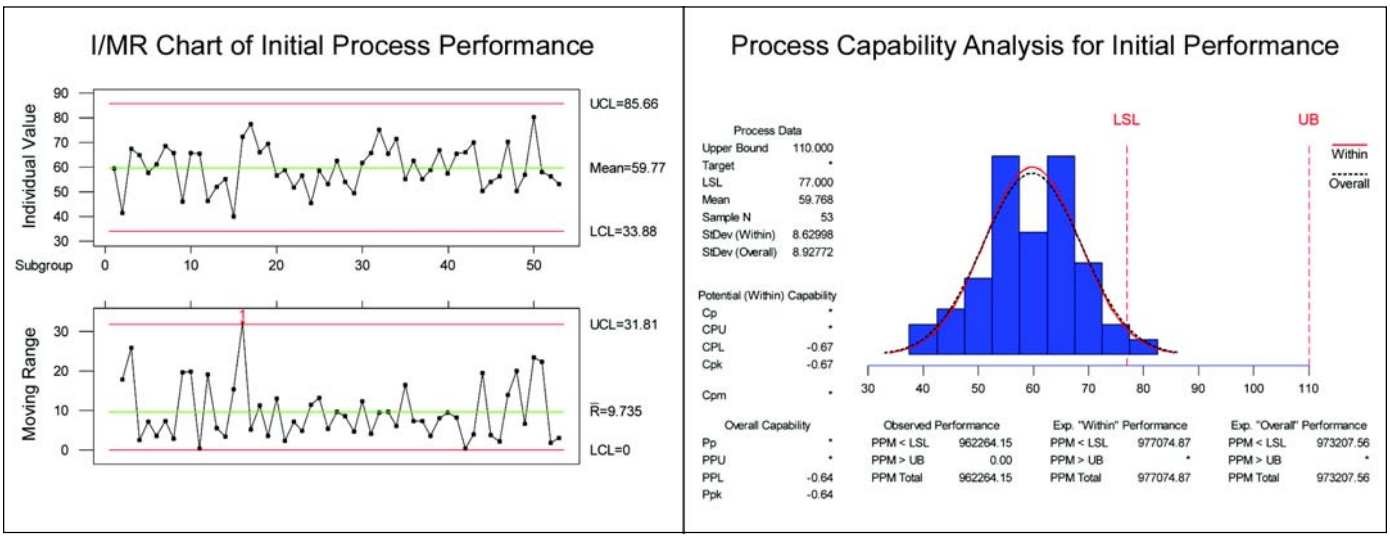

Figure 3. Initial protein recovery I-MR and process capability analysis.

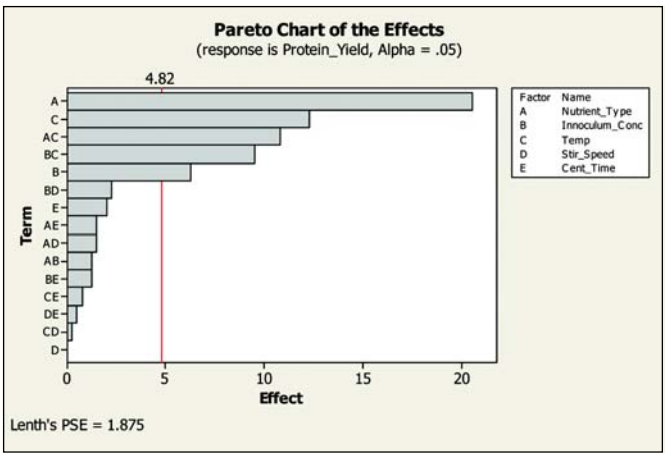

Figure 4. Pareto chart of effects for protein recovery.

set at 77 mg/l, which represented 70% of the expected theoretical yield for this unit operation. The target for between batch performance variation was set at 25 mg/l, providing a 50% reduction in process variation. Many times in the early development of a Six Sigma DMAIC project, the improvement team will move back and forth between the Define and Measure phases as they better understand the process, the customer needs, and the business requirements. Oftentimes, it is difficult to separate the exact deliverables for each of these two steps at the beginning of the improvement project. During project commissioning, if either the Green or Black Belts have difficulties understanding the specific requirements for each phase of the project, they obtain guidance from a technical support specialist called the Master Black Belt (MBB). The MBB is a resource who provides guidance in DMAIC project management, coaching and mentoring in tool selection, and training on the specific application of Six Sigma methods. Today, most world-class organizations provide an MBB for every 20 to 30 company improvement associates to ensure success in the Six Sigma deployment effort.

Measure

In the Measure phase, the process improvement team is tasked with completing four deliverables: 1) determine the key process measure(s) that are used to assess improvement, 2) define the performance standards or requirements based on customer needs, 3) verify that the measurement system can adequately measure the process, and 4) establish a baseline level of process performance. As indicated in the Define phase, the team decided to focus on process yield and use protein recovery as the key process measure. The performance standard was defined in two parts by the management team as greater than 77 mg/l protein recovery, and a between batch variation reduction of 50% below the baseline variation of 50 mg/l. Prior to measuring the process, the team verified the assay method used to measure protein recovery provided both accurate and reproducible results, and could adequately measure the process variation. To ensure the team had an adequate understanding of the process, they conducted a cause and effect analysis to identify all the likely causes of low process yield and high process variation. Next, the team created a detailed process map showing all steps in the process flow. Using the detailed process map and the results from the cause and effect analysis, the team then conducted a process risk assessment using a tool called Failure Modes and Effects Analysis (FMEA). The FMEA is useful in focusing the team into areas of the process where high business risk could exist. Identifying these areas would allow the improvement team to provide some quick improvements in the early phases of the effort using such methods as Mistake or Error Proofing.

Next, the team used a process control chart to assess process stability. They determined that the protein recovery process was stable, but displayed a large amount of between batch variation. Following the stability assessment, the team compared the present process performance to the new requirements, ≥77 mg/l of protein recovered per batch. This comparison of process variation to requirements is called a Capability Study. They found the present protein recovery process was able to meet the 77 mg/l requirement less than 5% of the time - *Figure 3*.

Analyze

In the Analyze phase the team was tasked with completing three deliverables: 1) developing a list of likely problem causes, 2) screening out the unlikely causes to produce a list of the key causes, and 3) establishing an initial improvement plan. As a part of the Measure phase, the team had already identified some likely causes using a Cause and Effect analysis. In the Analyze phase, the team developed a series of experiments to be conducted within the standard operating region of the process. These longer-termed designed experiments allowed the team to observe changes in the process during the actual production operation to identify the key inputs, while minimizing both yield and regulatory risk. The use of Design of Experiments (DOEs) to acquire process understanding is common in industry today, and is a central step in making fact-based process decisions. The approach used by the improvement team was novel, because most DOEs in the chemical and pharmaceutical industries are done in smaller pilot operations. While this is common practice in the pharmaceutical industry, it requires that the model used at the pilot level correlate to the manufacturing process. The challenge in achieving an effective characterization of the process in piloting operations is due to the disparity between the pilot results and the actual production operating parameters. This disparity is often the result of scale-up effects. Performing controlled experiments within a production environment is not a new practice. In 1957, Dr. G.E.P. Box developed a similar approach of performing small process experiments within the production framework called Evolutionary Operation (EVOP).[10, 11] The approach used by the improvement team extended the work of Dr. Box and others using factorial designs in place of the classical EVOP test approach. The improvement strategy employed by the team centered around achieving the protein recovery goal of 77 mg/L, which was set earlier in the Measure phase by the

Define

DELIVERABLES	ACTIVITIES/TOOLS
• Identify the Customer(s) • The Problem Statement • Develop list of Critical To Quality (CTQ's) from Customer Expectations • Select the team • Identify the Process(es) to Improve • Create a High-level Process map (SIPOC) • Scope and Charter Project	• Supplier-Input-Process-Output-Customer Requirements (SIPOC) Process Map • Bar Chart • Gap Analysis • Quality Function Deployment • Cost of Poor Quality (COPQ) Analysis • Cause and Effect Matrix • Stakeholder Analysis • Pareto Chart • Project Charter Form • Gantt Chart

Measure

DELIVERABLES	ACTIVITIES/TOOLS
• More Detailed Map of "As-Is" Process • Determine Project "Y" • Determine Requirements for Project "Y" • Verify Integrity of Measurement System • Data Collection Plan • Capability of "As-Is" Process	• Swim-Lane Diagram • Value Stream Mapping • Pareto Charts • Fishbone Diagram • Force Field Analysis • Check Sheets • Concentration Diagrams • Process Cycle Efficiency • Failure Mode and Effects Analysis (FMEA) • Measurement System Analysis/Gage R&R • Process Control Charts • Capability Studies

Analyze

DELIVERABLES	ACTIVITIES/TOOLS
• More Detailed Map of "As-Is" Process • Determine Project "Y" • Determine Requirements for Project "Y" • Verify Integrity of Measurement System • Data Collection Plan • Capability of "As-Is" Process	• Swim-Lane Diagram • Pareto Charts • Fishbone Diagram • Check Sheets • Concentration Diagrams • Process Cycle Efficiency • FMEA • Measurement System Analysis/Gage R&R • Process Control Charts • Capability Studies

Improve

DELIVERABLES	ACTIVITIES/TOOLS
• Determine Relationship between Key X's and Project Y • Develop Potential Solutions • Select the Best Solution • Optimize the Solution • Pilot the Solution • Establish Operating Tolerances	• Process Flowcharting • Response Surface Methods • Monte-Carlo Simulation • Value Stream Mapping • Solution Selection Matrix • Mistake Proofing • Pull Methodology • Setup Reduction • Total Production Maintenance (TPM)/5S • FMEA • Line Balancing • Process Tolerancing

Control

DELIVERABLES	ACTIVITIES/TOOLS
• Documented Process Changes and Controls • Process Control Plan • Training Plan for New Process • New Process Metrics • Expected Financial Benefits • Approve Improvement Commissioning Plan • Replication Opportunities	• Risk Assessment of Changes -- FMEA • Control/Action Plan • Standard Operating Procedures • Project Commissioning Plan • Process Validation • Process Control Charts • Capability Studies • Visual Controls • Preventative Maintenance

Table A. Summary of DMAIC phase deliverables.

Estimated Effects and Coefficients for Protein_ (coded units)						
Term	**Effect**	**Coef**	**SE Coef**	**T**	**P**	
Constant		65.250	0.6626	98.47	0.000	
Nutrient	20.500	10.250	0.6626	15.47	0.000	
Innoculum	-6.250	-3.125	0.6626	-4.72	0.001	
Temp	12.250	6.125	0.6626	9.24	0.000	
Nutrient*Temp	10.750	5.375	0.6626	8.11	0.000	
Innoculum*Temp	-9.500	-4.750	0.6626	-7.17	0.000	
Analysis of Variance for Protein_ (coded units)						
Source	**DF**	**Seq SS**	**Adj SS**	**Adj MS**	**F**	**P**
Main Effects	3	2437.50	2437.50	812.500	115.66	0.000
2-Way Interactions	2	823.25	823.25	411.625	58.59	0.000
Residual Error	10	70.25	70.25	7.025		
Lack of Fit	2	7.25	7.25	3.625	0.46	0.647
Pure Error	8	63.00	63.00	7.875		
Total	15	3331.00				

Table B. ANOVA analysis of protein recovery DOE.

Project Sponsor. If the team could achieve this goal using the experimental results, then there would be no need for additional experimentation during the Improve phase. However, if the team could not achieve the recovery goal with the results from the Analyze phase, then it would attempt to improve protein recovery using sequential optimization experiments during the Improve phase. The challenge in any improvement effort is balancing the need to achieve an optimal process within the business realities of cost and time. The DMAIC approach to process improvement provides guidelines for success that are coupled with the business goals. Using the business goals, improvement teams across the business work to ensure the right level of effort is used. In the Analyze phase, the primary goal in process characterization is to identify which variables influence the process. For this project, a fractional factorial design was used instead of a full factorial, because it required half as many lots (16 vs. 32) while providing the required experimental efficiency. Running experimental trials within the production scheme took 18 weeks to complete. All data were analyzed using a standard statistical software package. Figure 4 provides a quick view of the experimental results using a simple Pareto chart of effects. This chart compares the effect of each process factor or input and their corresponding interactions to a level of significance of 5%. The level of significance, alpha, is the risk of incorrectly identifying an input as being key in the process.

Figure 4 reveals that Tank Stir Speed and Centrifugation Time are not significant players in this process. It also reveals that the Nutrient Type, Innoculum Concentration, and Temperature linear effects are significant as are the interaction effects between Nutrient Type and Temperature, and Innoculum type and Temperature. Additional insight is obtained from the Analysis of Variance (ANOVA) table in Table B. In ANOVA, one uses a statistical approach to compare the means of grouped data. The ANOVA table allows us to statistically assess the significance of each input and their interactions by comparing the p-value in the right column of the table to the desired alpha level of 5%. A factor is considered statistically significant if its p-value is less than the alpha level of 5%. The ANOVA results shown in Table B confirm our understanding from the Pareto chart shown previously in Figure 4.

The analysis indicates the key variables for the Cell Culturing process are Nutrient Media Type, Innoculum Concentration, and Tank Temperature.

The team used the results of this phase to establish the best settings for the process. Using the results from the DOEs in the Analyze phase, the team prepared a plan for process improvement to be implemented in the next phase of the project.

Estimated Coefficients for Protein using Data in Uncoded Units	
Term	**Coef**
Constant	-98.5625
Nutrient	-35.4375
Innoculum	2.48333
Temp	5.09375
Nutrient*Temp	1.34375
Innoculu*Temp	-0.0791667

Table C. Coefficients of the predictive equation for cell culturing process.

Improve

In the Improvement phase, the improvement team is tasked with completing two key deliverables: 1) determine the relationship between the key inputs and outputs of the process, and 2) establish the best settings for the inputs to achieve the requirements set in the Measure phase. To improve the process, the team needed a predictive model that provided a relationship between the key inputs and outputs. In the

Improve phase, the team used the experimental data obtained in the Analyze phase to develop a low level predictive model of the process. The terms of this predictive model are shown in Table C.

The coefficients in Table C were used to develop the following predictive equation:

Protein Recovery = -98.56 - 35.44 (Nutrient)
+ 2.48 (Innoculum) + 5.09 (Temp)
+ 1.34 (Nutrient × Temp)
- 0.08 (Innoculum × Temp)

The predictive equation obtained from the earlier fractional factorial experiment provides, at best, an imperfect view of the process. Model development using screening data is often considered similar to reading your future using a crystal ball. However, given the methods used to obtain these experimental data are sound, we can gain some limited yet useful insight into process understanding from these data. In order to find the best process settings, the contribution of each input variable was initially evaluated using what are called Main Effects and Interaction plots. To simplify the presentation of the experimental results, the team presented the Cube Plot shown in Figure 5 to the management team and asked management to assist them in finding the best settings. Based on these analyses, the best conditions were identified for the critical variables - Nutrient, Innoculum Concentration, Tank Temperature; and set points were identified for the non-significant variables - Tank Stir Speed and Centrifugation Time. The best settings for achieving protein recovery are shown in Figure 5.

Figure 5 shows that the highest recovery yield can be achieved using Nutrient Type B, a low Innoculum Concentration, and operated at a high Tank Temperature. The expected yield for these new settings is 94 mg/L, which is equivalent to an expected recovery of 85% of theoretical. Therefore, we might expect to see an improvement of more than 30% using the new process settings. The team used the results of this analysis to run three confirmation batches. The protein

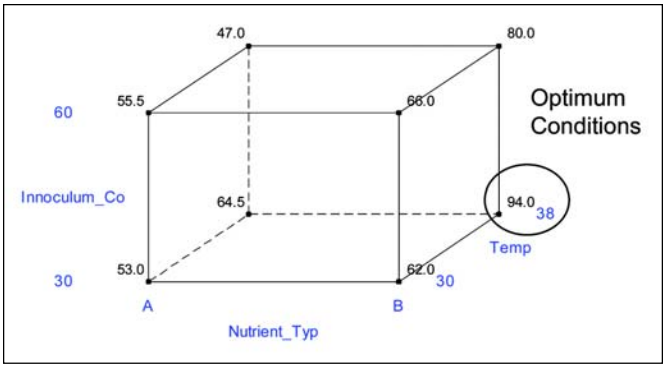

Figure 5. Cube plot for protein recovery.

recovery for all three runs exceeded 80 mg/L.

At this point in the project, the team had a couple of options available to them: 1) the team could elect to continue with sequential experimentation to develop a better predictive model and possibly improve the protein recovery over the new level observed, 2) the team could elect to remain in the Improve phase and conduct a few more runs with the best settings to better confirm their initial observations, or 3) the team could elect to move into the Control phase and establish a process monitoring plan to observe the level of improvement over a longer period. For this project, the team elected to move into the Control phase, because the results were far better than they had expected, ≥80 mg/l observed compared to a 77 mg/l project goal.

Control

Using the new process settings, a process capability study was conducted after processing 20 lots to determine the performance of the improved process. The new process was found to operate in a stable mode with an average protein recovery of greater than 85 mg/l. If you remember, the baseline process had a mean protein recovery of 60 mg/l, which was outside the desired management goal of 77 mg/l. The original process performance resulted in a process capability of zero (0) sigma. After the Six Sigma improvement effort, the resulting protein recovery exceeded the target

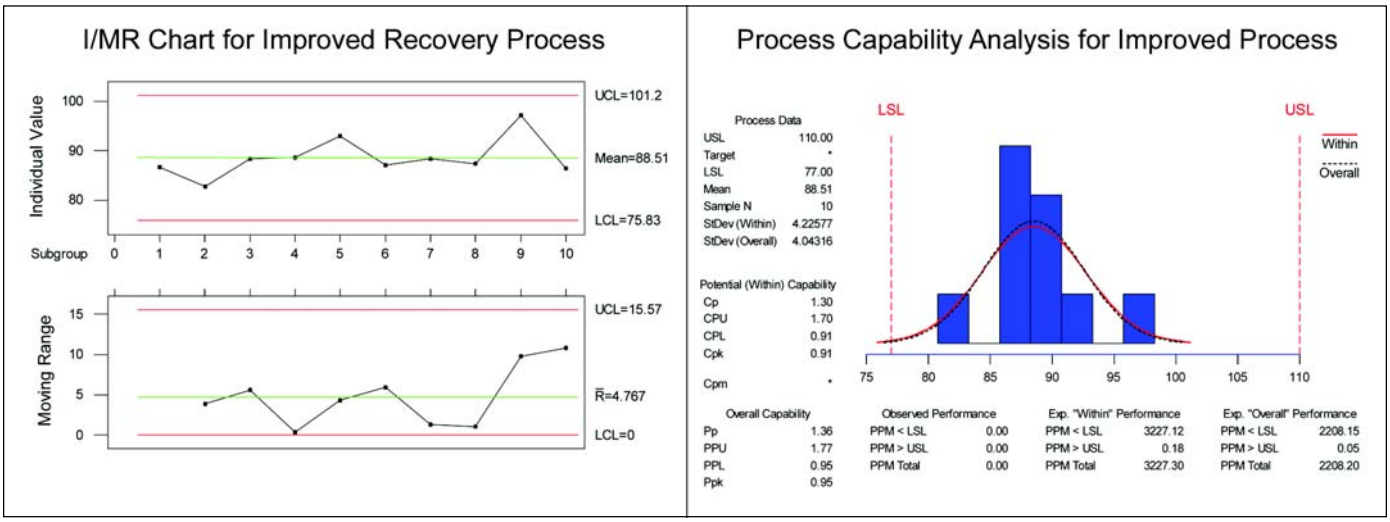

Figure 6. Final protein recovery I-MR and process capability analysis.

recovery rate allowing greater than 90% of the batches produced to meet the new requirements. In addition to mean performance improvement, the team found that between batch variability was reduced by more than 50%. This total improvement translated into an overall process capability of 4.2 sigma, a 97% level of improvment. The results are shown in Figure 6.

The team completed the Control phase by updating all required process control documentation, and putting in place a process monitoring scheme that ensured the process would remain on target and operating at the lowest between batch variation.

Conclusion

The application the Six Sigma methodology for optimizing processes is highly effective, particularly in its ability to focus an organization on a clear business need and define a tactical path toward resolution. By organizing a multidisciplinary team whose members are schooled in the elements of Six Sigma, the greatest results can be obtained in the shortest possible time. The application of Six Sigma methodology in a coordinated effort allowed the team to characterize, stabilize, and improve the process. Ultimately, the entire effort, which took less than six months to implement allowed the company to realize a 40% increase in available capacity without making significant capital investments.

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This article provides a definition of Advanced Process Control (APC), a viable implementation technique, introduction to associated tools, and statement with regard to sources of expertise.

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Advanced Process Control Simplified

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Introduction

Since the introduction of practical pneumatic control early in the 20th century, followed by digital control some time later, conventional Proportional Integral Derivative (PID) control had considerable benefits over the manual alternatives, thereby leading to significant increases in manufacturing productivity. Key benefits include reduced direct manpower requirements, increased equipment utilization, and reduced variation.

Throughout the final quarter of the 20th century, global competitive pressures swayed many manufacturers toward APC as an alternative to large capital outlays for incremental expansions, product shifts, and/or (in some cases) plant closures. Unfortunately, the limitations in computer technology and software availability had held the practical implementation of APC to a relatively slow pace until the late 1980s and 1990s. As more powerful computers evolved, the availability of a variety of software packages and associated implementation methods increased significantly. However, as with many revolutionary new technologies, practical execution is not necessarily in-synch with popular theory. Therefore, many users were swayed to believe that the product was the solution, without consideration for the multitude of other factors with consequential influence over the ultimate success of an APC project.

Although subject to a different approach to control algorithm development, batch processes may benefit a great deal from APC solutions as well. The sections to follow describe some of the more common reasons why process control solutions, driven by APC methodologies, have gained in popularity despite the inherent benefits of conventional PID, and why control solutions should consist collectively of a multitude of influencing factors, both physical and intangible.

Advanced Control Decision

The implementation of an Advanced Process Control project can be a complex, yet highly rewarding endeavor. Cost, however, need not be a determining factor. True APC projects can be implemented at a reasonable cost, using existing hardware and control infrastructure, as well as software tools that reside on existing operating platforms. The complexities of such an effort depend highly on the process application and the influences that most significantly impact unit operations. For this reason, there is a great deal to gain by understanding the process as well as those factors that directly influence process performance. A large and increasing amount of research and experience in APC techniques repeatedly demonstrates that few, if any, physical processes (continuous or batch, new or old, hybrid or legacy) exist that cannot be improved through APC. Therefore, the decision should not be "should APC be applied, but where and how." These challenges are addressed in the following sections.

Advanced Control Justified

Despite the advantages and simplicity of the PID algorithm, conventional PID control is not without limitations. Among these shortfalls include the following:

1. PID control loops are inherently reactive, acting on variations in the controlled variable only after a disturbance had propagated through the controlled process.

2. PID control loops assume process linearity as evidenced by the frequent need to retune as operating conditions change.

3. PID control loops do not account for other measurable parameters interacting with the controlled variable.

4. Conventional PID implementations do not compensate directly for measurable disturbances, but depend on changes to the controlled variables before the disturbance is indirectly compensated for.

5. Conventional PID algorithms do not inherently compensate for dead time, and are not well suited for processes with excessively long lag times.

Process variation is the key consequence of the PID shortfalls listed above, as well as a key "selling point" for APC. Excessive variation leads to operating margins that are subject to exploitation, and subsequent increases in operating efficiency, by applying one or more of the variety of advanced control methods (such as Model Predictive Control, or MPC).

In cooperation with conventional control, Advanced Control methods provide the following:

1. supplements (not replaces) and enhances conventional PID control
2. reduces operational margins through decreased variability (enables the targeted process to operate closer to constraints)
3. predictive and Supervisory Control
4. practical interface to Real Time Optimization (RTO)
5. decoupling method for interacting variables
6. dead-time compensation
7. unique operating philosophy

With regard to the capabilities of APC, the perceived benefits of engaging in such an effort often justify the financial and time commitment, even while evaluating unit operations for potentially high- to moderate-yielding candidates. Considering that a 1% efficiency improvement results in significant recurring returns - with payback periods of less than one year for typical APC projects - imagine the benefits derived from a more typical 2-3% improvement opportunity for processes made up of conventional PID loops exclusively.

Advanced Control Implementation

The processes involved while engaging in APC projects go beyond those of platform selection and software configuration, but entail specific steps from process selection through post-project evaluation and analysis. The steps listed below should be considered, as a minimum, to ensure the maximum potential for success - any deviation from which is likely to increase the risk of not meeting the targeted objectives.

Process Selection

Following a preliminary review of all process units within a production facility, the decision should be based on the process unit that: 1) possesses the greatest potential for improvement in terms of quantifiable savings, 2) equipped with adequate instrumentation coverage to enable accurate and viable model identification, 3) positive product market conditions, and 4) operator/maintenance personnel receptiveness. Although the decision to apply continuous, batch, or supervisory control can be (and should be) made during Process Selection, the specific methods, i.e., linear vs. nonlinear, predictive vs. fuzzy, are more difficult to predict until collected data is processed for model identification. Note that a "specific tool should be selected to fit the problem, do not try to adjust the problem to fit a specific tool."

Define Performance Targets

Performance targets provide both project objectives and goals set during conception, and metrics for analyzing project successes. The three key determinants of operational performance are efficiency, throughput, and quality - one or more of which are assigned targets by which success is measured.

Influencing the performance goals includes the identification and screening of key Controllable Variables (CVs) that

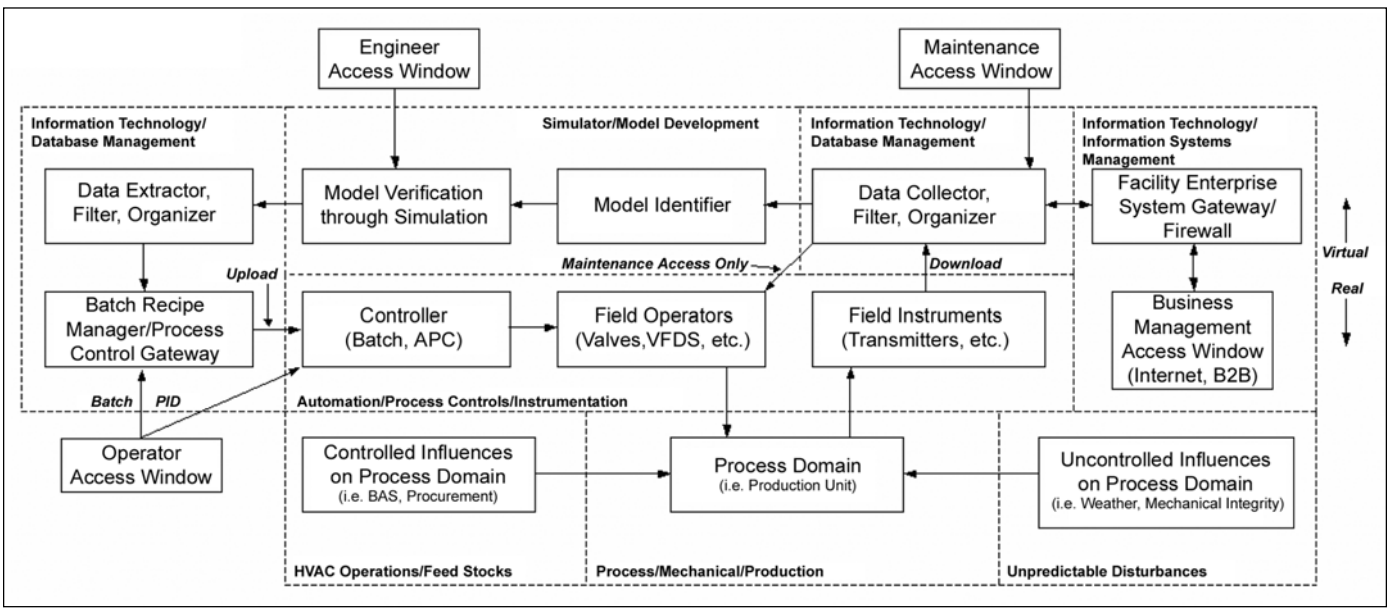

Figure 1. Implementation summary (closing the loop with automation.)

may be directly or indirectly linked to one or more of the key determinants listed above; which in turn are influenced by selected parameters capable of being directly manipulated (MVs) to drive the targeted process to optimum performance. Without measurable Disturbance Variables (DVs), either by direct means or inferentially determined, controller adaptation would not be viable.

Data Collection and Processing

Advanced Control models cannot be reliably identified without collecting real-time, time determinant process data. Two classes of "direct measured" data are collected: dynamic and steady state. Perhaps consisting of the most time consuming steps of APC implementation, both are required to ensure transient behaviors and measurement reconciliation are covered. While the collection of process data often consists of "plant testing" via coordinated and practical moves of manipulated variables, processing of data consists of screening (i.e., via Experimental Design), filtering (i.e., via Finite Impulse Response [FIR]), prioritizing, and grouping data to enable accurate model identification.

In some cases, data may not be directly collected, but still be required for model development. For these cases, inferential computation may be necessary to satisfy these voids. Other non-time dependent data includes information that quantifies operator acceptance and maintenance receptiveness. Of course, with the magnitude and significance of data collected, security policies and authentication procedures should be included throughout the data collection and processing time periods.

Analysis and Characterization

The analysis parts of APC project execution include the determination of relationships among collected variables. These relationships involve associating them to one or more of the performance determinants (quality, efficiency, and throughput), prioritizing them according to impact toward ultimate objectives, and characterizing them as interacting or non-interacting parameters. Their prior classification into CVs, Manipulated Variables (MVs), and DVs (both controlled and uncontrolled, dependent and independent) shall be preserved during the analysis and characterization processes.

Model Identification

Considering the advancements in computer-based technologies, identifying the model consists, perhaps, of the most important, yet often least time consuming set of tasks. The identification approach should have been decided upon during project conception, and no particular APC tool should have been selected until all prior project phases completed. Although batch, continuous, or supervisory control is decided upon prior to or during Process Selection, whether to apply a Neural Network (NN) or Model Predictive Control (MPC) approach may not be possible until the data is analyzed (hence process well understood). Following a thorough understanding of the process performance factors, it may be that all that are required are relatively inexpensive control system enhancements such as Smith Predictors (for dead-time compensation), de-couplers, or simple, feed-forward algorithms.

Other factors that influence the "tools of choice" include standards and regulatory compliance requirements. For example, ISA standard S88 may directly affect the way batch code is organized, or 21CFR, Part 11 may force certain remediation efforts to protect data collected and stored if applying classical methods. Another example involves the Environmental Protection Agency (EPA), which often influences the way furnace and boiler controls are managed, particularly if production wastes are used as fuels.

Model Testing and Simulation

Following model identification, offline testing is essential to ensure the proper relationships (both dynamic and static) have been established. Additional real-time data may be collected, screened, processed, and applied to the model in multiple attempts to prove model integrity. An "open loop" approach should be applied to prevent potentially harmful process upsets due to unperceived process anomalies and non-linearity. As a precursor to model adaptation, simulation also provides invaluable opportunities to arbitrarily upset the "virtual plant" without affecting real production - the better the model, the more effective offline testing. Depending on the type of model identified, hence process targeted, further real-time data collection may be performed at different operating conditions in an effort to determine the degree of linearity over a broad operational spectrum. One important note to keep in mind is the fact that some approaches to Advanced Control perform better than others. For example, a highly non-linear process requires a more discrete (or step) approach rather than model predictive

Advanced Process Control

Advanced Process Control (APC) collectively describes the collaborative efforts of those (as well as their processes, machines, and software algorithms) engaged in identifying areas for operational improvements, along with all steps required to collect and interpret data, identify process models, and the implementation of such model developments to closed loop control. Typically viewed as the efforts put forth to enhance control above and beyond conventional Proportional Integral Derivative (PID) wisdom. APC, if implemented properly, can prove to be a valuable and cost-effective approach to improving manufacturing processes, and well worth capital investment. The perception of complexity should not be a discouraging factor. To acquire a more complete understanding of the implementation and benefits of APC, and/or perhaps a much greater in-depth coverage of the theory behind the technology, there is a great deal of literature available for public access (on the Web, in your public or local college library, and through periodicals such as *Pharmaceutical Engineering* magazine).

exclusively - the latter of which is often applied within tightly constrained operating domains.

Closing the Loop

Arguably the true "money making" phase, loop closure (by feeding back controlled variables into the model and comparing them to their respective targets) enables consistent and continuous model adaptation in response to changing operating environments. The influx of disturbances is why we involve ourselves with Process Control in the first place. Therefore, without process disturbances, the open loop model may be all that is needed to be applied for each defined operating condition.

Batch control, due to its inherent discrete nature, generally demonstrates qualities of open-loop control. Therefore, closing the loop for batch processes provides the greatest benefit for tasks involving production scheduling and related optimization activities.

Recurring effects and continuous adaptation are the primary contributors to the benefits of loop closure for Advanced Control techniques. After all, elemental PID control, the most commonly applied algorithm in continuous control, has historically shaped many facets of manufacturing, arguably more so than any other control entity. Advanced Controllers should apply a similar approach to self-adjustment. The loop closure implementation phase includes all tasks required to install the models into a viable control system and establish all necessary links.

Model Adaptation

Typically, a product of closing the loop, model adaptation is a special characteristic of APC that enables the model to update its fundamental identifying components in response to changing environments. Unlike conventional PID that applies an integral (or accumulative) term to re-adjust the model in response to sustained changes in operating conditions (without necessarily changing its response characteristics), advanced model adaptation intelligently compensates for the differences between "theory" and "reality," and/or between two or more unique operating conditions. Although highly dependent on the way the Advanced Control algorithms are authored, Neural Networks (NNs), for example, are synonymous with "artificial intelligence" considering its inherent ability to identify patterns through "learning" and recalling the same recognizable patterns as they occur. Therefore, NNs can be successfully applied to highly non-linear, and even highly discrete batch processes. Model adaptation also may apply iterative loops to converge on optimum performance - such as fuzzy or iterative convergence control philosophies.

The model adaptation phase also should provide the opportunities to fine-tune the online advanced controller as more is learned about model compatibility with the process, as well as the receptiveness of those operating and maintaining the controller.

Performance Assessment

At this point, the advanced control model is in production and most likely resulting in a return on investment for the owner. However, to ensure the ultimate objectives have been satisfied, the performance of the controller should be evaluated. Some key components of this assessment phase include: a) magnitude of adaptation required (or continues to be required), b) controller response to disturbances, c) proximity to theoretical optimum using statistical methods, d) ease of use by Operations, e) degree of required maintenance, f) acceptance by users, and g) cost of implementation (vs. allocated budget).

Benefits Analysis

The "proof is in the pudding." After a time of continuous operation (one week to several months depending on the nature of process targeted), the recurring benefits should be

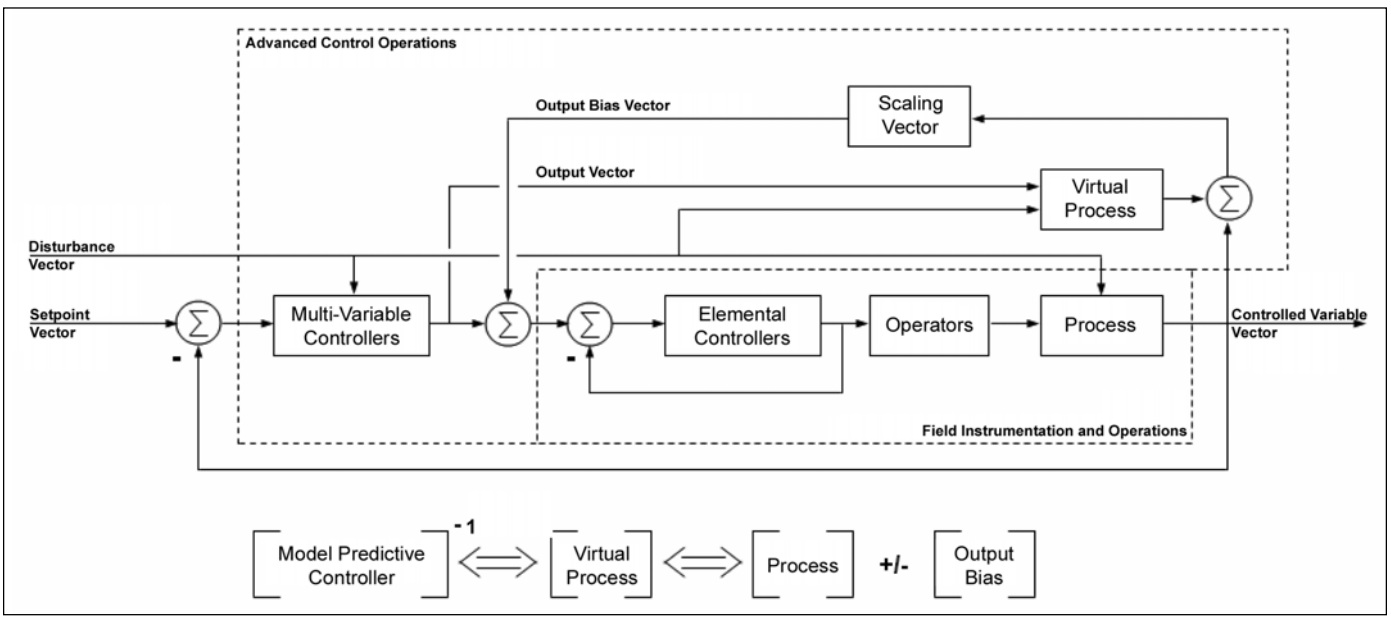

Figure 2. Advanced model predictive control model (controller adaptation via output bias.)

quite evident. A marked improvement in efficiency (less waste), quality (yield), and/or throughput (revenue) should be easily identified following a review of historical trends (either visually and/or statistically). If targeted goals have not been achieved, and there is evidence that operational improvements are still feasible, additional data collecting should be performed to further fine-tune the model. Otherwise, the owner should consider revising the process selection tasks. Overall, the total costs and benefits should be correlated to determine the rate of return (throughout the payback period) and ultimate recurring rate of return throughout the lifetime of the controller (factoring in routine maintenance and downtime costs).

With regard to the implementation phase (Closing the Loop), the key components of the closed-loop model are represented in Figure 1. The diagram depicted in Figure 1 implies the process selection phase had been completed and objectives/targets decided upon. The next steps, therefore, involve automatically feeding back plant data into the virtual plant model, processing and subsequently adjusting the manipulated controller outputs through field operators, thereby closing the loop. Sustained deviations from set point (or target) may alert the controller to "learn," thereby adapting the model to new operating conditions. In addition to demonstrating a closed-loop model for advanced control, Figure 1 illustrates the various operational zones (maintenance access, operator access, and information technology links), as well as the boundary between the virtual control components and components of process control that play vital roles in the physical (or real) domains – such as transmitters and valve operators.

Assessing the Tools

The tools applied to simplify the implementation of APC tasks should not be regarded as the "solution," but rather methods to better organize data, coordinate tasks, compute model parameters, and manage the model execution after installation. These tools should not supersede the need to understand the process, identify opportunities to improve process performance, and sound engineering judgment. Among the many tools on the market for continuous, batch, supervisory, or a combination of the three, all can fit in as either open, canned, or hybrid applications (with advantages and disadvantages of each):

1. Open Applications. Open Applications are highly customizable and portable. Although the basic operating environments may be licensed (i.e., spreadsheets), the applications that reside within these environments may not be. Often associated with low initial capital outlays, Open Applications can be quite flexible and require significant custom program development. As a consequence, the initial cost advantages are often negated by large developmental costs followed by the uncertain availability of sustained software support.

2. Canned Applications. Although subject to licensing agreements, Canned Applications are often associated with relatively large up-front costs, but can be compensated for by lower implementation costs. Canned Applications, with the reputation to be somewhat inflexible, are not recommended for highly complex and specific processes (such as many specialty chemical and pharmaceutical processes), but can prove to be a great value for common and well-known processes (such as oil refining and power generation).

3. Hybrid Applications. Combining both open and canned algorithms, hybrids tend to be application-specific, yet highly configurable for the sake of usability, maintainability, and flexibility. With a cost structure generally between that of Open and Canned Applications, hybrids also allow the programmer to focus more on the required functionality of the code, without significant infrastructure-building.

Two common approaches to Advanced Control include Model Predictive (for linear processes) and Neural Networks (for non-linear processes) - both of which are depicted in the following illustrations (Figures 2 and 3 respectively). As shown in the figures, both consist of controlled, manipulated, disturbance, and in some cases, constraint parameters. Other characteristics include variable feedback for model adaptation, feed-forward for proactive manipulation of operators, dead-time compensation, and constraint control. Neural networks provide the added capacity to "learn," or self-adapt to changing operating conditions.

Depending on the needs of the user, an important consideration for selecting software applications or customizing existing ones involves code compliance. Various standards and regulatory agencies provide guidelines and restrictions, respectively, which may influence the development of control code. Examples of programming standards for batch processes include S88 (an ISA set of standards for code/recipe structure and terminology), and 21CFR, Part 11 for governmental regulatory mandates dealing with stored electronic data. Since this

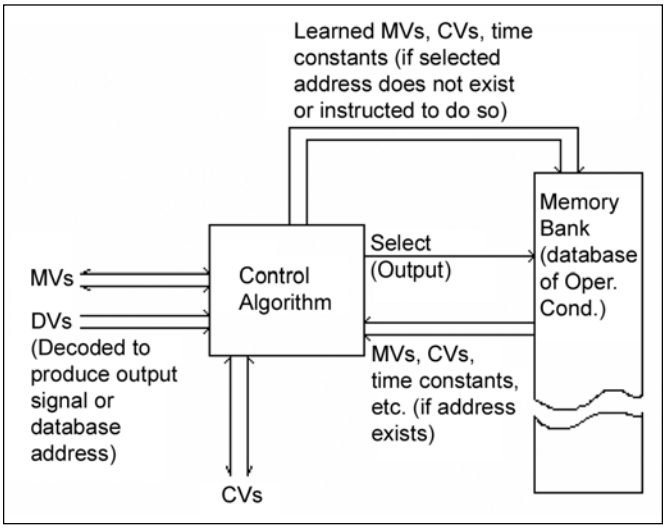

Figure 3. Basic neutral network model.

article is focused on Advanced Control methodologies, additional information on these standards may be found in various published references and established codebooks.

Internal vs Outsourcing

Since APC covers far more than simple PID integration to process control, outsourcing specialists in the fields of advanced control is not uncommon, and oftentimes preferred. Note, however, that since outsourced expertise may be proficient in the theory behind the technology, compatibility with existing process dynamics and operating philosophies brings forth vital factors of APC implementation, factors that cannot be ignored. History is filled with genuine attempts at APC integration that ultimately lead to failure. Note that the fate of a significant number of these attempts were set not by the accuracy/integrity of the tools, or the people responsible for collecting/processing the data for model identification, but rather an incomplete understanding of overall process dynamics and operating philosophies. Commonly overlooked sources of valuable operational data are those individuals that are involved with the day-to-day operation and maintenance of the process equipment... contributions from which should be mandatory for most (if not all) APC implementation projects.

Conclusions

As global competition increases leading to greater uncertainties in market conditions, the decision to incrementally expand production capacity becomes increasingly more difficult. Therefore, the alternatives, such as increasing the efficiency, quality, and throughput of existing production capacity, are often on the forefront of strategic planning. Common, practical, and cost-effective alternatives consist of the various APC techniques applied to "squeeze the most" out of existing production lines.

Following the decision to apply Advanced Control, the success of a project rests on the processes by which the execution of the project progresses. Undisputedly, the most important factors of APC implementation involve understanding the process, its degree of variation and instrument coverage, and empowering the ultimate users to take a stake in its development (in most cases, user acceptance is as equally important, if not more important, than model accuracy).

Some may argue that the majority of the benefit is derived from the processes followed to design and build the advanced controller module and not the operation of the controller alone. Take note, however, that the controller does more than stabilize unit operations, but adds a platform for real-time optimization and "24/7" operating consistency. To greatly increase the chances of a successful APC project, view the selection, design, installation, and operational phases of execution as collaborative efforts by all those involved in developing methods for process improvement - using software tools to facilitate the efforts and add the element of consistency to these operations. Virtually no process is exempt from the potential benefits of Advanced Control; and no magic formula exists to implement such an endeavor successfully.

Definitions

21 CFR, Part 11 (or Part 11) - A Code of Federal Regulations mandate encouraging the proficient use of electronic signatures and/or biometrics intended to link accountability to records (batch or otherwise) maintained and transmitted in electronic form. Currently promoted within the industrial sectors regulated by the Food and Drug Administration (FDA), the Part 11 practices and principles are essential to the security and integrity of all vital information stored, maintained, and shared electronically anywhere.

Advanced Process Control (APC) - This collectively describes the collaborative efforts of those (as well as their processes, machines, and software algorithms) engaged in identifying areas for operational improvements, along with all steps required to collect and interpret data, identify process models, and the implementation of such model developments to closed-loop control for adaptability and refinement. Typically viewed as the efforts put forth to enhance control above and beyond conventional PID wisdom.

Constraint Variable (AV) - A parameter of control that is often associated with model predictive identification techniques that collectively with other AVs define the boundaries of the control domain. An example includes the maximum temperature tolerated by a piece of equipment.

Controlled Variable (CV) - A parameter of control selected to be changed indirectly in response to a change in a Manipulated Variable (MV). CVs are often the focus of control. An example includes column bottoms (or base) temperature using steam flow as its associated MV.

Disturbance Variable (DV) - A parameter of control identified by its ability to influence the value of one or more CVs, but can be compensated for by adjusting an associated MV. DVs may consist of direct-measured or inferred parameters, and may or may not be modified as required. Examples of DVs include process unit feed rate, coupled interferences from adjacent processes, and weather-related events.

ERR - Model error as defined by the geometric or least squares difference between the virtual model and the actual process.

Fuzzy Logic Control - A nonlinear modeling technique that uses operating domains to converge on specific, more linear areas of control (i.e., fuzzification), and may output setpoints to conventional controllers as "singletons" within these areas of control (i.e., defuzzification). Fuzzy Logic is often used to enhance the performance of the more classical control techniques.

Gain - Gain is generally described as the change in output (of a process unit or controller) divided by the change in an associated input.

Iterative Convergence Control Technology (ICCT) - ICCT is a nonlinear modeling technique that applies "role definitions" for specific controlled and manipulated variables. Each role defined represents a specific purpose in the convergence toward an optimum operating regime (similar to Fuzzy Control).

Manipulated Variable (MV) - A parameter of control identified as a direct-adjusted variable selected to influence a controlled variable. An example includes the stem position in a control valve.

Model Predictive Control (MPC) - A linear modeling technique based on the computation of future trajectories of controlled variables (i.e., output vector) in response to changes in manipulated inputs (i.e., input vector).

Neural Network - A nonlinear modeling technique synonymous with artificial intelligence vis-à-vis its ability to learn (i.e., recognize patterns) using weighted inputs. Often used as "properties estimators" or "operating domain controllers."

Proportional Integral Derivative (PID) - Conventional closed-loop control algorithm that acts on the deviation between a SP (controlled variable target) and PV (controlled variable measurement) to determine a change in a manipulated parameter (i.e., valve operator). PID is an acronym for Proportional (Gain), Integral (Reset Action), and Derivative (Rate Action).

Rate Action - The derivative term that is proportional to the rate of change in the deviation from setpoint or step change in the controlled variable. Rate action does not eliminate error, but provides a "kick" to the response time in response to fast changing CVs.

Reset Action - The integral term that auto-adjusts a controller output function in response to sustained deviation from setpoint. Output changes are proportional to the integral of the error (SP-PV). Reset action attempts to eliminate error over time.

S88 - S88 is often described as an ISA batch programming standard that defines code structure and terminology to add consistency and a degree of interchangeability across batch programming projects.

Time Lag or Time Constant - The period of time it takes a controlled process variable to reach about 63% of its final value after influenced by a disturbance and/or change in an associated manipulated parameter.

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This article explores the relationship between the chosen randomization methodology for a trial and the medication management techniques used when incorporating Interactive Voice Response technologies.

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The Impact on Supply Logistics of Different Randomization and Medication Management Strategies Using Interactive Voice Response (IVR) Systems

by Damian McEntegart and Barry O'Gorman

Introduction

Interactive Voice Response (IVR) systems use the telephone as a means of inputting data. Pre-recorded prompts that list the various options available or that request responses to particular questions are played for the user. Toll-free telephone numbers are used to access the IVR system and data are entered and then written to the underlying databases by using the telephone touchtone keypad. Additionally, data contained within the databases also can be read back to the caller. For example, if dispensing medication to a patient, the IVR system may be configured to request the patient identification number and date of birth. After referring to the study data-

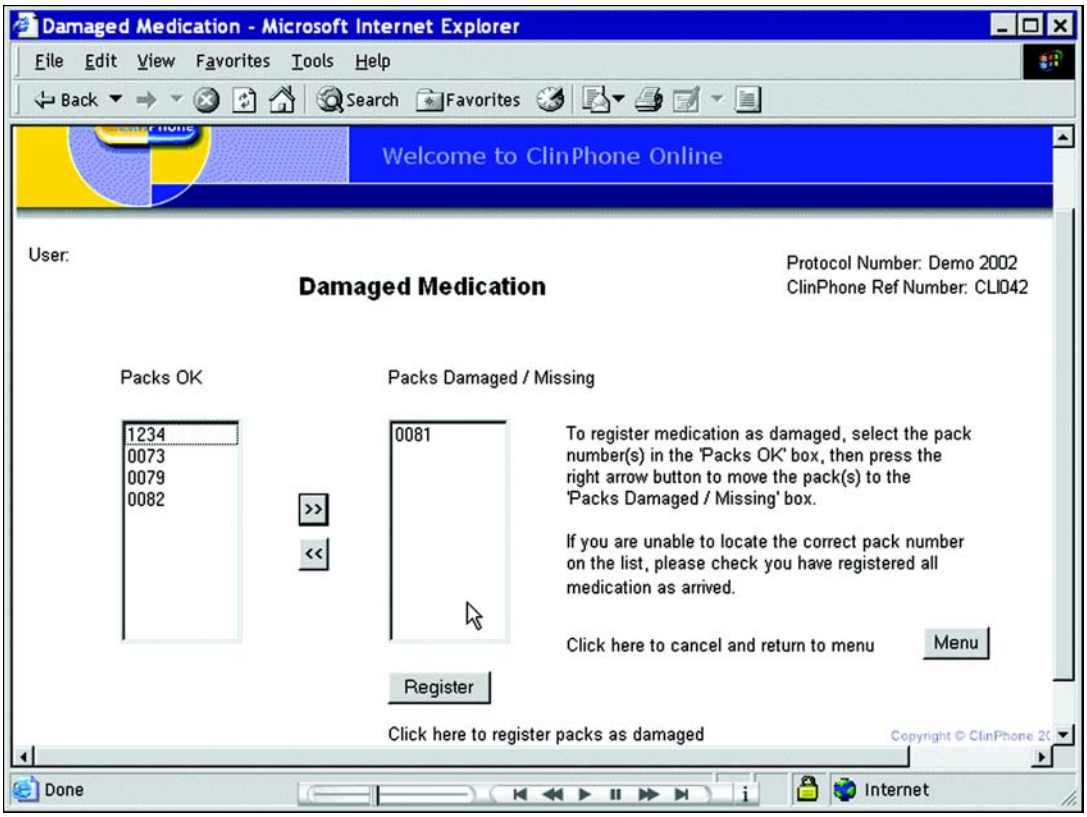

Figure 1. Representation of a typical (Web-based) IWR interface.

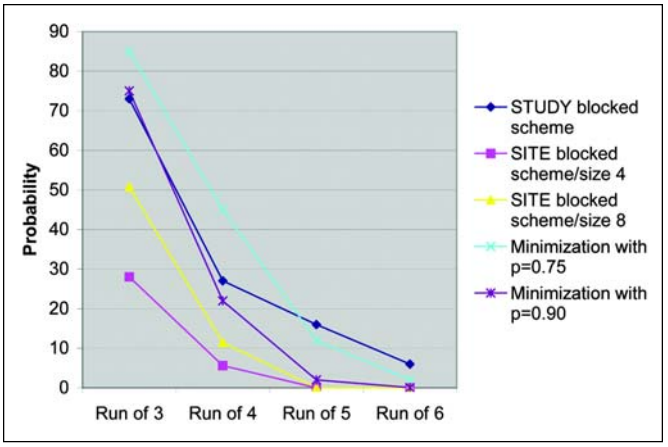

Figure 2. Probability of observing a run (sequence of successive repeated allocations to the same treatment) at a site that recruits exactly eight subjects.

base, the IVR system would then return the blinded medication pack number to be issued to that patient. IVR or Web-based (IWR) systems are commonly used to manage randomization and medication management in clinical trials - *Figure 1*. Other reasons for using IVR include real-time access to subject recruitment and tracking data, managing and ensuring the accuracy of complex dosage calculations and collection of patient reported outcomes data directly from subjects. A full description of IVR is provided elsewhere.[1]

A usual feature of IVR-managed trials is the separation of the numbering systems for the randomization list and the packing (medication ID) list. The fact that any medication unit can be given to any subject in any eligible treatment period allows savings of medication supplies compared to the traditional system of subject numbered packs. By means of introduction, this article describes the three medication management algorithms that are used with IVR to achieve these savings in medication.

The amount of medication overage necessary for an IVR trial depends on the following:

1. 'Fixed' factors relating to trial design, such as the medication unit, the supply chain, and the randomization method.
2. Variable factors such as delivery time and withdrawal rates.
3. The inherent uncertainty associated with the subject recruitment process.
4. The IVR algorithms and parameter settings employed.

This article concentrates on the relationship between the randomization technique and trial overage. After discussing the relationship, the effects of various different schemes will be examined by a simulation experiment.

Finally, some randomization and medication management solutions are presented for a problematic trial design often encountered by statisticians and supplies personnel, that of how to deal with trials with many treatments, but a relatively low average number of subjects per site.

Background on IVR Medication Management Techniques

A primary goal of IVR is to ensure adequate stocks of medication are maintained at each study site to supply new and existing subjects, while also keeping these levels to an effective minimum. By automating the resupply process, the clinical trial supply chain is directed to those sites actively recruiting subjects. Customarily, each site participating in the trial receives an initial supply of medication packs. Each medication pack is labeled with a unique numeric code that is used by the IVR system to individually track its location. At each dispensation to a subject, a member of the site personnel makes a call into the IVR or Web system, identifies the subject requiring medication, and the system informs the caller of the number of the medication pack to be dispensed. This pack will be picked from those contained in the inventory of the study site and according to the treatment group of the subject. Assuming no expiration date differences between available packs, it is recommended that packs be picked randomly by the system.[2] Upon each dispensation, the dispensed medication inventory at the study site is automatically updated. The available amounts of all the different medication packs are monitored centrally on a daily basis by computer. Stock at sites and depots is then automatically replenished when a supply need is identified, generally using one (or a combination) of the three methods detailed below.[3-5]

Trigger and Resupply Process

Each site within the study is assigned a trigger and resupply level for each pack type. Should the inventory of any one of the pack types fall to or below its predefined trigger level, a supply need is automatically generated for the site. When a resupply is made, it is usual to include quantities of each pack type so that all are restocked up to their assigned resupply levels. The values assigned to trigger and resupply levels are a function of site recruitment rate, delivery time to site, desired resupply frequency, site storage, and study overage. The trigger level should be sufficient to supply any subjects requiring medication while the newly requested stock is in transit to the site. The resupply levels are set at a value where, given the site recruitment rate, there is a minimum danger of medication expiring and site storage demands are maintained at a manageable level.

Predictive Resupply Process

This particular method applies to trials in which subjects return for scheduled redispensing visits as defined in the study protocol. Using this algorithm, the computer takes advantage of the known dispensing visit schedule. A site's supply need for redispensing visits is calculated by looking ahead over a defined time horizon (the check range) and estimating the number of packs required by returning subjects. Where a supply need is identified (requirements for the check range are greater than the site's inventory), the algorithm recalculates the number of packs required by estimating resupply needs over a longer time horizon (the prediction window) which helps to minimize repeat shipments. The

	Number of subjects recruited in specified month									
	0	1	2	3	4	5	6	7	---	10
Probability	0.14	0.27	0.27	0.18	0.09	0.04	0.01	0.003	---	0.00004

Table A. Distribution of number of subjects recruited at site per month following a Poisson process with rate two subjects per month.

length of the prediction window is principally determined by the frequency of scheduled visits, delivery time, withdrawal rates, and storage capacity at sites.

Randomization Code Lookahead Scheme

This method of medication management requires that the randomization methodology be a pre-defined blocked scheme that is balanced at the site level. Site medication needs are determined by the randomization schedule, and so by looking forward in the schedule, it is possible to inspect future treatment allocations relative to the medication currently at site. Supply orders are generated for sites when the inventory levels fall below or equal to that required to randomize the next X number of subjects to the treatments listed in the randomization code schedule. Resupply orders are generated to supply enough medication to randomize Y subjects according to the treatments listed in the schedule. For example, using values for X and Y of three and five; if a site has only enough stock to randomize subjects to the next three available entries according to the randomization schedule, the IVR generates an order of medication packs to allow a site to randomize the fourth and fifth subjects to the treatment groups listed. Alternatively, resupplies can be linked to the numbers of subjects in an initial screening period. It is this method of IVR medication management that is most comparable to the traditional method of subject numbered packs.

Effects of Randomization Technique

For a given set of trigger level settings, average recruitment rate, and delivery time distribution, the incidence of randomization scheme failures will be related to the degree of control of successive randomizations to same treatments at individual sites. A randomization scheme failure or stockout is defined as a failure to dispense the required medication to a subject due to shortage of the relevant packs at site. The more tightly controlled the allocation then, in general, the less stockouts there will be. Randomization failures are caused by excessive calls on the reserve amount of stock (equal to the trigger level) in the time taken to deliver new supplies after the trigger level is reached (in reality, it need not be the triggered stock that fails, but the principle about stock utilization vs. delivery time is the issue). Such excessive calls on the site stock of any particular treatment are more likely when the site level balance is not controlled or is only lightly constrained. When allocation is not constrained, there is a greater chance of sequences (runs) of successive allocations to the same treatment.

Figure 2 shows the probability of successive runs of subjects being randomized to the same treatment group at any given site for five separate randomization schemes that are balanced at the overall (STUDY) level or the site (SITE) level or both. Three schemes employed blocked randomization lists and two were minimization schemes with factors to balance at both the study and site levels.[6] The minimization schemes incorporated different random elements. The study simulated required 280 subjects recruited from 35 sites, giving an average of eight subjects per site randomized in a 1:1 ratio to two treatment arms. Ten-thousand simulations were performed.

For each scheme, the graph shows the separate probabilities of observing allocation sequences (runs) of three, four, five, and six subjects to the same treatment. The graph illustrates that runs of this magnitude are perfectly possible depending on the randomization schemes employed. These chance occurrences may increase the possibility of stockouts in a study. The two schemes that give the greatest chance of a run of successive same treatment allocations are the central unstratified randomization list and minimization with an allocation probability of 0.75. For instance, both have a greater than 10% chance of seeing a run of five allocations of the same treatment. The maximum number of runs for a site blocked scheme of block-size four is four. This can happen when two adjoining blocks are constructed as AABB BBAA.

Simulation Techniques to Explore the Relationship between Randomization and Medication Management

Optimizing the medication supply chain strategy and managing it using IVR involves many factors and can become rather complex. The impact of the chosen randomization methodology and other features of study design are difficult to account for. Simulating the IVR management of a clinical trial allows the supplies group and clinical team to experiment with a variety of strategies and to model different scenarios, and thus quantify the impact of various randomization schemes on the supply algorithm and overage required for any given trial. In this way, the amount of clinical material required can be identified and the way the supply chain is managed can be optimized.[4]

The simulation principle is to build a model that simulates the interaction of the randomization methodology and drug distribution process while mimicking aspects of the complete clinical trial such as recruitment, withdrawal, shipment times, etc. This allows effective optimization of medication management strategies and identification of how much material is required for upcoming clinical trials by evaluating different randomization and supply chain scenarios. It is well known that various study processes, such as subject recruitment, are variable and it is important that the modelling approach used incorporates known variability in a study so that the full range of possible outcomes can be studied.

In our simulation model, using the proprietary software

Study details	
Number of treatments:	2 (active and placebo)
Randomization ratio:	2:1
Number of subjects:	800
Number of depots:	10: 1 central + 9 local (1 per country)
Number of sites:	66 (55% in two countries)
% sites fail to recruit:	10%
Site recruitment types:	0.5 subjects/week – LOW 1.5 subjects/week – MEDIUM 2.5 subjects/week – HIGH
Screening period:	14 days with 20% failure rate
Treatment period:	10 months
Pack types:	Experiment 1: One 10 month pack Experiment 2: 10 one-month packs
Withdrawal rate:	20%
Delivery time:	4-8 days to sites 21-35 days to local depots
Labeling restrictions:	None
Site activation period:	1-28 days of country start date

Figure 3. Study details of the simulation experiment.

MedSim,[5] we define the randomization and supply methods for a study in terms of some 50 parameters. The majority of the parameters are fixed as part of the study design, e.g., number of countries. Twelve of the parameters are subject to random variation; these include subject recruitment at each site, withdrawal rates, titration patterns, delivery times, proportion of damaged packs, and other parameters. Using Monte Carlo simulation, the system accounts for the random variation and provides summary statistics on the expected distribution of any of the variables incorporated into the system, e.g., amount of stock shipped, need for packaging campaigns, risk of stockouts, etc.

To explain how Monte Carlo simulation works, consider how the technique applies to predicting subject recruitment. Site recruitment is generally modelled to follow a Poisson process (this process describes the number of random events over a defined time period). Thus while the average study recruitment for a group of sites may be two subjects per site per month, there is a chance that an individual site may recruit zero subjects or as many as six or seven subjects in any particular month - *Table A*. Monte Carlo simulations account for this random variability by using a computer random number generator to determine the recruitment for each site for each month that the trial is enrolling subjects. The random number generator is programmed so that in the long run it returns numbers in the proportions that underlie the theoretical distribution. The same concept is applied in the model for other study parameters that add variability into the clinical trial process, e.g., delivery times, withdrawal rates, etc. In this way the model can incorporate the variability observed in the real world when performing its calculations.[4]

Having defined the model, a number of simulations are performed. Each simulation progresses through every day of the duration of a study tracking all study events such as subject recruitment, consignments raised, consignments delivered, stockouts, etc. Specifically:

- Sites are activated and supplied with initial stocks of medication in the same way as that occurring in a real trial using the IVR system.
- Subjects are recruited on a daily basis according to an approximate Poisson process based on the recruitment rates given for each site.
- Their subsequent visits are randomly sampled from the target visit date range that has been defined for the study.
- Subjects are withdrawn from the study in a random manner on a daily basis according to the withdrawal rates input into the system.
- Site stocks are maintained using the defined IVR resupply algorithms that run at the end of each day.
- Orders are raised with the depots as defined in the supply chain and dispatched with the lead times sampled from an underlying distribution.
- Medication is expired and replaced according to the defined expiration information.

Summary statistics are then calculated as an average over all simulations for a given scenario while also providing a range of possible outcomes.

Simulation Experiment to Investigate the Impact of Randomization Schemes on Medication Management

The simulated study was a double-blind, multi-site placebo controlled trial of two treatments to be conducted in nine countries - *Figure 3*. The randomization ratio was 2:1 for active:placebo with 800 subjects to be randomized. There were 66 sites unevenly distributed across the countries. Three types of site were identified before the study start - low, medium, and high recruiters. Supplies were to be distributed from one central depot to nine local depots, which in turn supplied sites in the respective countries. The duration of the randomized treatment period was 10 months. Two pack types were investigated in two separate experiments. In the first experiment, a single pack to cover the whole trial was dispensed at the baseline visit. In the second experiment, packs containing medication to cover a single month were dispensed at baseline and nine resupply visits spaced at monthly intervals.

In each experiment, four potential randomization strategies were investigated. Three of these strategies involved a blocked randomization list with a block size of six. The treatment allocation ratio was balanced at different levels for each of these schemes: central unstratified randomization (study level balancing - STUDY), randomization stratified by country (country level balancing - COUNTRY), and randomization stratified by site (site level balancing - SITE). The fourth scheme was minimization with factors for site balance and study level balance (a single level factor of overall treatment allocations applicable to all subjects). In this scheme, a random element was employed to reduce predictability as recommended by regulatory guidelines.

For all randomization schemes, medication inventories were managed by trigger-resupply for the local depots and sites, and in the case of Experiment two, by prediction for subject resupplies. For the local depots, the initial supply levels and trigger-resupply settings were determined in accordance with the expected recruitment levels in each country. They were set to give approximately three shipments per depot for the STUDY randomization scheme. Even though it may be possible to lower them due to maintenance of a more strict balance at the depot level, no attempt was made to alter these settings for any of the other randomization schemes in order to give a fair comparison. The site settings were chosen so that the mean number of randomization failures was less than one subject when averaged over all the simulation runs. These settings were determined by trial and error.

For the SITE stratified randomization scheme, an additional medication management scheme involved using the randomization code lookahead technique to control inventories at the site level.

In Experiment one, the resupply levels for the local depots were set to zero following randomization of 90% of the subjects. The trigger-resupply levels for the site inventory management were also reduced at this milestone to limit over-supply at sites.

In Experiment two the resupply levels to the local depots were reduced after both 90% and 100% of the subjects had been randomized and set to zero when there were only four months to closure (as predicted by the system from monitoring of ongoing subjects). The trigger-resupply levels for the site inventory management were reduced after 90% of subjects were randomized and then set to zero after all subjects were randomized, i.e., the resupplies for all ongoing subjects were handled by the prediction component of the algorithm. The predictive algorithm checked the resupply needs for returning subjects for the next 14 days and if a resupply was needed, restocked the site with sufficient stock to meet the supply needs for the next 28 days (all stocks also were topped up to their resupply levels); the need for a resupply was determined by the stocks at site, the predicted supply needs and the trigger levels.

In each experiment using each randomization method, 100 simulations were performed.

Results

The mean duration between first and last subjects randomized was 15 weeks (maximum=17).

Table B presents the overage results for the two experiments. For each run, overage is calculated as the difference between the quantity shipped from the central depot and the quantity used as a percentage of the quantity of packs used. Both mean and maximum overages are presented. Arguably, the maximum overage is of more interest than the mean as it shows the need for medication at the extremes when the randomly sampled parameter values interact to produce a higher need for supplies that the sponsor would generally want to meet. For Experiment one the maximum overage across the randomization schemes for the active treatment ranged from 109% to 154% and the maximum overage for the placebo treatment ranged from 176% to 244%. Thus, it can be seen that one determinant of overage is the allocation ratio; packs with a lower allocation ratio will need proportionately more overage. This is because of the need to set relatively higher trigger levels to keep randomization failures to a set level. This finding is confirmed by the results of Experiment two. The STUDY and COUNTRY schemes had very similar overages, and both schemes operated with higher trigger and resupply levels than the SITE scheme in order to ensure the number of stockouts remained below 1%. The SITE and MINIMIZATION schemes produced only a small reduction in overage, mainly for the placebo, which reflects the randomization list block size and unequal allocation ratio. A more substantial reduction was seen for the SITE with lookahead scheme (respective maximum overages of 109% and 176%).

In Experiment two, the approach of splitting the 10-month kit into 10 one-month packs results in significant medication savings. However, within this experiment, the schemes are all relatively similar in terms of overage. This is because the post-randomization dispensing period of 10 months is rela-

Randomization Strategy	Treatment	Single Pack (Experiment 1)		Ten Packs (Experiment 2)	
		% overage mean (max)	Max shipped (x10)	% overage mean (max)	Max shipped (x10)
STUDY	ACTIVE	141 (154)	13710	22 (28)	6126
	PLACEBO	231 (244)	9280	27 (32)	3181
COUNTRY	ACTIVE	141 (154)	13680	22 (28)	6152
	PLACEBO	230 (244)	9200	27 (31)	3215
SITE	ACTIVE	136 (150)	13540	22 (26)	6104
	PLACEBO	211 (231)	8720	26 (31)	3196
SITE with lookahead	ACTIVE	94 (109)	11080	22 (28)	6123
	PLACEBO	159 (176)	7390	26 (31)	3230
MINIMIZATION	ACTIVE	139 (144)	13140	22 (28)	6175
	PLACEBO	210 (218)	8520	26 (30)	3189

Table B. Overage required for a single pack dispensing study vs. a study with packs dispensed at multiple visits.

tively long compared to the four-month enrollment period. There is thus the opportunity to run down depot and site inventory levels as described previously. However, it must be noted that this will not always be the case.

It is instructive to compare the results of the two experiments to examine the effects of splitting the single pack into smaller dispensing units. Clearly the percentage overage is far lower for Experiment two with a range across the allocation schemes of 26% to 31% for the active pack and 30% to 32% for the placebo pack. But this comparison is potentially misleading, as it does not account for the fact that fewer monthly units will be dispensed in Experiment two because of subject withdrawals. The more correct and fair comparison is of the maximum packs shipped for both experiments with the single pack figure calculated as a monthly pack equivalent, i.e., as if the subject was given 10 monthly packs at their single dispensation. The figures for Experiment one are a factor of two higher for the active pack and a factor of three higher for the placebo pack. The savings shown by splitting the packs into smaller dispensing units and managing by IVR can represent substantial cost savings.

Table C presents the results of the number of consignments and the number of randomization and resupply failures. The number of consignments for the randomization code lookahead method is higher than for the other two methods. Comparing against the SITE scheme managed by trigger–resupply, the mean number of consignments is almost doubled (an 84% increase) for Experiment one compared to a 15% increase for Experiment two. The difference between these two figures reflects the lower base in Experiment one. The number of randomization failures is low for all the schemes, which is not surprising given that this was a design feature. The failures are highest with the STUDY scheme. Note that in Experiment two there is also the small chance of resupply failures as the packs sent for a resupply visit may be used to randomize a subject who would otherwise have been a randomization failure.

Dealing with Many Treatments and Few Subjects per Site

We have shown that randomization balanced at the site level proves to be the most economical in terms of medication overage required and especially in single pack dispensing studies. However, site level balancing can compromise the balance across treatment groups at the study level. A consequent quandary that frequently presents itself to clinical teams is how to successfully manage randomization and trial supplies when faced with many treatments and few subjects per site. In such trials, to maintain an acceptable level of study balance, central unstratified randomization is frequently used. The consequent dilemma is that at any site, there may be successive allocations of the same treatment to new subjects (discussed earlier). From a drug supply management perspective, relatively high trigger and resupply levels may be required to avoid high numbers of randomization failures or the alternative of forcing the randomization to be made from the subset of treatments for which packs are available.[7]

Strategies exist within IVR to maintain the study level balance while minimizing or eliminating the chances of successive allocations to the same treatment group at a site. An IVR variant of Zelen's 1974 scheme is effectively a site stratified scheme, which dynamically constructs (forces) the site blocks with the study level balance taken under consideration.[6-8] Consider a trial with five treatment groups. In this situation, subjects are allocated the treatment corresponding to the next unused randomization code from a central unstratified randomization list with a block size of five that does not cause the site imbalance (maximum allocation minus minimum allocation) to exceed one. In effect, blocks of size five are being used at the site level and supplies can be based on this. Initially, each site can be supplied with enough medication to cover the first block from the randomization schedule and then trigger a resupply of another complete block when two or three subjects have been randomized. Further discussion including regulatory implications is given elsewhere.[6] An alternative random and highly unpredictable technique, involves sending a number of packs to a site in sequence order from a medication identification list constructed in blocks, and then forcing assignment of treatments to randomized subjects corresponding to medication available at the site.[7]

Conclusion

Substantial reductions in overage can be realized when IVR medication management techniques are utilized to control the supply logistics of a clinical trial. IVR systems allow sites to start off with minimal supplies and can effectively target available supplies to sites that are actively recruiting and

Randomization Strategy	Single Dispensing Study Consignments Mean (max)	Multiple Dispensing Study Consignments Mean (max)	Single Dispensing Study Randomization Failures Mean (max)	Multiple Dispensing Study Randomization Failures Mean (max)	Multiple Dispensing Study Resupply Failures Mean (max)
STUDY	246 (259)	1101 (1173)	0.83 (5)	0.15 (3)	0.15 (12)
COUNTRY	242 (255)	1097 (1157)	0.89 (11)	0.08 (2)	0.00 (0)
SITE	286 (300)	1171 (1243)	0.75 (9)	0.08 (2)	0.09 (4)
SITE with lookahead	526 (554)	1351 (1414)	0.13 (6)	0.03 (3)	0.00 (0)
MINIMIZATION	269 (282)	1169 (1227)	0.80 (3)	0.07 (1)	0.00 (0)

Table C. Number of consignments required for, and rate of randomization and visit failures in a single dispensing study versus a study with multiple dispensations per subject.

retaining subjects. Such systems also ensure sufficient shelf life of the medication dispensed, relative to the expiration date.

The amount of overage required depends upon a variety of factors with the randomization scheme used being one of them. But the magnitude of the effect of the randomization scheme depends upon the precise circumstances of the trial. Balancing a trial at the site level may prove beneficial, but the feasibility of this depends upon other design features such as the number of treatments and subjects. Techniques exist to enable acceptable balance levels at both the site and study level in trials of many treatments and few subjects per site. Also, as the simulation results presented in this article demonstrate, the allocation ratio of the treatments plays a key role in the percentage of overage required. Treatments allocated proportionately less require a relatively higher overage, especially in trials where subjects receive medication only at the point of randomization.

Savings in supplies can be further augmented when there are a number of dispensations per subject during the trial, rather than a single dispensation at the time of randomization. IVR prediction algorithms enable the breakdown of medication into smaller dispensing units to be efficiently managed by ensuring that the supply needs for individual subjects are met. The duration of the post-randomization follow-up period compared to the length of the enrollment period also plays a leading role in overage reduction. Longer post-randomization follow-up periods allow greater reductions in buffer stocks at both sites and depots.

Computer simulations provide a highly effective mode of quantifying the medication requirements for any given clinical trial. The use of simulation techniques also allows one to quantify the potential risks associated with their chosen scheme of randomization. Ultimately, they eliminate the guesswork in the estimation of trial supply requirements, which inevitably leads to conservative overestimations, and thus, greater wastage of expensive compounds.

Glossary

Forced Randomization - if the medication for the treatment group originally allocated by the randomization algorithm is unavailable at a site, the algorithm will be forced to allocate to an alternative treatment type that is available.

Minimization - a dynamic randomization allocation scheme to achieve balance on stratification factors. The scheme works without a list and is based on counts of prior treatment group allocations within each stratifying factor level.

Monte Carlo Simulation - a simulation technique that randomly generates values for variables with unknown values over and over again to simulate the range of real-life situations that may be encountered.

Stockout - a failure to supply a subject with the appropriate amount of medication for a randomization or resupply visit.

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This article describes how project managers can contribute to enhanced product delivery through improved manufacturing processes and facilities which deliver value-driven products with lower costs, better compliance, and lower risks.

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Delivering Affordable Innovation: Opportunities in Pharmaceutical Manufacturing Processes and Facilities

by Andrew A. Signore, PE

Introduction

What do the following famous achievements have in common: the Panama Canal, Hoover Dam, moon race, the Chunnel, and the Airbus 380? Answer: they all are remarkable successes which employed innovative technologies, exceptional teamwork, and novel project delivery methods. Each worthy project was clearly motivated and project sponsors understood the risks of failure. Some campaigns were delivered ahead of schedule (moon) and under budget (Hoover Dam). These programs responded to compelling needs for progress. Outstanding results confirmed the value of clear vision, dedicated teamwork, and the resolve to deploy new (unproven) technologies. History agrees the gambles were worthwhile.

How can these inspirational victories help the pharmaceutical industry (pharma) deliver Affordable Innovation (AI), which may be defined as: the global challenge to deliver life-enhancing medicines to a needy, growing, aging population at lower cost and with certainty of fitness for use (quality)? What can we learn from these team successes toward achieving advancement in manufacturing processes and facilities? Start with the consensus that current pharma production models are in stress. A call for delivering AI has emerged as an urgent industry goal and presents an opportunity to improve manufacturing facilities and processes. Former FDA Commissioner, Mark B. McClellan, MD, PhD, described the need for Affordable Innovation in several addresses during his tenure.[1]

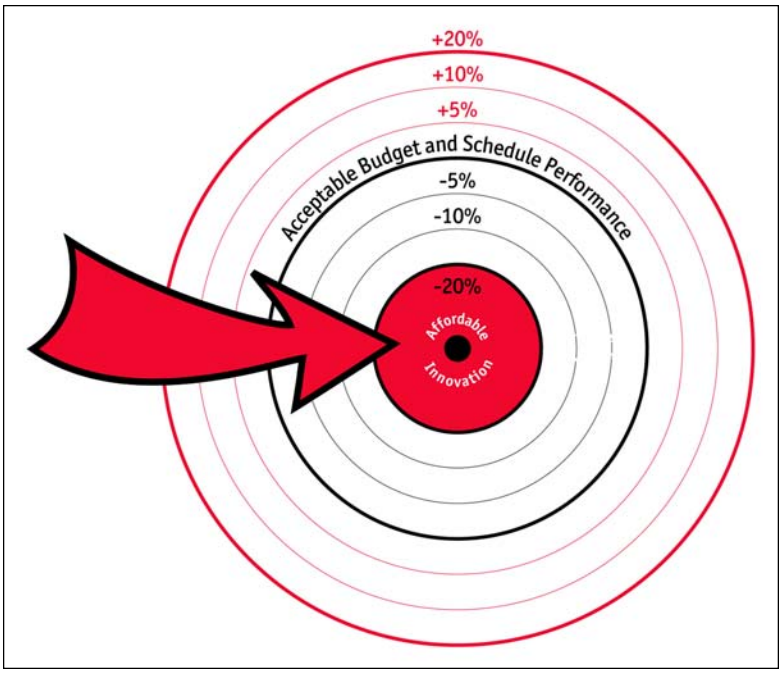

Figure 1. Targeted project delivery success.

An organized drive to deliver AI could be a powerful way to elevate manufacturing performance and build upon recent successes. Some AI has been achieved through processes and facilities which have yielded lower production costs and faster, more flexible facilities with repeatable confident processes (quality). Recent manufacturing advances include wider use of vision systems, continuous processing, real-time control and processes for quick dissolve wafers/tabs, extended shelf life

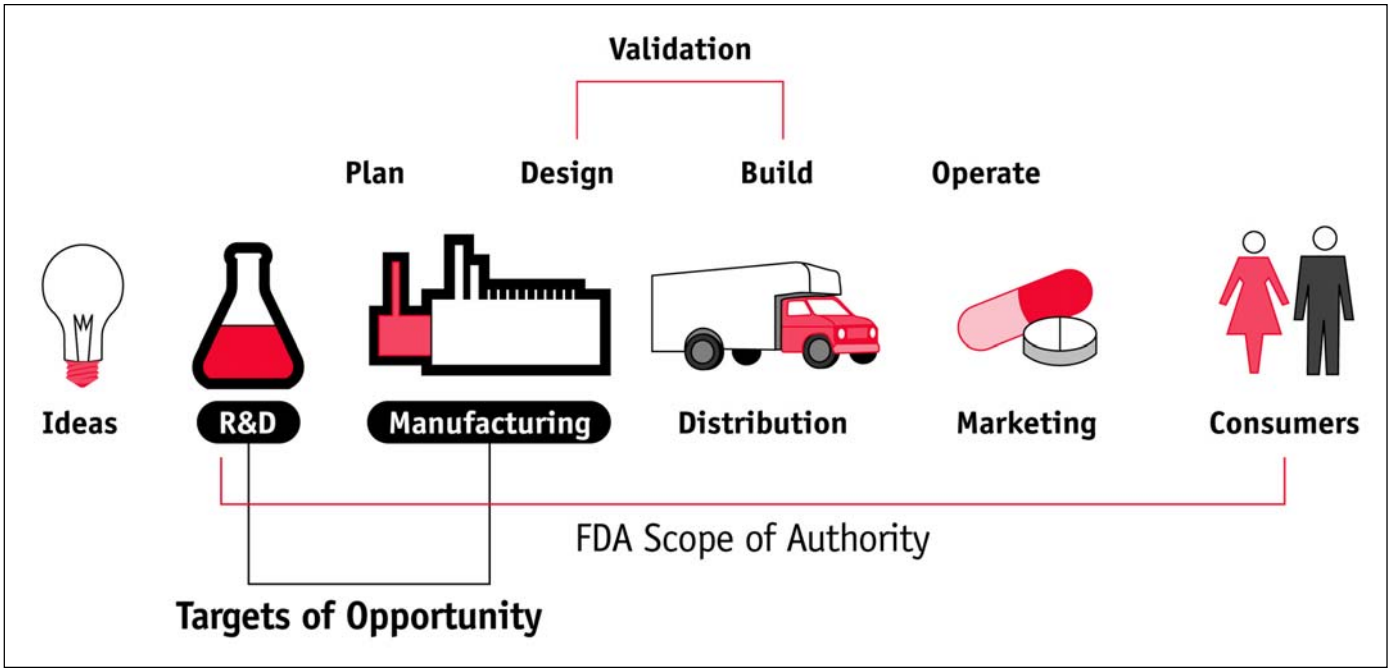

Figure 2. Affordable innovation.

dosages, chewables, and lower cost OTC switches with modified dosing (processes) resulting in lower cost non-prescription presentations.

Can improved (best) manufacturing processes and facilities make a significant impact on society? Will new therapies and novel dosage forms actually drive costs up even further? How can project professionals help contain (and lower) the cost of medicines? Do current pharma manufacturing techniques do enough to discourage quality failures, avoid excessive construction and operating costs, and prevent product launch delays? Successful production relies on responsive and cost-effective processes and facilities. Exploiting new processing technologies will demand clearer knowledge of underlying processes, innovative project delivery approaches, and a culture of continuous improvement to further contain production costs. Current project delivery methods include too many quality related, time-consuming activities with wasteful efforts to satisfy "perceived" compliance mandates. Examples of project delivery waste include delays due to burdensome equipment inspections by owners imposing too many homegrown standards on vendors, overlapping and inefficient commissioning/validation efforts, costly field rework due to inadequate documentation, and under-coordinated (over planned?) field verifications. Significant construction capital could be saved with innovative, yet simplified project delivery methods such as design/build and broader use of pre-engineered, pre-tested systems. Project schedules can be compressed through more effective project delivery methods driven toward clear and compelling goals.

Pharma could issue a "call to arms" with a great urgency mustered to deliver more value through confident and efficient manufacturing. A vigorous campaign can be waged to deliver to consumers. The mission is to introduce improved manufacturing processes and facilities, which deliver value-driven products with lower costs and better (prudent) compliance at lower risks. The FDA's Risk Based Approach (Sept. 2004)[2] final report encourages these outcomes. Such operating economies would allow capital to shift to other critical business activities, including R&D of efficient technical processes to meet the demands of new therapies such as bio-derived, custom gene-sensitive medicines. A more confident, less costly supply of valuable medicines would become available to the consumer.

Current Situation

The pharma industry is under enormous public pressure to find ways to lower costs and assure the effectiveness of life-enhancing medicines. Daily headlines are strong reminders of the wide spread and political nature of this struggle.[3] Recent vaccine shortages due to manufacturing failures reinforce the drive for more government intervention. High profile product recalls strain an industry, which must maintain the consumer's loyalty while publicizing the increasing costs for product discovery, development, and regulatory compliance. Government leaders will continue a very public debate as the argument grows for greater industry reform. The industry is responding to the challenge. Consolidations, mergers, acquisitions, outsourcing, advertising, and supplier alliances are increasing strategies to provide more leverage and economic opportunity. Manufacturing (processes and facilities) also can contribute with safer, confident manufacturing and lower cost, faster response times, and higher value propositions to consumers.

Novel dosage delivery forms, highly specific targeted therapies, bio-derived therapies, and med device (combo) GMP products are examples of promising new products, which will require complex manufacturing processes and facilities. The shift to outside contract manufacturing can defer certain

capital costs and reduce operating risks for larger firms. While this strategy is widely accepted in oral/solid dose manufacturing and packaging, outsourced biotech production is not yet practical. A new world of generic/contract bio-processing is emerging with the need to establish bi-equivalency standards to support the movement. There is also dialogue on projected capacity shortages of bio-processing and sterile filling facilities to accommodate expected demand. These dynamic issues influence manufacturing processing and facility strategies and demand creative approaches to meet the challenges for AI delivery.

Traditional pharma manufacturing costs consume 15% to 30% of annual sales revenue. Complex new processes and facilities such as bio-production are very expensive, costing $1,500 to $2,000 per square foot of production space, and requiring three or more years to design, build, and validate. Traditional, oral-solid dosage facilities can cost $200 to $400 per square foot and require 12 to 24 months to deliver. Recent materials inflation (lumber, steel, etc.) has driven US construction costs up about 10% (in 2003-04). Soft costs for design activities for GMP production facilities consume 8-10% of the total construction budget. In recent years, a similar amount has been devoted to compliance documentation and commissioning, qualification, and validation of facility and processes. These efforts are time consuming and expanding, as process complexities demand higher levels of automation/control and related demonstration.

Many commercial scale pharma processing technologies (coating, drying, containment) have been borrowed (and improved) from other batch industries (candy, food, electronic). In spite of this history of sharing, there is a widespread under-appreciation for how other industries maintain Six Sigma quality levels and introduce new processes. This condition offers a rich opportunity for pharma manufacturers to learn quickly from others. A counterpoint is that other industries do not have the FDA with strict mandates for documentation and validation, which present obstacles (cost and schedule) for innovation and economy.

Project Management Leadership

Project Managers (PMs) can help the organization achieve the strategic imperative to deliver value. With economic stakes and implementation obstacles rising, how do pharma project professionals deliver the progress and accelerate the journey toward improved facilities and processes? PMs can help the industry deploy new technologies, some from related clean "batch" industries, vendors, suppliers, and system integrators, as pharma manufacturers' address the challenges of producing novel therapies and new dosage forms in confident, cost effective ways. PMs are natural problem solvers and integrators. They also need to be opportunity seekers, willing to try new approaches and committed to mustering the necessary enterprise support for introducing innovation. Many PMs are very busy and challenged to "sell" new approaches to their organization, especially as time and budgets get more restricted and risks (costs) of failure grow higher in terms of product recalls,

Top 10 Do's and Don'ts

Here are some suggestions on how to pursue the achievement of AI through better manufacturing processes and facilities.

Don'ts

10. Aggressively cut capital spending and cheapen projects to the point where operating costs rise and flexibility to accept innovation is significantly diminished.
9. Tighten up procurement practices so much that service providers cannot earn enough profit margin to sustain service levels.
8. Reduce outlays for internal training and development while expecting brighter contributions from your staff.
7. Over shift commercial risks to suppliers and soft service providers who are not able to accept the pressure of penalties and destructive low margins.
6. Don't share your organizational goals and strategies with your supply chain. Keep them a well-guarded secret.
5. Keep manufacturing process advances to yourself and never discuss in advance with the FDA or share with peers.
4. Camouflage destructive procurement policies as "preferred" service agreements, which do not align reward structures of supply chain members.
3. Cut back on facility maintenance outlays and staffing levels in response to near term cash management issues, yet expect excellent quality and lower operating costs.
2. Over rely on management consultants who can elegantly describe intellectually appealing improvement projects, but do not focus on implementation and delivery.
1. Over spend on manufacturing automation systems which promise labor savings and quality enhancements without establishing the support staff to sustain the new complex operations.

Do's

10. Thoughtfully eliminate non-productive efforts (waste) to commission, qualify, and validate facilities and systems.
9. Explore imaginative ways to share risk and rewards with service providers which reduce acquisition costs and raise efficiencies for all parties.
8. Experiment with single source project delivery (design/build/validate) on a few projects and observe possible economics.
7. Share significant project goals with supply chain providers (A/E/CM and key vendors/Subcontractors) to attain alignment and better teamwork.
6. Explore "soft" improvement alternatives in revised methods and manufacturing approaches, which could avoid heavy capital outlays. Reduce administrative burdens and explore creative (adaptive) review of facilities which could avoid/reduce "hard" solutions.
5. Drive toward higher utilization of existing assets while planning for new (improved) facilities and systems.
4. Benchmark and learn from other industries. Gather/apply lessons from manufacturers in other clean, batch, advanced businesses.
3. Collaborate with advanced equipment vendors/system integrators and leading designers/builders to identify and deploy cost saving opportunities and promising new manufacturing techniques.
2. Increase training and development activities for technical and business applications, especially for project managers who you expect more from in order to gain leverage from the supply chain.
1. Establish a budget to improve manufacturing methods. Do more R&D on applied processing approaches. Name a chief process technology officer/director.

Delivering affordable innovation.

fines, and negative publicity.

PMs can start by demanding clearer project goals. Better definition and more thorough development of project scope will improve the efficiency of deployed capital. PMs must seek clarity as they gather the input and support of management and key project stakeholders. Only stouthearted, aggressive, and committed individuals need apply. When scope clarity diminishes, the program invariably suffers from inefficiencies, misdirection, misunderstanding, and waste. Fortunately, opportunities are improving to support enhanced team communication, dialogue, and data sharing. PM tools are getting better, simpler (PCs and Internet ASPs) to use and offer cost effective support for project management.

Pharma does not have the strongest legacy of leadership in manufacturing innovation and engineering supremacy when compared to other tech driven industries. Some processes and techniques have been borrowed (some improved) from batch processing industries. If pharma is to make significant progress to deliver more AI, a nurturing culture of process innovation is needed. Top technical and PM talent can be developed within a progressive atmosphere of advancing the application of promising new techniques (best manufacturing practices).

Knowledge is Power

Knowledgeable project practitioners who are well grounded in production technology and GMPs and have the drive, team mindedness, and strong communication skills can make a difference. PMs with a solid background in GMP production processes, industrial pharmacy, quality control, and related operational activities make very effective practitioners. PMs could get better grounded in the basics with intensive field and factory training assignments to expose relevant practices. Job rotation, a fading yet good practice, can quickly (relatively) help the PM gain an effective working knowledge of production fundamentals.

Better project results will flow from business-aligned project practitioners who are skilled in modern PM techniques. Better-educated, competent PMs will lead outsourced consulting and design/construction teams to better outcomes. This process begins by raising skills and proficiency levels through training and formal demonstration of competency (testing) through certification programs. The Project Management Institute (PMI) offers a PM program. ISPE and other pharma associations provide a growing curriculum of training/development programs in pharma manufacturing. Companies committed to developing highly trained, motivated, and well-rewarded professionals will gain strategic advantage in the quest to deliver AI.

Project Delivery

Smarter project delivery practices can support the accelerated achievement of AI. There are opportunities to shorten project delivery cycles and to achieve lower first cost investments. Business friendly plants and processes will cost less to operate and can flexibly deliver desired products with consistent output. Smarter project delivery practices include use of pre-qualified, preferred designers and equipment suppliers, integrated design/build/validation contractors, and incentive-based procurement with alliance partners. The project management challenges here are clear and well understood. Assembling teams of qualified owners, designers, suppliers, and contractors who are focused on clear economic and technical goals also are better practices. Deploying "standard" designs and industry accepted "guides," such as ISPE's Baseline® Guides[4] Series and recent FDA guidance such as for Sterile Drug Products[5] also can shorten cycles and encourage efficiencies. Armed with adequate budgets and chartered to seek value, these teams can drive toward outstanding results.

The risks associated with embracing novel technologies and project practices are manageable. However, empowering project teams in new ways can be upsetting to traditional organizations. Deploying project delivery methods to obtain single-source responsibility is a worthy new approach to achieve lower cost and better schedules. Using skid-mounted processing units (tools) and other pre-engineered, modular techniques offer new means to achieve economic goals. Benchmark studies of relevant "related" facilities and processes can identify solutions that could accelerate the use of new techniques at acceptable risks. Driving project purchasing toward "target costs" can motivate teams to innovate. Pre-established facility costs, goals, and even better, product costs, will focus key decisions and drive behaviors toward "value" approaches. Time and budget pressures will continue to challenge the implementation of new practices.

Project Managers

Talented, well-experienced project team members are a key to better outcomes. Most practitioners learn by "doing," often taking many years to develop expertise. Training, development, and mentoring programs, while generally under-utilized, offer opportunities to compress the learning curve. Based on an accepted body of knowledge and practices, certification processes appear to be growing throughout project delivery communities. ISPE, for example, has been actively studying the development of a professional certification program to encourage learning and help the industry recognize the value of contributions from individuals who have demonstrated their competency in the basics of their job. PMI has developed a Project Management Professional (PMP) certification which has certified more than 50,000 individuals within the last 20 years. Some pharma organizations have defined formal technical career paths to acknowledge the value of project contributions and encourage individuals to continually learn, advance, and be rewarded for their personal development and achievements.

Sharing information among peers is also important for manufacturing advancement. Professional societies and training organizations need to offer more opportunities for individuals to meet, discuss and exchange ideas. More is also needed to promote networking among pharma professionals and with other benchmark industries who manufacture through clean, advanced processes. The exchange of practical

technical information could be further encouraged. Establishing more "peer-reviewed" manufacturing publications also would support enhanced information transfer. More networking opportunities for professionals to attend, participate, share, and lead information exchanges, are also valuable ways for individuals to learn and grow, to the benefit of the industry, and ultimately, the consumer.

Supply Chain

Service providers who bring value added contributions are essential to achieving AI. Professional designers and builders routinely provide critical services to the pharma industry. Most design firms are small to mid-size groups, relatively thinly capitalized, and experiencing reduced profit margins over the last five years. These firms are expected to bring a great deal of skill and experience to pharma manufacturing projects. These providers also are having difficulty attracting top talent and training their staffs. Given such dynamics, fundamental change is needed to strengthen the design community. Builders (construction managers) tend to be larger than design firms with some national/international presence. However, they too are competing fiercely for shrinking fees and in weakened position to train staffers or conduct R&D on much needed improvements to traditional construction methods.

Recent procurement (sourcing) practices by pharma have included a growing use of alliance agreements with A/E/CM service providers. These "partnership" strategies intend to reduce acquisition costs and encourage efficiency. Most programs seek discounted fees and promise lower service provider marketing costs. As pharma continues to streamline in-house resources, a greater reliance on outsourcing for project delivery necessarily raises the dependence on good service. A delicate balance is needed between the pursuit of economy while maintaining a healthy service group industry, one capable of earning acceptable profits necessary to recruit, retain, and develop the needed talent to provide excellent service.

Process equipment and systems integrators are also key elements in the supply chain as they provide valuable knowledge and tools for effective manufacturing. Certification of key process equipment and system suppliers could save millions of dollars and months of project delivery time. Current practices have owners applying multiple quality standards on equipment vendors who accommodate a steady stream of owners' descending on vendors' shops to apply varying demands, often on "proven process" technologies. The practice is wasteful yet well meaning in terms of compliance and risk management. Vendors can bring more value to owners as closely coordinated allies. Unfortunately, low profit margins and tight buying practices do not encourage collaboration. Vendors also have limited capacity to conduct valuable R&D and application advancement.

Barriers to Success

Progress requires clear vision and long-term commitment. A short list of some barriers to success for achieving AI is worth exploring. Pharma devotes more resources to marketing and less toward basic engineering and manufacturing process development. Technical advancements needed to deliver AI will require sustained investments and creative, leveraged collaborations. Certain internal costs may actually rise to accommodate these investments, thus further aggravating profit margins. Some companies are increasingly adopting outsourcing as a part of their strategic approach to manufacturing. The organizational challenge of process advancement may prove difficult to shift to vendors, suppliers, and contractors who compete for "low bid" awards and struggle with their cost models. Companies are now outsourcing some manufacturing to entities that typically earn lower profit margins and may not be well positioned to support tool development and the organizational demands of technical advancement. These strategies address shorter term cost issues, but may not achieve all goals for innovation in the longer run.

Pharma has many senior leaders with marketing, sales, and general management backgrounds, leaving a dearth of engineers and scientists in top management. Top tech schools and talented graduates have moved on to other, perhaps more glamorous and rewarding fields of study at the expense of basic engineering, process development, and technology. Few universities teach pharmaceutical manufacturing or engineering specialties directed toward unit operations and processes. Other challenges include project managers who are sometimes under rewarded and do not enjoy "obvious" career paths. Constraints on time and costs also may be driving management to compress decision cycles. The time allowed to engineer and deploy technical advancements is shrinking. In this environment, learning time is reduced and risk taking may be discouraged with novel approaches, which require time to implement, refine, and improve.

Pharma manufacturing typically consumes less cost than sales, marketing, and research.[6] This spending balance may not provide enough resources to achieve AI goals. These priorities may shift as operating costs and potential penalties of manufacturing failures (recalls) are encountered. As manufacturing costs are likely to rise in response to processing complexities, the organization may adopt new priorities for capital. Corporate groups are also emphasizing focused sourcing and acquisition processes as they seek discounts and preferred treatment. These strategies may not encourage innovation over cost of supply. In addition, some companies have reduced technical training outlays leaving more to an individual's resources to pursue their own personal career development.

Recommendation

Over the coming decades, unprecedented sums will be devoted toward R&D of novel medicines and innovative delivery systems. While the number of new chemical entity approvals by the FDA has been trending downward, we can be assured that in the years ahead, there will be hundreds of new product introductions, many with advanced process technology and complicated facility requirements. The time is right to respond to the pressures coming toward manufacturing, in-

cluding the people, the facilities, and processes that will be required to sustain a superior product flow for the enterprise, as well as achieve the goals of AI for society. New complex facilities and technologies will require effective teams for successful implementation among groups of designers, suppliers, innovators, builders, validators, and owner-maintainers. The FDA has recently fueled the dialogue through promised new GMPs, PAT, and other initiatives,[7] which promote risk-based strategies and quality outcomes with a sound business alignment. The time is at hand for pharma to boldly seize the opportunities to deliver AI. Mustering the organizational "energy of activation" is possible and necessary for "breakthrough" results in manufacturing. One approach could be for pharma to promote enhanced AI delivery through group funding of "technical" institutes who conduct cost effective R&D to advance processes and project delivery methods to be shared among manufacturers. Could pharma achieve cost and quality advancements like those in microelectronics and certain food industries? History has consistently rewarded those entities with clear vision and the team resolve to see programs through to successful completion.

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This article presents practical risk-based advice regarding the implementation and management of computerized aspecis of a Building Management System.

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Position Paper:
Use of Building Management Systems and Environmental Monitoring Systems in Regulated Environments

by the ISPE GAMP® Forum, Special Interest Group

Building Management Systems (BMS) have evolved over many years, along side the development of Heating, Ventilation, and Air Conditioning (HVAC) and other building system technologies. Increasingly, BMS technology has adopted control system architectures and philosophies to satisfy the need for advanced automation. The consequence has been that BMS is widely deployed throughout healthcare companies with modern day solutions being based on standard software and hardware design. Further, a BMS provides standard inbuilt functionality, based on many years of building automation solutions. As such, a BMS is often an effective solution to cost conscious building management strategies. The implementation of a modern day BMS brings several benefits to organizations including, but not limited to:

- effective control of building related processes and equipment
- real time visibility of building management system performance
- early warning of process deviations
- predictive maintenance planning
- centralized and/or remote control of facilities and equipment
- optimization of utility costs
- secure management and storage of process and equipment performance data
- implementation of standardized building management strategies
- availability of state of the art and expandable technologies
- effective system management and support

The requirements pertaining to the use of BMS within regulated environments has been debated within the healthcare industry for many years with differing views remaining today. Several reasons are cited for this discussion, the commonly recurring themes being:

(i) BMS are used to control, record, monitor, and alarm a variety of processes of varying risk to the attributes of the manufactured product (e.g., purity, safety, quality, and efficacy).
(ii) Product characteristics vary widely, and therefore, similar BMS implementations may have different product risk.

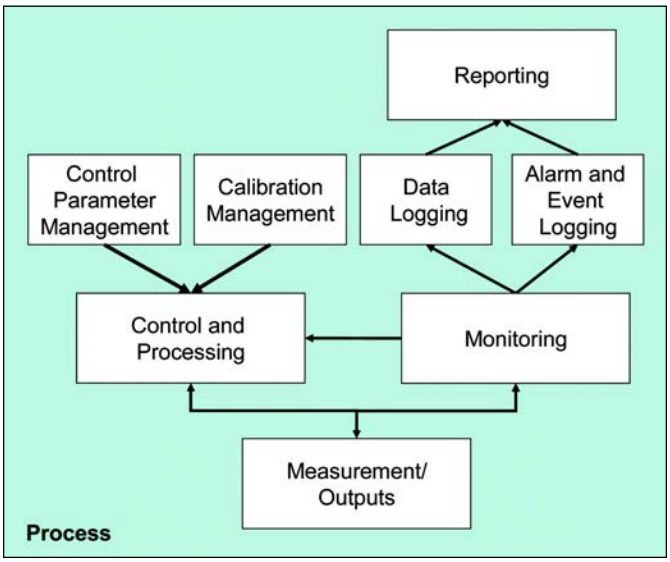

Figure 1. BMS functional model.

(iii) ability to readily detect product attributes downstream of the process
(iv) BMS often cover both regulated and non-regulated processes concurrently.
(v) BMS can sometimes be difficult and expensive to validate, especially when deployed centrally, utilizing older technology, evolved over a period of time
(vi) There are a number of different implementation strategies that impact the criticality of the BMS (e.g., use of independent monitoring systems)

A number of topical issues are considered by this position paper including:

(i) the need to validate BMS controls when validated/calibrated independent monitoring is in place
(ii) relationship between BMS risk and process/product risk
(iii) good design practices for new BMS
(iv) good Engineering Practice
(v) mitigation options for existing BMS
(vi) electronic record implications

The ISPE GAMP® Forum has developed this position paper to provide practical risk based advice regarding the implementation and management of a BMS within regulated healthcare industries. In drawing its conclusions, this position paper attempts to utilize and build on existing guidance currently available within industry, in particular ISPE Baseline® Guides.

This position paper focuses on the computerized aspects of BMS; however, the principles and issues raised by this position paper also may be beneficial when considering associated equipment (e.g., HVAC and other examples). Within the context of this position paper, the term 'process' relates to environmental control and monitoring, storage condition control and monitoring, and utility production, etc. The examples used in this position paper relate to environmental control.

It is recommended this position paper is considered within the overall context of the ISPE GAMP® Good Practice Guide: Validation of Process Control Systems.

BMS Scope and Definition

BMS may be used as a collective noun for a range of computerized systems including Programmable Logic Controllers (PLC), Supervisory Control and Data Acquisition Systems (SCADA), Distributed Control Systems (DCS), Outstations/Controllers and Instrumentation.

BMS may be deployed and managed centrally as a large network of systems that may comprise different vendor products, or as a low complexity standalone system.

The type of computerized system deployed and the scope, size, and complexity of the system will determine the level of difficulty in demonstrating that the system is fit for purpose.

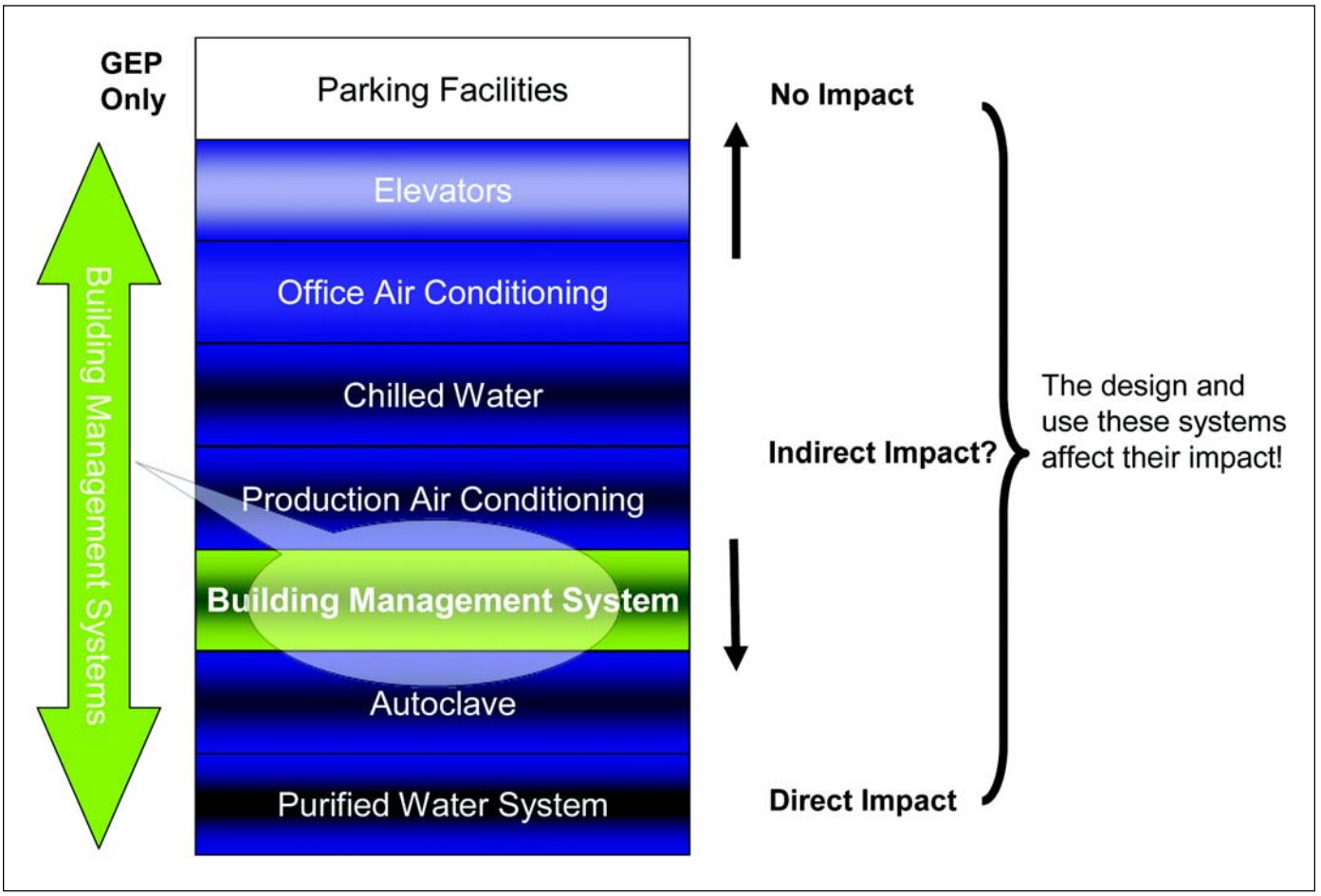

Figure 2. Adaptation of the ISPE Commissioning and Qualification Baseline® Guide Impact Spectrum.

Some of these issues are discussed later; however, initially this position paper focuses on a functional model of the BMS rather than its physical architecture - *Figure 1.*

Instrumentation and Devices

Instrumentation and devices communicate measurements and status information to the control and monitoring logic usually in the form of digital and analogue inputs. Such information is interpreted by the control logic in order to deduce control actions that are used to refine the process control. The installation, calibration, and tuning of such instrumentation is critical to the process control and monitoring.

Control

Control is typically provided by assembling standard control functions, e.g., control loops (P&ID or Ratio) and Start/Stop functions, into the required control scheme. Control and calibration adjustment parameters are inputs to the control scheme that establish process characteristics, process timings, and responsiveness of the control scheme.

Monitoring

Feedback from instrumentation influences the control scheme that will respond, in order to maintain process parameters within configured limits. Integrated and/or independent monitoring functions scale and check inputs against pre-configured statuses and limits, setting alarm conditions when deviations are detected.

Control Parameter Management

Control Parameter Management enables users to change control parameters in order to achieve the desired characteristics of the process, e.g., temperature and humidity setpoints, tolerances, time spans, alarm limits, dynamics. Such parameters are usually entered via centrally/locally located graphical user interfaces or local/remote devices. Control parameters are usually configured and tested during initial system implementation and modified following process change.

Calibration Adjustment Parameters

Calibration adjustment parameters are established and configured during periodic calibration of instruments.

Data Logging

Data logging (historical and point in time) enables the capture and recording of process events and data in order to enable process optimization, investigation, or monitoring. Critical data often forms part of regulated records such as batch records.

Alarm and Event Reporting

Alarms typically warn of pending, actual, and continued deviations from process limits. Events typically provide indication that a process step or condition has been achieved (e.g., start-up complete). Alarms and events may be used to indicate the need for maintenance and/or to report process deviations. Alarms and events may be logged in addition to display and/or printing. Alarm annunciation and reporting may take several forms depending on the purpose and priority of alarms (e.g., screen alarms, email, pagers, buzzers, printouts).

In terms of core functionality therefore, the BMS is no different to any other process control system. The nature of the processes controlled and monitored and their impact on the manufactured product is therefore what defines the BMS criticality. As can be seen from the list below, these processes vary in risk to product:

- Production Facility Heating, Ventilation, and Air Conditioning
- Office Heating, Ventilation, and Air Conditioning
- Laboratory Heating, Ventilation, and Air Conditioning
- Water Purification
- Cold Storage Facility Control and Monitoring
- Fire and Security Alarm Systems
- Energy Management

A basic premise of this position paper is therefore established; *"The criticality of the BMS is dictated by the impact of the process parameters being controlled by the BMS on product purity, safety, quality, and efficacy, not the functionality of the BMS itself."* A blanket statement of whether BMS should or should not be validated is therefore invalid.

It is essential that the impact of the BMS controlled process on product attributes is clearly determined by a team of knowledgeable people that should include Quality Assurance and Engineering.

Definitions

The definitions below are derived from ISPE Baseline® Guide, Volume 5 Commissioning and Qualification and ISPE GAMP® 4.

Good Engineering Practice (GEP)

Established engineering methods and standards that are applied throughout the project lifecycle to deliver appropriate, cost-effective solutions.

Process Validation (PV)

Establishing documented evidence which provides a high degree of assurance that a specific process consistently produces a product meeting its pre-determined specification and quality attributes.

Qualification Protocol

An individual detailed document that describes the system under consideration, the testing plans, the acceptance criteria, and the test results that ensure that a system is installed and operates in accordance with predetermined specifications.

Regulatory Insight

Having established that the process should be the focus of

risk assessment, it is possible to review regulatory citations over a number of years in order to identify regulatory concerns associated with typical processes controlled and monitored by BMS.

US FDA Warning Letters

Table A summarizes example citations from US FDA Warning letters. While not all of the Warning Letters listed indicate the use of a BMS, the processes and equipment referred to are typical of those associated with BMS.

When reviewing regulatory citations, care should be taken because the context within which the citation is raised is not always apparent. Several of the citations indicate the importance of monitoring key (environmental) parameters against predetermined limits such as temperature, humidity, and differential pressures. Although predominantly focused on

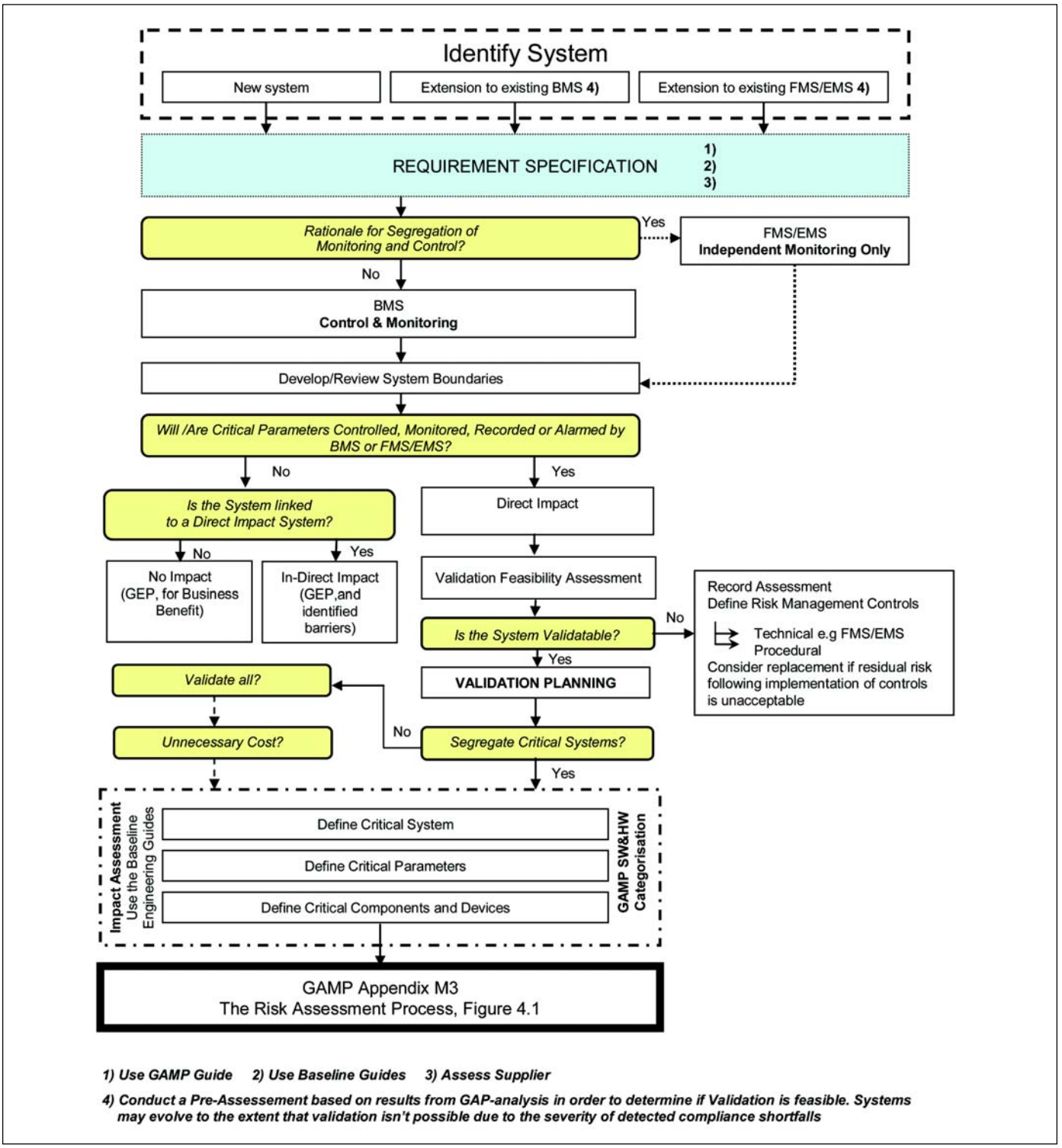

Figure 3. Decision tree.

monitoring, some of the citations indicate a lack of validation/qualification of controls although the criticality of the cited systems to product attributes is not clear from the citation.

Although access to specific European regulatory observations is restricted, anecdotal evidence from industry forums such as ISPE GAMP® Forum suggests that a number of companies have been challenged by European regulators about control of their BMS. Table B provides a summary of regulatory citations from the UK Medicines and Healthcare Product Regulatory Agency (MHRA), published February 2003. Although these observations reflect a fixed period in time, they serve to demonstrate that processes controlled and monitored by a BMS, and where implemented, independent monitoring systems are considered important by regulatory authorities.

The MHRA inspection findings reiterate the importance of monitoring critical (environmental) parameters while also demonstrating the importance of sterility assurance and cross contamination risks.

By raising issues relating to temperature, humidity, differential pressure, containment, and sterility, it might appear natural to conclude that, as a BMS often controls equipment that maintains such parameters, the BMS must be critical itself. However, the criticality of the BMS can be determined only through a risk assessment that considers the consequence on product attributes of failure of a parameter. The probability of impact and ability to detect such a failure also must be considered. ISPE GAMP® 4, Appendix M3 provides guidance on risk assessment.

Review of Existing Industry Guidance

The ISPE Baseline® Guides provide guidance on a number of BMS related issues. Table C, Summary of Current BMS Guidance Related documents, highlights some of these issues.

The extracts reviewed are mainly based on Environmental Control and Monitoring Systems (e.g., HVAC), as much industry discussion emanates regarding these systems. As with the review of regulatory citations, some key messages can be derived from the guidance:

- It is important to monitor and where necessary log critical parameters.
- Aseptic processes should be considered as direct impact.
- Consideration should be given to validation of direct impact systems.
- Independence of monitoring systems from control may simplify validation considerations.
- Monitoring systems may range from manual, hand held monitoring devices through to computerized Environmental Monitoring Systems (EMS).
- The selected monitoring method should be based on criticality of monitored parameters with respect to product attributes.

Figure 2, reproduces a figure from the ISPE Baseline® Guide, Commissioning and Qualification. The Baseline® Guide diagram largely relates to processes; however, a BMS is a computerized system used in the control and/or monitoring of such processes. As such, a BMS may better be considered as a sliding scale of impact. Clearly, the diagram indicates the need for increasing Quality Assurance rigor as process criticality increases. As such, where a BMS is used to control and/or monitor such processes, the criticality of BMS components increases in line with process criticality. As with all computerized systems, the extent of the BMS criticality is determined by the influence of the BMS on critical product attributes.

Citation	Clause (where stated)	Warning Letter Date
"Qualification and control of the ambient temperate and accelerated temperature stability rooms is inadequate ....."	211.166	July 01, 1999
"The alarm system that communicates, records, and controls alarms such as air balance and temperatures for production, warehouse and testing areas lacked validation documentation"	Not stated	January 2001
"No evidence that your firm investigated temperature failures that occurred for the incubators and refrigerators"	211.22(a)	January 16, 2001
"There is no written procedure in place for, nor is there any testing performed, for the environmental monitoring ....."	211.160(b)	
"Failure to validate equipment for example ..... Failure to document the rationale behind established alarm times to monitor the specified differential air pressures within the manufacturing areas"	211.168	March 02, 2001
"You have failed to validate the HVAC system used to control temperature and relative humidity in your manufacturing and warehouse areas". "No formal specifications for temperature or humidity have been established for these areas." "You were noted to have portable chart recorders for monitoring of temperature and humidity in Suites 1 and 2 and one recorder was noted in the warehouse." "A wide range of temperatures and humidity was noted in our review of the data from the monitored areas. ...."		August 14, 2001
"IQ and OQ which support .... production .... The list of deviations include ... replacement of HVAC systems and its control system." "IQ and OQ which supports coating ..... list of deviations and resolution plan include failing acceptance criteria for temperature and pressurization flow direction ..... updating control system ... converting to a... control system" "IQ and OQ which supports coating ..... list of deviations and resolution plan include failing acceptance criteria for temperature, HVAC alarm and interlock testing ....."		February 15, 2002
"No documentation of the validation of the air handling system or the water system used in production"	211.42	October 10, 2002

Table A. US FDA regulatory citation examples.

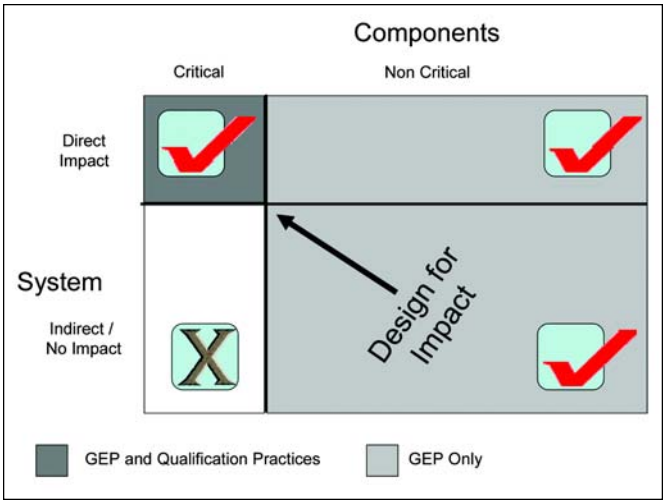

Figure 4. ISPE Baseline® Guide, Commissioning and Qualification – System/Component Criticality.

Risk Assessment

Review of regulatory citations and industry articles has illustrated the importance of risk assessment to determine the criticality of BMS components and functions and where implemented, independent monitoring systems. Figure 3 describes the decisions to determine the appropriate strategy for new and existing systems.

The key to the risk assessment is in understanding what the critical process parameters are. In the context of this position paper, critical process parameters are those parameters that have a high probability of affecting product attributes if they deviate from stated limits for a defined period of time. A functional risk assessment in accordance with ISPE Baseline® Guide to Commissioning and Qualification and GAMP® 4 will determine the consequence of functional failure, probability of impact, and ability to detect product impact. When conducting the risk assessment, there are many considerations that need to be made when determining the risk, some of which are listed below:

- criticality of the product (e.g., final product, intermediate, bulk)
- product characteristics (e.g., is the product hygroscopic)
- probability of a process parameter deviation (e.g., temperature, humidity, airflow) impacting product attributes (e.g., if product temperature is critical to stability, how likely is a deviation in air temperature to affect product temperature for a sufficient duration to affect stability)
- probability of a critical parameter deviation being detected before it could reasonably affect product attributes
- probability of a simultaneous failure of control and monitoring functions
- Is data from a component of the system used to demonstrate compliance with a registered process?
- Is data from a component of the system recorded as part of the batch record, lot release, or other GMP record/documentation?

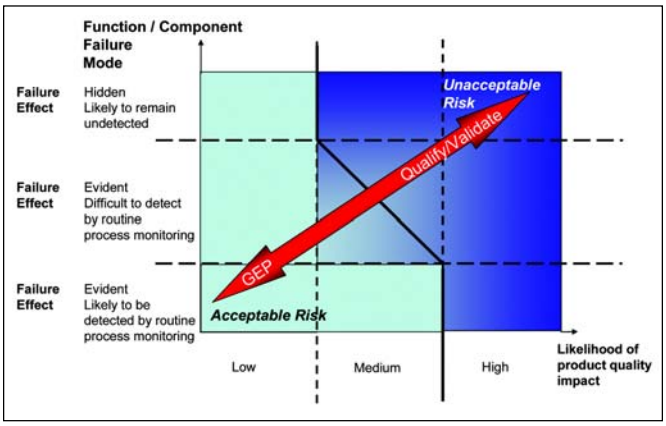

Figure 5. GEP vs. qualification/validation.

When conducting the risk assessment, it is important that individual components and functions of the system are assessed (e.g., alarm annunciation and reporting, instruments, outstations, data historian, network) within the context of their use (e.g., maintenance management, GMP compliance,). The criticality of the BMS, like any other process control system, is dependent of the criticality of the individual components within the system. As illustrated in Figure 4, qualification should be considered in addition to Good Engineering Practice for critical components of a 'Direct Impact' system.

When determining whether or not to qualify aspects of the BMS and any associated monitoring system, it is important to consider the relationships between the process being controlled, equipment (e.g., HVAC) and the computerized aspects of the BMS. It is important to understand the role of the BMS and associated equipment in establishing and monitoring process parameters and ultimately the impact of such process parameters on product attributes. It is important that each component of the overall computerized system be considered including automated and non automated components and that criticality is not assumed simply by association (e.g., aspects of the process are critical therefore the equipment and automated controls must be critical). Some examples of the relationship between product, process, equipment, and BMS are illustrated below:

- consequential impact (e.g., a raise in temperature may not directly impact product; however, the resultant heat profile may give rise to changes in humidity or particulates)
- parameter relationships (e.g., room differential pressure may not be an accurate reflection of air change rates)
- monitoring strategies (e.g., not all critical parameters may be covered by the monitoring system, such as environmental recovery rates, air change rates, air flow patterns)
- criticality of controlled equipment (e.g., HVAC) may not infer criticality of a BMS (e.g., HEPA filter may be critical, but is not necessarily controlled or monitored by the BMS)
- relationship between control parameters and product (e.g., deviation from control parameter may not impact product quality within a reasonable timeframe)

Validation of process endpoints must be considered, such as

environmental conditions as prescribed by international standards such as ISO 14644 and US Federal Standard 209E.

It is likely as with all systems that any validation effort will be focused on critical functions and components only and that the approach to validation of critical components will be scaled according to size, complexity, and standardization of the component.

Change Control

Change control is essential to any system. Changes to the control strategy must be subject to appropriate GEP and/or qualification practices. In particular, it is important that critical process characteristics are proven following change to control schemes.

Implementing New Systems or Enhancing Existing Systems

User Requirement Specifications (URS) are important irrespective of the GMP criticality of any system. For a complex, centralized BMS, there may be several "users" including engineering, system owners, data owners, and QA. It is important that the needs of all stakeholders are captured in the URS (see ISPE GAMP® 4, Appendix D1, Production of a User Requirement Specification). The URS must clearly define the relationships between the BMS (and independent monitoring systems where implemented) and the process(es) being controlled and monitored.

It is important that each requirement be categorized in order to define whether the requirement is safety critical, GMP critical (Direct Impact), business critical, or otherwise. The categorization of the requirements will help determine the most appropriate approach to implementation each requirement, i.e., GEP or validation.

Figure 5 illustrates that the decision to apply GEP or qualification/validation is determined by combining the likelihood of product impact with the ability to detect, and where possible, correct failure. Guidance on approaches to GEP, qualification, and validation can be found in the following guides:

- ISPE Baseline® Guide Volume 5, Commissioning and Qualification
- ISPE GAMP® 4
- GAMP® Good Practice Guide: Validation of Process Control Systems

Irrespective of the criticality of any system, the principles of validation are important in terms of:

- understanding system operation and capability
- understanding and managing system vulnerabilities and constraints
- verifying continued performance
- managing and verifying the impact of system change
- understanding and managing system accountabilities
- enabling recovery from system failure and disaster

Critical GMP Deficiences 02/04			
CATEGORY	RANKING	NO.	
Sterility Assurance	1	6	
Contamination Risk - Non microbial	2	4	
Design and maintenance of premises	3	4	
Environmental monitoring	4	4	
Contamination Risk - Microbial	5	3	
Serious GMP Deficiences 02/03 Third Country Manufacturers			
CATEGORY	RANKING	NO.	%
Contamination Risk - Non-microbial	1	25	16.3
Contamination Risk - Microbial	2	17	11.1
Design and maintenance of premises	3	13	8.5
Environmental monitoring	5	8	5.2
Serious GDP Deficiences 02/03			
CATEGORY	RANKING	NO.	%
General storage - temperature control and monitoring	1	66	32.2
Cold storage - temperature control and monitoring	3	34	16.6
Premises, equipment, calibration	4	17	8.3

Table B. MHRA, BMS related inspection trends.

Specifying New BMS Functionality

The design of the BMS will determine the ease with which the BMS can be implemented, quality assured, and managed in its operational life. Requirements specifications, design and operational controls may consider the following items in Table D.

Where new (greenfield) systems are implemented, some of the issues raised by this paper may not be relevant. New systems should incorporate, where relevant, the design considerations highlighted by this position paper. Further, business benefits rather than compliance benefits may be achieved through the validation of new BMS. Such business benefits may include:

- verification and consistency of control strategy
- increased clarity of system operation and support responsibilities
- improved system maintainability
- defined system enhancement strategy and capability

Existing Systems

As with new systems, risk assessment will determine the need to implement additional Quality Assurance measures for existing systems. A Gap Analysis should be conducted against company standards in order to determine shortfalls. The risk associated with such shortfalls should be documented and appropriate corrective actions taken. It should be recognized that it may not be possible or practical to fully address all identified shortfalls and some degree of operational history may be used to determine adequacy of system operation and control. Typical shortfalls may include:

- Systems may not have been developed to current quality system expectations (supplier and manufacturer quality

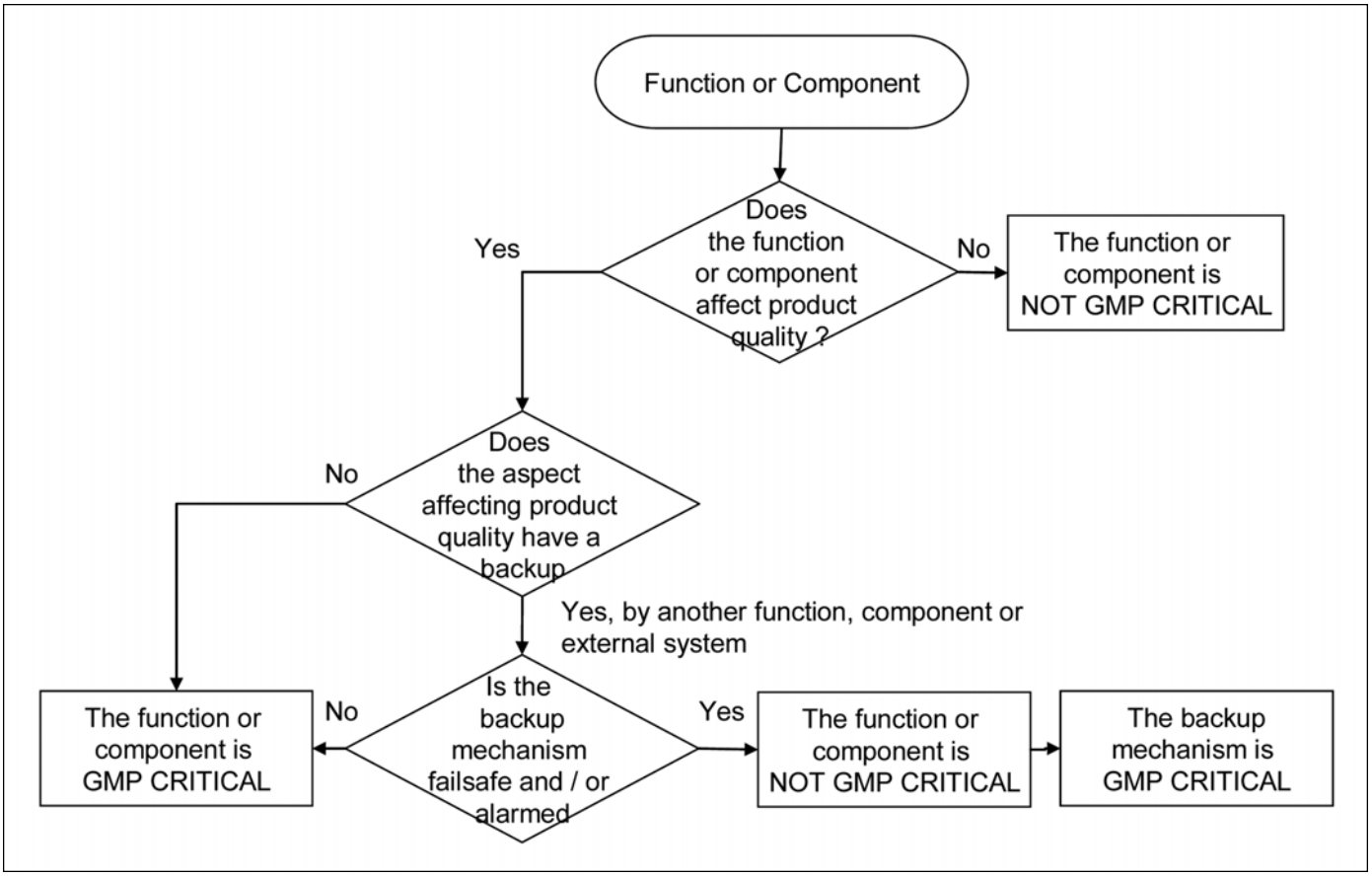

Figure 6. GMP impact and backup systems.

standards).
- Old technologies may be in place that do not allow for implementation of current control requirements.
- Original design may be difficult to modify.
- The scale of technology upgrade required may not deliver acceptable cost/benefit returns.

In such cases, mitigation controls including procedural and where cost effective, technical controls should be considered. Such controls may include:

- redesign (where practical)
- implementation of appropriate automated and/or manual monitoring regimes at a frequency commensurate with risk (including where appropriate validation and calibration)
- implementation of available logical security features (e.g., password controls, review and reorganization of security access rights)
- introduction of physical security controls where possible (e.g., locked cabinets, tamper evident labels, etc.)
- implementation of procedural security measures where technical controls are inadequate (e.g., periodic password change, periodic review of control parameter and alarm settings, control of access to programming devices, periodic review of I/O override settings)
- re-commissioning of areas of the system in accordance with ISPE Baseline® Commissioning and Qualification Guide
- review and adjustment of calibration schedules
- regular system backup

The degree and nature of mitigation controls will obviously depend on the current status of the BMS.

Defining BMS Alarm Strategies

BMS alarms are used to provide information for a variety of purposes including notification of events, pending and actual equipment failures, control limit excursions, loss of controlled conditions. It is important to understand the purpose of all alarms in order that processing and response to such alarms is commensurate with the information being conveyed. For example, an alarm notifying actual loss of critical controlled conditions will warrant a different response to an alarm notifying engineers of the need for equipment maintenance and calibration.

The alarm strategy should consider:

- purpose of each alarm
- priority of each alarm derived from the purpose
- routing of the alarm based on priority
- segregation of high priority alarms from lower priority alarms
- requirements for retention of alarm history

The priority of alarms also will determine who reviews and responds to alarms. For example, where alarms indicate possible product attributes issues, they may need to be investigated by production and Quality Assurance departments. Investigation of such alarms is enhanced when product attributes related alarms are clearly differentiated from other alarms such as maintenance alarms. Such differentiate can be achieved by highlighting product attributes related alarms, routing product attributes related alarms to a dedicated printer or logging device, use of independent monitoring system or otherwise.

Review of Electronic Records and Electronic Signatures

Where the BMS (and/or associated monitoring system) is determined to be GMP critical, an assessment of the impact of electronic records and electronic signatures should be made. A BMS (or associated monitoring system) holds data for a variety of reasons including business management, engineering maintenance, and GMP decision making. The context within which such records are used determines whether they are regulated electronic records or otherwise.

European (Chapter 4, Annex 11, PIC/S), US (21 CFR Part 11), and Japanese (MHLW Guideline) regulations and guidance should be considered as appropriate when determining management controls. Table E defines typical data held by a BMS (and associated monitoring systems) and rationales for electronic records compliance determination or otherwise. The requirements for electronic signatures used within BMS are no different than for any other computerized system.

The risks associated with potential BMS electronic records should be determined in parallel with the BMS functional risk assessment.

Electronic records and electronic signatures considerations should be defined in BMS User Requirement Specifications and verified during design and test activities.

A BMS may be maintained remotely by the BMS supplier or specialist maintenance contractor. Remote access to the system raises questions about the open or closed nature of the system. Controls need to be established that ensure:

- Remote access sessions do not increase vulnerability of the IT infrastructure.
- Security codes are managed by the pharmaceutical organization.
- Remote access sessions are authorized and monitored by

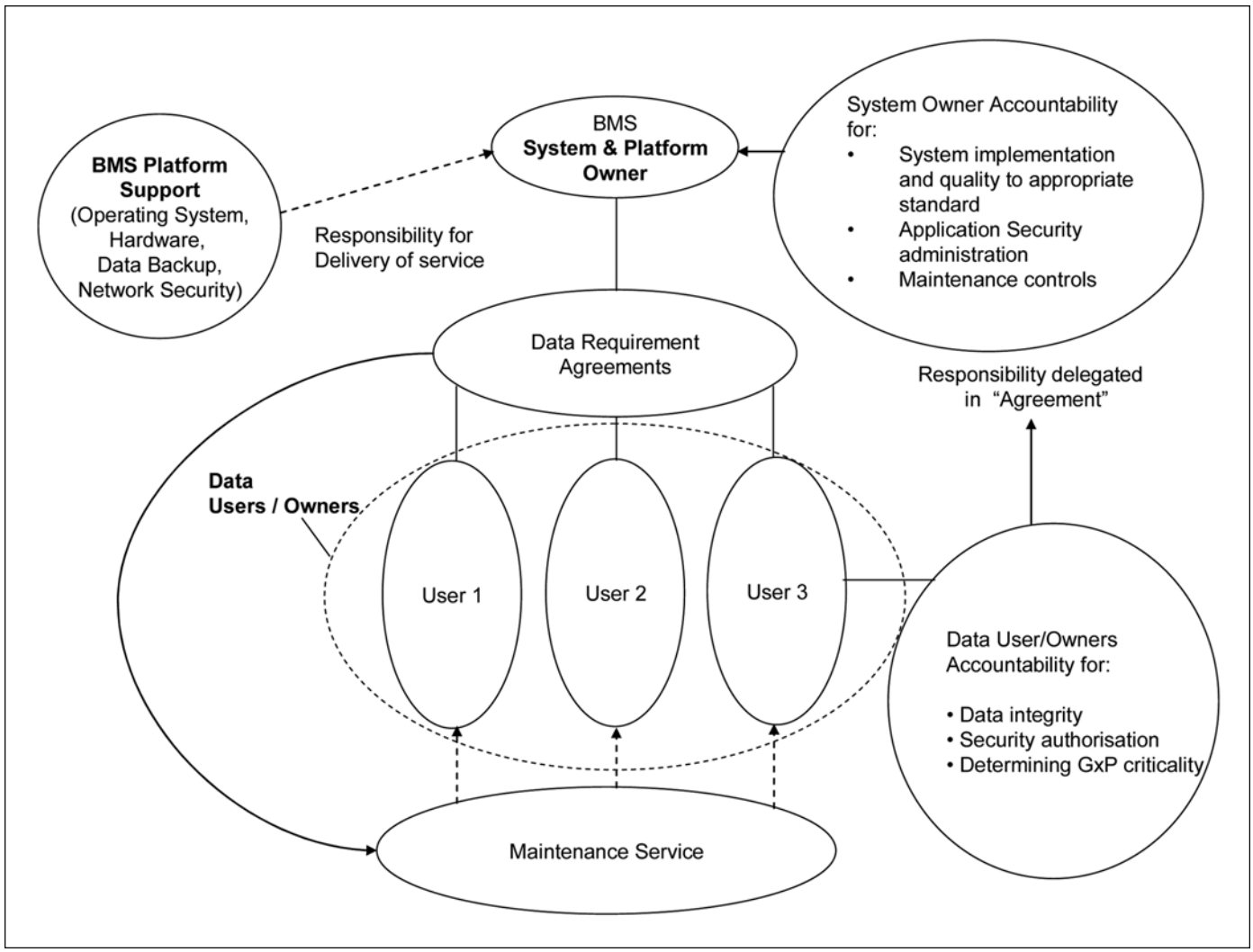

Figure 7. Governance relationships.

the pharmaceutical organization.
- Security audits are conducted to ensure that access controls are not violated.
- Procedures are in place to manage changes and maintenance.

Supplier Relationships

BMS suppliers are integral to achieving appropriate compliance. As with all computerized systems, suppliers may have developed systems prior to the establishment of Quality Management Systems. Suppliers must review current systems and consider practical remediation actions to confirm the quality of systems currently marketed. It is acknowledged that it may not be practical to retrospectively establish design and test documentation for older systems. However, where older systems are still supported, historical performance data should be established to provide a degree of assurance as to the quality of such systems. Such performance data shall be largely based on support records including:

Document	Key Principles	Inference
ISPE Baseline® Guide, Volume 1: Bulk Pharmaceutical Chemicals, Section 6.8 HVAC	Instrumentation should be provided to monitor and record critical room parameters and alarms. It may be possible to monitor, record, and alarm with portable or other instrumentation which is not a part of the HVAC control system in order to avoid validation of proprietary software. It is good practice to monitor the performance of equipment such as fans, coils and control components, but it is not a regulatory requirement, as long as critical parameters meet acceptance criteria. Critical parameters should be monitored, either continuously through the HVAC control or process control automation, or frequently by manual methods. Many commercial HVAC (DDC) control systems provide adequate control, data handling and alarming capability, as long as the system can be validated for critical parameters	Monitoring of critical parameters is important. Monitoring system could be BMS, EMS, portable equipment, chart recorders as appropriate. Avoid controls validation (Bulk Pharmaceuticals). Critical parameters should be monitored at a frequency relevant to criticality of parameters. Monitoring system could be BMS, EMS, portable equipment, chart recorders as appropriate. Component performance monitoring is a GEP issue, not regulatory issue. Where possible to validate HVAC (DDC) for control, data handling and alarming of critical parameters, independent monitoring may not be necessary.
ISPE Baseline® Guide, Volume 2: Oral Solid Dosage Forms, Section 2.4 Extent of Validation	Systems are considered critical, and should be validated when they are either in direct physical contact with the drug product or used to measure, monitor, control or record a critical parameter. Support systems, such a heat transfer systems, electric power and non-process contact water are not critical and need not be validated. The monitoring and control of critical parameters that these support systems affect, however, should be validated	Validate Direct Product Impact Systems. Validate Critical Parameter Monitoring Systems. Support systems do not require validation, however, Good Engineering Practice should be applied.
ISPE Baseline® Guide, Volume 2: Oral Solid Dosage Forms, Section 6.6 HVAC	Instrumentation should be provided to monitor critical room parameters and alarms. It is possible to monitor, record, and/or alarm with portable or other instrumentation, which is not a part of the HVAC control system. Many commercial HVAC (DDC) control systems provide adequate control, data handling, and alarming capability, as long as the system can be validated for critical parameters. However, some commercial grade sensors often are less desirable than industrial grade sensors for critical parameters, from a life cycle cost standpoint, driven by reliability, drift, repeatability, and maintenance cost.	Critical Parameter Monitoring is important (this may be independent automated or manual monitoring). Use of commercial HVAC control systems for critical parameter monitoring may be beneficial if the system can be validated. Quality and accuracy of sensors is dependent on the risk of what they are being used for.
ISPE Baseline® Guide, Volume 3: Sterile Manufacturing Facilities, Chapter 5 HVAC	[5.8.2] ..., it is the monitoring and documenting system that provide "GMP Critical Parameter" data to production staff, hence these systems are direct impact and require qualification studies... It may be preferable that the monitoring and documenting of these "GMP Critical Parameters" should be isolated from any HVAC (Building Management System: BMS) control systems, to avoid qualification complications. [5.8.10] By its nature, the HVAC system serving aseptic manufacturing suite must be a "Direct Impact System", i.e. its failure to perform may directly affect final product attributes. Therefore, qualification, testing, and commissioning, in line with Good Engineering Practice, needs to be considered carefully.	Critical parameter monitoring should be treated as direct impact. Critical Parameter monitoring should be validated. Independent monitoring may avoid complications of BMS validation. Aseptic environments should be considered as direct impact.
ISPE Baseline® Guide, Volume 3: Sterile Manufacturing Facilities Chapter 8 Control and Instrumentation	[8.7.1] Control System Choice HVAC industrial nature in clean room applications may not justify use of PLC or DCS based solutions. Pharmaceutical HVAC can be controlled satisfactorily using HVAC industry control systems. [8.7.2] HVAC Control Systems As the application's scale, complexity, and remote monitoring demands increase, the use of BMS rapidly becomes more cost-effective.	The type of BMS applied is not essential. Business benefit may be derived from using BMS as the scale of the process increases.

Table C. Summary of current BMS guidance related documents.

- reported faults
- risk assessment of reported faults (e.g., potential consequence of failure of reported faults)
- system vulnerabilities (e.g., shortfalls against current industry expectations)
- availability of patches for known faults

BMS suppliers provide support services enabling fault rectification and system enhancement. Such services are provided by remote or on site support. Control and traceability of support services, in particular system modifications, is important. Suppliers are able to enhance client systems and procedures by providing documented, control mechanisms that ensure BMS changes are reviewed, approved, and documented.

Monitoring Systems

The importance of monitoring systems has been established by this position paper and other referenced material. Wingate, in his book *Validating Computer Systems*, uses Figure 6 to demonstrate how backup systems can affect the criticality of the functions

Requirements Aspect	Design Considerations	Comments
System Partitioning	Physically segregate GMP and non GMP BMS	Avoids conflict between GMP and non GMP functions and I/O. Enables boundaries to be put around GMP critical aspects of BMS.
	Logically segregate GMP and non GMP functionality and I/O	Avoids conflict between GMP and non GMP functions and I/O. Enables boundaries to be put around GMP critical aspects of BMS. Must be able to demonstrate that there are no conflicts between GMP and non GMP functions and I/O.
	Segregate (physical or logical) GMP and non GMP databases	Avoids conflict between GMP and non GMP aspects of the system. Not always possible or desirable for operational reasons, e.g., viewing multiple databases.
	Independent local network for BMS	Segregates critical aspects of the system and avoids conflict with non-GMP operations. Security is also easier to manage.
Alarm Handling	Alarm Management strategy defines alarm prioritization that clearly differentiates product quality alarms from maintenance alarms, tolerance alarms and system alarms	Critical process alarms are clearly differentiated from other alarms. Process alarms easily identified. Defined within Alarm Management Strategy
	Separate alarm printouts/logs for product quality alarms	Those alarms requiring Quality Assurance review are differentiated.
Security	Outstation security controls	Prevents inadvertent modification of the control logic and/or critical control parameters.
	Restricted access to maintenance functions.	Minimizes risk of false readings, e.g., through forced I/O settings.
	Workstation multilevel security access.	Ensures that roles can be differentiated and appropriate controls applied, e.g., Engineering Administrator, Quality Assurance, Users, Data Stakeholders.
	Ability to synchronize security settings across the BMS infrastructure.	Changes to one Workstation reflected across all workstations in order to ensure consistency of access from different points.
Instrument Failure Detection	Detection of instrument failure, isolation, manual override.	Enables validation of data input/output and ensuring integrity of process control and monitoring.
Communication Failure	Detection of data transfer failure	Ensures integrity of process control and historical data capture. Ensures integrity of data timestamping.
Data storage failure	Detection of data overload following communications failure or similar events	Ensures that critical events and data are recorded in accordance with design.
Planned Enhancement Capability	Built in expansion to allow for easy addition of control and monitoring points	Easier validation/GEP of upgrades. Reduces pressure to combine GMP and non GMP functionality.
	Backwards compatibility to enable controlled upgrade	Easier to maintain validated/GEP status following upgrade.
Testing	Simulation Tools	Enable setting of I/O and status conditions to facilitate controlled testing (note these features can also be detrimental to validation if not provided under appropriate access control).
Documentation Tools	Software tools to enable documentation to be created (also part of baseline of the system. Auditing of future differences against change control records)	Enables ease of documentation and record creation and verification of differences between current and new versions of BMS.

Table D. BMS requirements/design/operational considerations.

within the main system. With respect to BMS, an independent monitoring system would be such a backup system.

Monitoring of critical parameters is essential to ensuring that process performance is established and maintained. Validation/testing/calibration of monitoring systems is important to ensuring:

- accuracy of critical data
- timely notification of potential process deviations
- organization of critical and non critical process performance data

Data Type	Use	Electronic Records Determination (Direct Impact, Indirect Impact, No Impact)	Comments
HISTORICAL DATA LOGGING			
Critical Process Measurements	Support regulatory decision, e.g., batch release Support regulatory investigation, e.g., product adulteration	Direct impact, if used for batch release and investigation Indirect impact, if used for maintenance purposes	Potential to be inspected by regulatory authorities
Non Critical Process Parameters	Used to determine equipment performance and maintenance requirements	Indirect Impact	Indication of maintenance requirements does not necessarily indicate a process failure or product impact
Energy usage profile	Determine alternative energy strategy or report energy usage	No impact	None
Equipment Failure and performance status	Condition Based Monitoring	Indirect Impact	Indication of maintenance requirements does not necessarily indicate a process failure or product impact
ALARM AND EVENT LOGGING			
Critical Parameter Deviations	To determine process deviations	Direct Impact, if alarm logs are retained in electronic history files to support future investigation or used in batch record. Indirect Impact, if alarm logs used for maintenance.	If alarms simply annunciate and are then printed, no electronic record exists. If alarms are saved to removable storage media, then such media should be managed to prevent unauthorized change.
Equipment Failure and performance alarms	To determine need for maintenance	Indirect Impact	Indication of maintenance requirements does not necessarily indicate a process failure or product impact
System Events	To determine system performance	Indirect Impact	Indicates system status, e.g., communications failure, I/O failure, disk storage failure. Requires investigation and backup data to verify process performance during failure.
CALIBRATION PARAMETER MANAGEMENT			
Calibration adjustment settings	To ensure accuracy of instrument and equipment feedback.	Indirect or No Impact	GMP decisions are not made on calibration adjustment parameters. Change control or operational procedures should be used to manage calibration adjustments. Calibration adjustment parameters should be secure from unauthorized or inadvertent change.
CONTROL PARAMETER MANAGEMENT			
Critical process setpoints, control actions and alarm limits	To establish required control scheme	Indirect Impact	Parameters should be subject to change control/configuration management. Parameter should be secure from inadvertent or unauthorized change. Regulated decisions are made on process performance rather than input parameters. Audit trails may bring business benefit
Non critical Process setpoints, control actions and alarms	To establishing required control scheme	No impact	Non GMP or Indirect Impact processes
CONTROL			
Control logic	To ensure consistent and accurate performance of process to stated specification	Indirect Impact, control logic is software that should be validated or subject to GEP to demonstrate that the system is fit for purpose.	Change control and configuration management should be adopted.
INSTRUMENTATION			
Any readings or records held by instruments are typically transient.	Readings and status of process sent to control logic	No impact, assuming measurements are transmitted to control and monitoring system and not retained and used within instrument i.e. they are transient in nature.	Instruments may be configured in order to establish operating ranges and control parameters. Such configuration should be subject to configuration management.

Table E. Electronic records rationales.

The above may be achieved by integrated or independent monitoring functionality and equipment. However, cost or historical technology issues may warrant the implementation of independent monitoring systems such as EMS. The implementation of independent monitoring systems also may bring the added benefit in terms of minimizing the risk of simultaneous failure of control and monitoring functions. This consideration may be of particular importance when considering existing systems based on older technologies.

It is important with such systems that scan frequencies and measurement accuracy is appropriate to the process and product risks. Where current BMS instrumentation is not capable of meeting such accuracy or reliability requirements, the installation of independent instrumentation may be necessary.

When considering monitoring strategies, automated monitoring systems alone are not likely to demonstrate control of critical process parameters. For example, environmental control, periodic monitoring of airflow, environmental recover rates, non viable, and viable particulate levels may be achieved through manual procedures.

Where the IT infrastructure supporting the BMS has not been qualified, it may be beneficial to establish an independent qualified IT infrastructure to host the environmental monitoring system.

BMS Governance

Many BMS systems are large, complex systems controlling and monitoring a range of GMP and non-GMP processes and data. As such, unlike many other systems, defining a single point of contact for system administration, system ownership and data ownership may be difficult. Nonetheless, it is essential that a model be established that clearly defines the role and responsibilities for:

- platform configuration, maintenance, and support
- system configuration, maintenance, and support
- system use
- data access and management

The model illustrated in Figure 7 is an example of a networked BMS solution. The actual model implemented within an organization will be dependent on the defined roles and responsibilities within the organization. However, the model illustrates the need to consider different roles and responsibilities for the BMS's development, operation, and support. Such roles will include both internal and external organizations.

These BMS management, operation, and maintenance roles should be appropriately documented, for example in a Service Level Agreement between the Engineering Department and other functions in order that all parties understand the potential consequence of their actions on other areas of the system. In particular, it is important that security profiles, configuration management, and change control systems are established in order to minimize the potential impact of a given group of users on another group of users.

Maintenance and Operational Controls

Maintenance and operational control requirements for the BMS are no different to any other computerized system; however, there are some special considerations that warrant inclusion in such procedures:

- provision of system overview
- identification of system and data owners and definition of system and data change authorities
- Changes to controlled and monitored processes and equipment need to consider BMS, including a BMS maintenance strategy.
- System faults and anomalies should be recorded and investigated.
- Controls should be in place to manage and document external support activities, including remote access support (e.g., records of on site and remote support activities must be documented), including potential "open system" controls.
- Change control or equivalent operation controls should be in place to manage changes to alarm limits, alarm messages, graphics, control schemes, data logging.
- Operational data change procedures should be in place (procedural or automated) e.g., set-points.
- Changes to BMS do not always propagate throughout the system. Procedural controls need to be in place to ensure changes are implemented at all locations, e.g., security changes to workstations.
- disaster recovery and business continuity (guarding against data loss)
- risk assessment for acceptable downtime and recovery rates

Good Engineering Practice

The application of GEP differs considerably from organization to organization. GEP has been established for many years and requires the robust specification, design, construction, commissioning, testing, and handover of systems in order to ensure that they are fit for their intended use.

GEP shall ensure that systems are appropriately documented and maintenance organizations are trained in system design and operation.

ISPE Baseline® Guides refer to the need for documented design, design review, commissioning plans, and test records. In this sense, GEP is not significantly different to qualification other than in the rigor applied to the development of documents and extent of Quality Assurance input during the commissioning and test process. This said, the Baseline® Guide to Commissioning and Qualification recognizes the importance of the Quality Assurance role. Dependence on GEP should, therefore, be viewed as the application of professional practices to ensure that systems satisfy their predefined specification and not as an opportunity for inadequate design and testing of systems.

Conclusions

This position paper has illustrated some of the complexities in managing BMSs and the issues faced when determining the most appropriate Quality Assurance strategy for the

BMS. The key points raised by this paper are summarized as:

- Validation/qualification/GEP of existing systems may be difficult or not cost effective due to long term evolution in the absence of appropriate quality management controls.
- Strategic planning of BMS use is essential to clarity of BMS benefits and GMP impact.
- Risk assessment is essential to determining criticality of BMS and any associated monitoring systems (manual or automated).
- Risk assessments must focus on the probability that a BMS controlled process will impact product attributes.
- Validated and/or calibrated independent monitoring systems can reduce the reliance on BMS for GMP decision making and enable a balanced cost/benefit approach to BMS Quality Assurance.
- Consideration should be given to validation/qualification of potentially high criticality aspects of the BMS controls (e.g., aseptic environmental controls).
- GEP should be applied as a minimum Quality Assurance standard for indirect and direct impact BMS systems. GEP represents a professional engineering approach to assuring a system is fit for intended use.
- Documented governance model is essential to control operation, support, and the development of BMS.
- Replacement of older aspects of the system to use current technologies and meet current industry standards may not provide an appropriate cost/benefit balance.

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ISPE Tours Human Genome Sciences, Inc. Clinical Manufacturing Facility and Interviews Joe Morin, Vice President of Engineering.

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PHARMACEUTICAL ENGINEERING Interviews Joe Morin, Vice President of Engineering, Human Genome Sciences, Inc.

by Cathy Middelberg, Wyeth Vaccines, ISPE Communications Committee Chair

During the June 2005 ISPE Washington Conferences, delegates to the seminar "Bioprocess Pilot Plants: Balancing Cost, Flexibility, and Compliance" toured Human Genome Sciences, Inc. (HGS) Clinical Manufacturing Facility (CMF) at their Belward Research Campus in Rockville, Maryland. Delegates were given the rare opportunity to enter the manufacturing area, as the tour was scheduled around a production changeover and cleaning campaign. The engineering and operations staff, acting as our tour guides, were knowledgeable, informative, and open to questions about the facility construction, operation, maintenance and qualification approach.

The tour was kicked off with an informative overview of the facility by Joe Morin (JM), Vice President of Engineering for HGS, who later talked with *Pharmaceutical Engineering* (*PE*) about his career, project management approach, and the facilities he has constructed with HGS.

Q Can you tell us about your career in the biotechnology industry?

A I have about 17 years of experience in the engineering and biotechnology industry. My first experience in the biotechnology industry was in 1993 as a field engineer for Celltech Biologics (now Lonza Biologics). Since then, I have been involved, as a project manager or project director, in the design, construction, commissioning, validation, and operation of five separate biotech facilities. As Vice President of Engineering for HGS, I am responsible for capital projects, engineering operations, maintenance and calibration activities, and validation.

Relevant Project Experience

- 200L/2000L Cell Culture Contract Manufacturing Facility
- 750L/87,000 square foot Microbial Clinical (Pilot) Production Facility
- 1600L/43,000 square foot Mammalian Cell Culture Clinical Production Facility
- 250L/7,000 square foot Microbial Clinical Production Facility
- 635,000 square foot main campus facility for administration, development and clinical production
- Two 1600L trains/Mammalian Cell Culture Clinical Production Trains. Part of the 635,000 square foot main campus.
- 2 ´ 20,000L/290,000 square foot Mammalian Cell Culture Manufacturing Facility

Buffer preparation.

About Human Genome Sciences, Inc.

Human Genome Sciences (HGS) is a biopharmaceutical company with a product pipeline developed with their proprietary genomic technology. Founded in 1992, HGS currently employs approximately 850 individuals in their facilities in Rockville, Maryland. Though they do not currently manufacture a commercial product, they have seven products in Phase I and II Clinical Trials. HGS primarily focuses on two therapeutic areas: immunology/infectious disease and oncology. Their gene-based protein and antibody drugs will treat such diseases as cancer, lupus, rheumatoid arthritis, hepatitis C, and HIV/AIDS. They also are pursuing long-acting versions of existing drugs through their albumin fusion technology, which creates an altered protein by fusing the gene for human albumin to the gene that encodes the active protein drug.

- 50,000 square foot QA/QC lab/office facility
- 75,000 square foot animal research facility

Q Could you describe the facility the delegates have toured?

A The Clinical Manufacturing Facility (CMF) we toured is a 130,000 square foot microbial, yeast, and mammalian cell culture facility. There is 87,000 square feet dedicated to microbial and yeast production, and 43,000 square feet of mammalian production. These Biological Safety Level 1 (BL1) production lines are operationally segregated. The basic unit operations of both manufacturing areas are the same. Each line is comprised of cell bank and inoculum preparation areas, buffer and media preparation suites, fermentation suites, recovery, purification, and bulk filling areas. A central utilities area serves both production lines with segregated distribution systems for WFI, purified water, clean steam, and gases. HVAC for each manufacturing area is dedicated. Each train is equipped with a thermal deactivation system that feeds a central neutralization system to treat all fluid waste prior to discharge. With the addition of our new Large Scale Manufacturing (LSM) facility, we will add an additional 290,000 square feet of manufacturing capacity at this campus.

Q During the tour, you mentioned that HGS staffed the CMF very early in the design phase. What was the benefit to this, and what roles did the staff play throughout the project?

A Early in the design phase, especially for our manufacturing facilities, we staff our projects with key operations personnel. Typically, this would include lead personnel from manufacturing, engineering operations, controls, validation, and facility maintenance. Part time leads, or as-needed leads, would be assigned from calibration, QA, QC, EH&S, materials management, security, IT, etc. Additional staff, per our staffing plan, is hired as we progress and some of the part time leads become full time project team members. One of the benefits to front-loading resources is having the operational owners of the facility involved early in the decision making process. There is buy-in and ownership to the decisions that we make. The project staff is involved, at varying levels, in design, construction, start-up/commissioning, and qualification. This knowledge is gained and retained by project staff (as opposed to contractors) and allows for a quick and efficient transition from the project phase into operations. The operational benefit of staffing our projects early is the ability to complete many operational requirements such as training, procedures, batch records, etc., during the project phase, which allows us to be operationally ready when qualification is complete. Obviously, having a good owner's project team, which we have (or had), makes the difference between getting a project done versus getting a project done well, while providing operations with a facility that meets their needs from the start.

Q What was the commissioning and qualification approach to the CMF? How were the testing results from commissioning utilized in qualification?

A The approach utilized for this facility is different than our current commissioning/qualification approach. For the CMF, engineering performed commissioning and the validation group performed the qualification. We did not leverage the commissioning work to support qualification. Today, we take a more integrated, or matrix, approach with engineering, validation, operations, and QA that eliminates the typical "hand-off" to validation. Validation, operations, and QA review and approve all commissioning plans and protocols for direct impact utilities and process equipment. We are now able to leverage commissioning work to support qualification. This eliminates duplicating some of the commissioning work we have performed during qualification on past projects.

Q Is the CMF a licensed facility? Will you potentially manufacture commercial product in the CMF?

A No and yes. The facility is not currently licensed; however, it was designed, constructed, qualified, and currently being operated as a potential launch/initial market supply facility for some of our potential products. The intent, depending on the outcome of our clinical trials, is to license the CMF for commercial product.

Q HGS potential products are in Phase I and II Clinical Trials. What drove the decision to design and build the 290,000 square foot LSM facility this early in the product life cycle?

A Our business plan includes the manufacturing capability to manufacture protein and antibody drugs for preclinical studies, clinical trials, and the initial commercialization of our products. It takes close to five years to design, construct, commission, and validate a large scale facility. Building early is a risk-based decision and we know that external capacity fluctuates, with respect to availability, and

is difficult to predict. If the products we have in the clinical phase are delayed or fail, we may have excess capacity. However, if the products we currently have in the clinics work, which we believe they will, we are in the position to manufacture and meet market demand. The risk of not having needed capacity, or the inability to meet market demand, is greater than the risk of having excess capacity. Also, should it exist, excess capacity is potentially marketable.

Q Did HGS consider contract manufacturing during this decision making process?

A HGS entered into a contract manufacturing agreement with Diosynth Biotechnology in June 2004 for process development and clinical supplies manufacturing for a monoclonal antibody product HGS has under development, while we were expanding our manufacturing capabilities. Depending on many factors, such as clinical trial outcome and facility licensing, we may elect to pursue contract manufacturing for other products in our pipeline.

Q What do you estimate the cost per square foot to be for the CMF? For the LSM facility?

A The cost for the CMF was about $550/square foot and LSM facility is closer to $800/square foot. This is an "all-in" cost from concept through qualification of the facility and equipment. Due to the scale differences, 1 ´ 750L microbial and 2 ´ 1,600L mammalian for the CMF vs. 2 ´ 20,000L for the LSM facility, you really can't compare apples to apples between the two facilities. Also, for the metric to be meaningful, we would need to provide facility data and detailed cost breakdown for each facility. However, our cost per square foot is in-line with industry averages, and is actually on the lower end of the cost range with facilities of similar size and scope.

Q Are there any process improvements developed in the CMF that will be implemented in the LSM? Will there be a higher level of automation in the LSM as compared to the CMF?

A Process improvements are product specific, and since this is not my area of expertise, I am not able to provide those details. However, one the most substantial process improvements the operations and development groups have implemented company wide is the consolidation of raw materials to a single platform. Regarding process changes and associated equipment at the LSM facility, we did install and will utilize a pasteurizer for media and a cryogenic control rate freezer for bulk drug substance. With respect to automation, the LSM facility, which has a well-defined process, is designed and implemented to a higher level of automation than the CMF. The CMF is a PLC-based control system. The LSM facility utilizes what we call a Manufacturing Execution and Control System (MECS). The MECS is a central automation system that controls and monitors all the process area equipment and some of the direct impact utilities. The system utilizes many advanced levels of control that were not implemented in our clinical facilities. Key features of the MECS include: batch aware/recipe based system utilizing the S88 Batch Control standard, Windows security features, three high-level data historians (Batch, Continuous, and Events), audit trails, advanced graphics/interfacing, smart device digital input/output interfaces (Fieldbus, DeviceNet), class-based programming which simplifies design, testing and qualification of reusable modules, and two-way interfacing to all packaged equipment skids. We also have a Facilities Management and Control System (FMCS) for all utility and HVAC systems. Although similar to systems installed in our clinical facilities, in the LSM facility, we divided the FMCS into two separate control systems. One system manages and controls Indirect Impact systems, such as office AHUs, boilers, cooling towers, chillers, etc., and is fully commissioned. The other system controls our Direct Impact systems, such as our GMP AHUs, and is both fully commissioned and qualified.

Plant steam boilers.

Q Is the LSM basis of design the same as or similar to the CMF?

A No. Same process (mammalian), but due to scale, the LSM facility basis of design is significantly different from the CMF. The CMF was designed to be highly flexible with most of the downstream, from recovery through bulk fill, equipment (vessels and recovery/purification skids) being portable to accommodate a range of processes. Due to scale, most of the equipment at the LSM facility is fixed and our manufacturing processes need to be developed to fit the facility. That being said, we are now developing our manufacturing processes at our smaller scale facilities (such as the CMF) to mirror the manufacturing process we will be performing at the LSM facility.

Q Will the LSM be a multi-product facility like the CMF?

A Yes. Both are multi-product facilities with single product campaigns. Changeover is performed between product campaigns.

Q Will the LSM follow the commissioning and qualification concepts developed in the CMF?

A No. Our current approach to commissioning and validation of the LSM facility is in-line with current ISPE guidance. We will perform most of the operational testing as part of commissioning with the qualification of the equipment focused on meeting the User Requirements. As mentioned earlier, we are taking an integrated approach to commissioning and qualification. Validation, operations, and QA have been "pulled forward" into the commissioning process to allow us to leverage our commissioning work to support qualification.

Q What project management concepts or techniques have you consistently utilized in the construction and expansion projects you have run at HGS?

A It varies. It's dependent on project size, type, and internal resource availability. For our manufacturing facilities, we direct contract Construction Management (CM) and engineering design services. We always contract with a full service design firm and bring the CM and some key subcontractors on board early to provide pre-construction services. We perform a thorough preliminary design, which is the basis for our scope of work for detailed design. Having an approved and comprehensive scope of work (preliminary design) allows us to control and maintain the project cost and schedule. Procurement is performed through our CM with technical bid evaluations performed by the owner and engineer. The CM, owner, and engineer establish a cost control estimate during the preliminary design phase with periodic updates as the project progresses. Using the control estimate, we start construction on a cost-plus basis. When detailed design is nearly complete, we establish a guaranteed maximum price with our CM. We usually establish an incentive program with our CM, which provides for bonuses or penalties for performance factors related to safety, cost, schedule, and quality.

Q In all of the projects you have managed, what has been your biggest challenge?

A I would have to say it's people. There are always tecnical challenges, or permitting problems, or schedule conflicts, but people are what really can make or break a project. It is imperative to have a good project team, which would primarily consist of the Owner's project team, the Construction Manager, and Engineer. You need to take the time to put the right people in all of the key positions and establish a project structure with clear responsibilities, expectations, scope, and deliverables. Even with all this upfront work to establish a good project team, due to personal issues, conflicts, performance issues, project changes, etc., you will need to make changes and adjustments to the project team to ensure project success. People will always dictate the successfulness of a project.

This article describes a method for the qualification of IT infrastructure that can be scaled down to fit multiple organizations, whether small or large.

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An Approach to IT Infrastructure Qualification

by David Stephenson

Introduction

Many pharmaceutical manufacturing organizations are currently struggling to establish a cost effective, efficient, and regulatory compliant approach to managing their enterprise-wide IT infrastructure. While the principles for accomplishing this are becoming more widely understood, pragmatic guidance is lacking for those organizations wishing to develop a pragmatic and holistic approach.

This article describes a pragmatic approach,

Table A. GxP regulations and guidance appertaining to IT infrastructure.

FDA Regulation	Short Description	Rule Section
21 CFR 211.25	Personnel Qualifications	Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions.
21 CFR 211.63	Equipment Design	Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.
21 CFR 211.68	Automatic, mechanical, and electronic equipment	Appropriate controls shall be exercised over computer or related systems. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance.
Guidance for Industry Computerized Systems Used in Clinical Trials (Section VIII:A) April 1999	Systems Documentation	Systems documentation should be readily available at the site where clinical trials are conducted. Such documentation should provide an overall description of computerized systems and the relationship of hardware, software, and physical environment.
Guidance to Inspection of Computerized Systems in Drug Processing (Section III) February 1983	Diagrams	For each significant computerized system, it may be helpful to prepare an OED schematic drawing of the attendant hardware. The drawing need only include major input devices, output devices, signal converters, Central Processing Unit (CPU), distribution systems, significant peripheral devices and how they are linked.
Guidance to Inspection of Computerized Systems in Drug Processing (Section III:A:5) February 1983	Distributed Processing	The interconnection of two or more computers... also known as distributed processing. A large CPU may also act as a "host" for one or more other CPUs. When such inspections are encountered during an inspection, it is important to know the configuration of the system and exactly what command and information can be relayed amongst the computers.
Guidance to Inspection of Computerized Systems in Drug Processing (Section III:B:1:b) February 1983	Electromagnetic Interference	Excessive Distances between CPU and Peripheral Devices. Excessively long low voltage electrical lines... are vulnerable to electromagnetic interference. This may result in inaccurate or distorted input data to the computer. In a particularly "noisy" electronic environment, this problem might be solved by the use of fiber-optic lines to convey digital signals.

which minimizes qualification/validation effort (by utilizing a risk-based approach combined with a layering/partitioning methodology) while at the same time being sufficiently robust to meet the requirements of regulatory inspection.

What is IT Infrastructure?

IT infrastructure is the collection of the computer systems in use, combined with their hardware, software (excluding business applications), network components, and associated processes and procedures used to run the business in question. This can be broken down into four specific areas:

- Servers
  - Hardware
  - Operating systems
  - Support applications (virus, backup/tools, etc.)
- Networks
  - Intelligent devices (routers and switches, etc.)
  - Cabling infrastructure (copper and fiber)
  - Support applications (network management/security, etc.)
- Desktop
  - Hardware
  - Operating systems
  - Support applications (virus, etc.)
- Management Applications
  - Security
  - Network management/performance

Each of these areas requires processes and procedures to be established and followed in order to be considered compliant.

What is Required of the Infrastructure?

IT Infrastructure is generally accepted as a commodity that exists to perform the required functions for all available and authorized users. It is therefore required to be potentially fault free and continuously available, almost like the electric and gas utilities that are part of our everyday life. In order to achieve a high level of fault tolerance and availability, we must strive to bring our infrastructure up to a certain level of compliance and demonstrated control. This is best achieved by implementing and executing a planned qualification process, reinforced by a set of procedures that will ensure ongoing compliance following completion of the qualification exercise.

Regulations Surrounding IT Infrastructure

When we start to consider IT infrastructure qualification and what it will involve, we must look closely at the reasons why we are doing it, and what the end result will be. Are we doing it because: everyone else is doing it; fear of a regulatory inspection; or we want to get control over our infrastructure?

There is probably a certain amount of each of the above in the decision making process; therefore, we need to consider all of the aforementioned criteria.

If everyone else is doing it, then surely there must be a reason behind it; the pharmaceutical industry does not spend

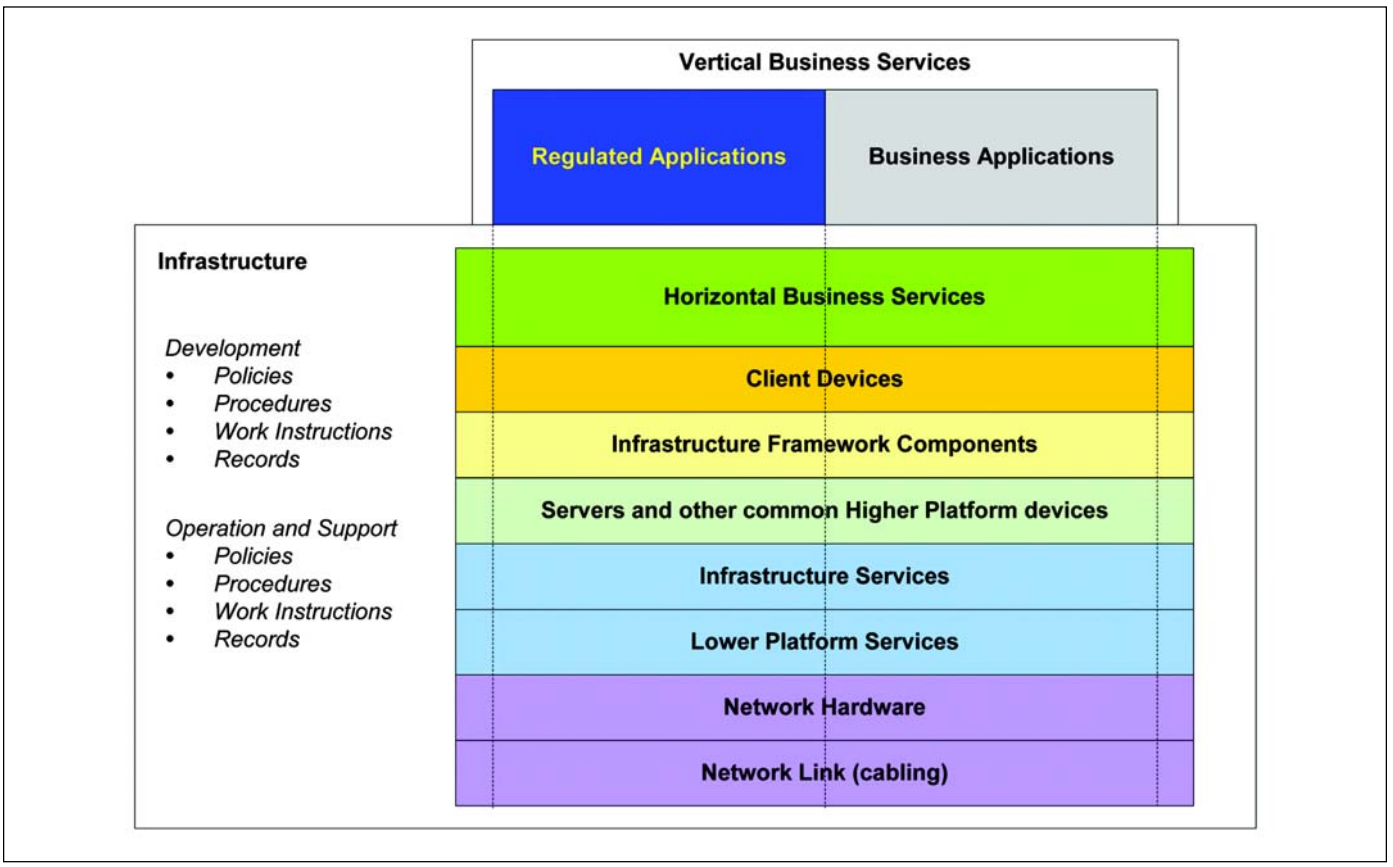

Figure 1. Infrastructure layer boundaries.

money on testing and documentation for no reason.

Regulatory inspection is becoming more of a common occurrence for IT departments in the pharmaceutical industry. It is not usually the case that IT departments are failing in their duties; often this is very far from the truth. However, it is quite common that the IT department does not document who, what, where, when, and how in a manner that is easily verifiable for the regulatory inspectors. Therefore, what we are usually faced with is a documentation exercise aimed at bringing all of the various existing processes and procedures together, and filling any gaps.

There are many cGxP regulations and guides that explicitly or implicitly relate to the qualification of IT infrastructure. Some examples are shown in Table A.

We have so far looked at the infrastructure, what it consists of, what is expected of it, and why we qualify it. The next step is how do we do it?

Methodology Background

The following methodology is one that has been used over a number of sites throughout Europe. It has been developed through both consultation with clients and with a weather eye on the quality and regulatory expectations surrounding IT infrastructure.

This methodology was set up to provide both compliance and practicality. In order to achieve this, there are some very basic requirements that must be met:

- We must produce a comprehensive yet manageable document set, which will be easy to maintain and understand.
- We must not overburden the qualification exercise with unnecessary testing and documentation. (We must carry out the correct level of qualification on a case by case basis, justified by a documented, risk-based rationale.)
- The infrastructure qualification status must be controlled so that ongoing changes do not affect the qualification status.
- We must ensure that the processes are easily operable on a day to day basis by the local site IT department, minimizing the ongoing maintenance burden.

If we now consider the last bullet point from the previous section, "***We want control over our infrastructure***," this can be achieved by a pragmatic qualification of the existing infrastructure, while tying in a quality service framework (see ITIL) that will keep the infrastructure both compliant and efficient as it moves through its working life.[1,2,3] This will ensure that the infrastructure qualification is understandable and compliant, and conforms to the local quality processes and procedures.

The following discussion will expand on the basic requirements of the cGxP regulations, and include the type of industry standard, service framework as set down by such bodies as IT Infrastructure Library (ITIL) and provide a combined approach that not only answers the regulatory requirements, but provides a known and trusted framework, which the IT departments themselves can benefit from. This then will give an added dimension to the exercise, which should help to get the buy-in of the IT community.

The process explained below covers all aspects of the infrastructure and describes documents that have been designed to meet the requirements of the System Development Life Cycle, but also takes into account the recommendations set down in ITIL (covered in the SOP section). It also has an approach to testing, which can be utilized to meet the requirements of both a large-scale organization, and those of a small single-site organization.

In order to understand these processes, we must first understand the boundaries that they encompass.

Therefore, we must define the infrastructure clearly, taking into consideration the scope of the formal infrastructure qualification (i.e., what to qualify). Based upon experience there are two main approaches:

- Partition the infrastructure into GxP and non-GxP critical components. Qualify only the GxP critical components and use good IT practices to commission and maintain the non-GxP critical components.
- Take a blanket approach and qualify all components.

Because of the broader business needs to qualify infrastructure, most medium and large size organizations are leaning toward qualification of the entire infrastructure. Partitioning will be less appropriate in the case of large multinationals with an integrated IT infrastructure.

In addition, different types of components will require different approaches to qualification, and similar components will have the same basic requirements to achieve a qualified status, e.g., a network switch may be configured differently to another switch (since the infrastructure is 'common' to all applications, the risk can be assumed to be common) but will have the same level of verification, testing, and controls applied to it.

We can categorize components into infrastructure layers based on the type of service or function they provide within the infrastructure. Components in the same layer will require the same basic qualification activities.

Figure 1 illustrates the boundaries within IT infrastructure and demonstrates that the IT infrastructure not only supports the business applications, but also is critical for maintaining the overall and ongoing compliance of the system.

Figure 1 shows a representation of the layers defined for infrastructure. A description of these layers is provided below.

Network Links

This layer defines the network hardware that physically connects the network (e.g., copper cable/optical fiber, outlets, patch cables, repeaters, hubs, Network Interface Cards, and device drivers).

Network Hardware

This layer is used for basic communication, addressing and routing, and includes switches, routers, hardware Uninterruptible Power Supplies (UPSs), and firewalls.

Lower Network Services

This layer includes items such as operating system, Virtual Private Networks (VPNs), DNS, or file system managers.

Infrastructure Services

There are a number of components that will be installed on servers to support the performance, integrity, and availability of the service.

Servers and other Higher Platform Devices

Servers, printers, pagers can be considered within this layer. Pagers and cellular mobile phones are possible vectors for system alert messaging. This is for sending alerts related to, for example, capacity management or intrusion detection to an engineer. Components such as BMC Patrol utilize this technology and correct configuration of these components enabling communication to the devices should be qualified.

Layer	Minimum Definition Requirements	Minimum Testing Requirements	Minimum Control Requirements
Network Links	• Standard technical specifications for component requisitioning	• Basic connection/power test	• Network Diagram (down to low level – e.g., labelling of network access point and patch panels) • Inventory management recording configuration details for applicable components (e.g., device drivers) • Ongoing monitoring of performance
Network Hardware	• Configuration specification and installation instructions for all hardware items by type based on supplier documentation	• Testing instructions and results for initial item of each type (carried out within a controlled testing environment), including performance testing against requirements • Basic installation testing for subsequent items of type tested	• Inventory management recording configuration details (item number, location, with each item identified on network schematic) • Ongoing monitoring of performance
Lower Network Services	• Configuration specification and Installation instructions (as part of server build), based upon supplier documentation	• Software updates/patches to be installed into a controlled test environment and monitored for a defined period prior to installation to production	• Inventory Management (e.g., license numbers, install location) • Privileged access usage procedures (e.g., for system admin [root] access) • Ongoing monitoring of performance
Infrastructure Services	Partial Lifecycle: • Definition of service requirements • Configuration specification and Installation Instructions based on vendor-supplied documentation	• Performance Testing based on requirements	• Inventory Management (e.g., license numbers, install location) • Change Management (to control software updates) • Ongoing monitoring of performance
Servers and other higher platform devices	• Configuration specification and installation instructions for all hardware items by type based upon vendor-supplied instructions	• Testing instructions and results for initial item of each type (carried out with a controlled test environment), including performance testing against requirements, based on supplier guidance • Limited installation testing for subsequent items of type tested	• Inventory management recording configuration details (includes log of installed items, including all installed services and applications) • Ongoing monitoring of performance
Infrastructure Framework Components *(In-house developed)*	Full Lifecycle Documentation: • URS • FS • SDS • DQ	Full Qualification: • IQ • Unit Test • Functional Test • Integration Test	• Software Change Control • Ongoing monitoring of performance
Infrastructure Framework Components (third-party)	Partial Lifecycle: • Requirements definition • Installation and Configuration Instructions based on vendor-supplied documentation	• Performance Testing based on requirements	• Software Change Control • Ongoing monitoring of performance
Client Devices	• Installation and Configuration Instructions for standard PC build	• Operability test	• Restrict user modification of system configuration (e.g., system clock, ability to install/uninstall programs) • Inventory management recording configuration details (e.g., location, RAM, processor) • Ongoing monitoring of performance

Table B. Layer qualification activities.

Infrastructure Framework Components (In-House Developed)

These can be both in-house developed and third-party. System frameworks perform low-level functionality on behalf of the caller and interact with the infrastructure services to realize the request. They serve as a bridge between the business service and the infrastructure service. This can be achieved using standard code or custom developed code and the supporting procedures and standard required to develop it.

Client Devices

These are services across the business that allow maintenance and control of the infrastructure. Examples include personal computers, laptops, PDAs, mobile RFI terminals, etc.

Horizontal Business Services (Package (Microsoft SMS), In-House Developed (Custom Code), In-House Developed (where service consists of configured framework components)

These are the infrastructure applications which provide company wide services, e-mail, SMS, print services, etc.

Layer Qualification Activities

The baseline qualification activities that should be performed for a component assigned to a particular infrastructure layer are described in Table C. In general, qualification activities increase as we go up through the layers. This reflects the fact that higher layers of the model will be more functional and will have more interaction with regulated applications than lower layers. It must be appreciated that this is one approach to defining qualification activities and organizations must define their own, specific to their individual needs.

Qualification Level Determination

In drug manufacture, companies will often use raw materials from a supplier with minimal or no testing, accepting the manufacturers test evidence as quality of the material. This is based on the trust the company has in the supplier to consistently provide quality raw materials. This trust is supported and evidenced by a combination of historic experience (what has the supplier provided in the past), supplier audit, and periodic monitoring of the material quality.

Infrastructure components can be seen as analogous to pharmaceutical raw materials in this respect as they are:

- basic building blocks of the final product or system
- simple compared with the final product or system
- often produced in a highly repeatable and consistent process

In addition, infrastructure components are often used extensively throughout the business world. This can provide us with a degree of confidence in the component that mitigates the need for high levels of qualification.

For example, we do not perform functional testing on the core functions of the UNIX operating system due to the confidence we have in Hewlett-Packard to produce the product correctly (Supplier Quality), it has a tried and tested install process (Implementer Expertise) and it is used without problem throughout industry (Component Reliability).

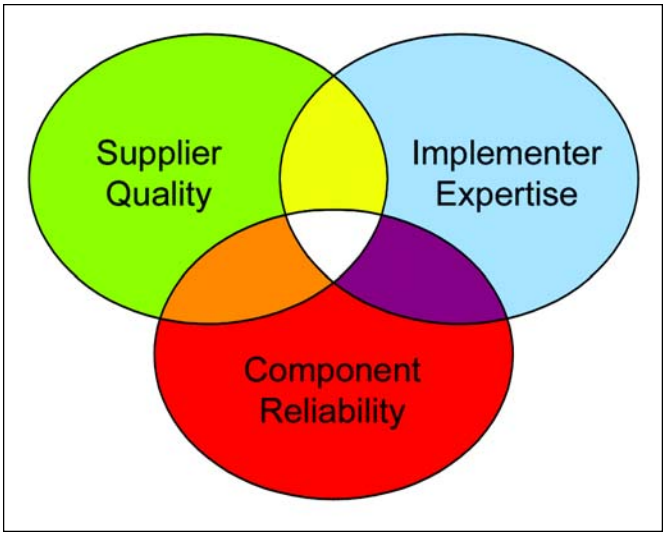

Figure 2. Factors influencing qualification level.

Therefore, there are three primary factors to consider when deciding on a pragmatic level of qualification - *Figure 2*.

The higher the confidence and trust we have in each of these factors, the lower the qualification burden on the company.

Assessing these factors allows us to reduce the qualification activities required where appropriate, and also apply a detailed risk assessment when necessary, bearing in mind that there is always a risk that a component may directly impact data that can affect the quality of the product or the safety of the consumer.

Therefore, this must be assessed where appropriate by performing a detailed risk assessment on a particular component, thus identifying its functions and/or operations that are at risk of failure and allowing us to quantify that risk and provide for risk mitigation.

Assessing Qualification Level

As shown above, assessing the key factors of Component Reliability, Supplier Quality, and Implementer Expertise allows a pragmatic level of qualification to be determined based on the baseline activities described in Table C.

Following the decision tree illustrated in Figure 3 allows this qualification level to be achieved. The qualification level can be used to modify the baseline set of qualification activities, providing a pragmatic set of activities for the component. Figure 4 describes the risk-based modification of the baseline qualification activities.

The infrastructure layer where the component resides provides a baseline set of qualification activities as defined in Table B. The qualification level determined for the component in Table C modifies this set of activities to allow for the possible risk derived from Component Reliability, Supplier

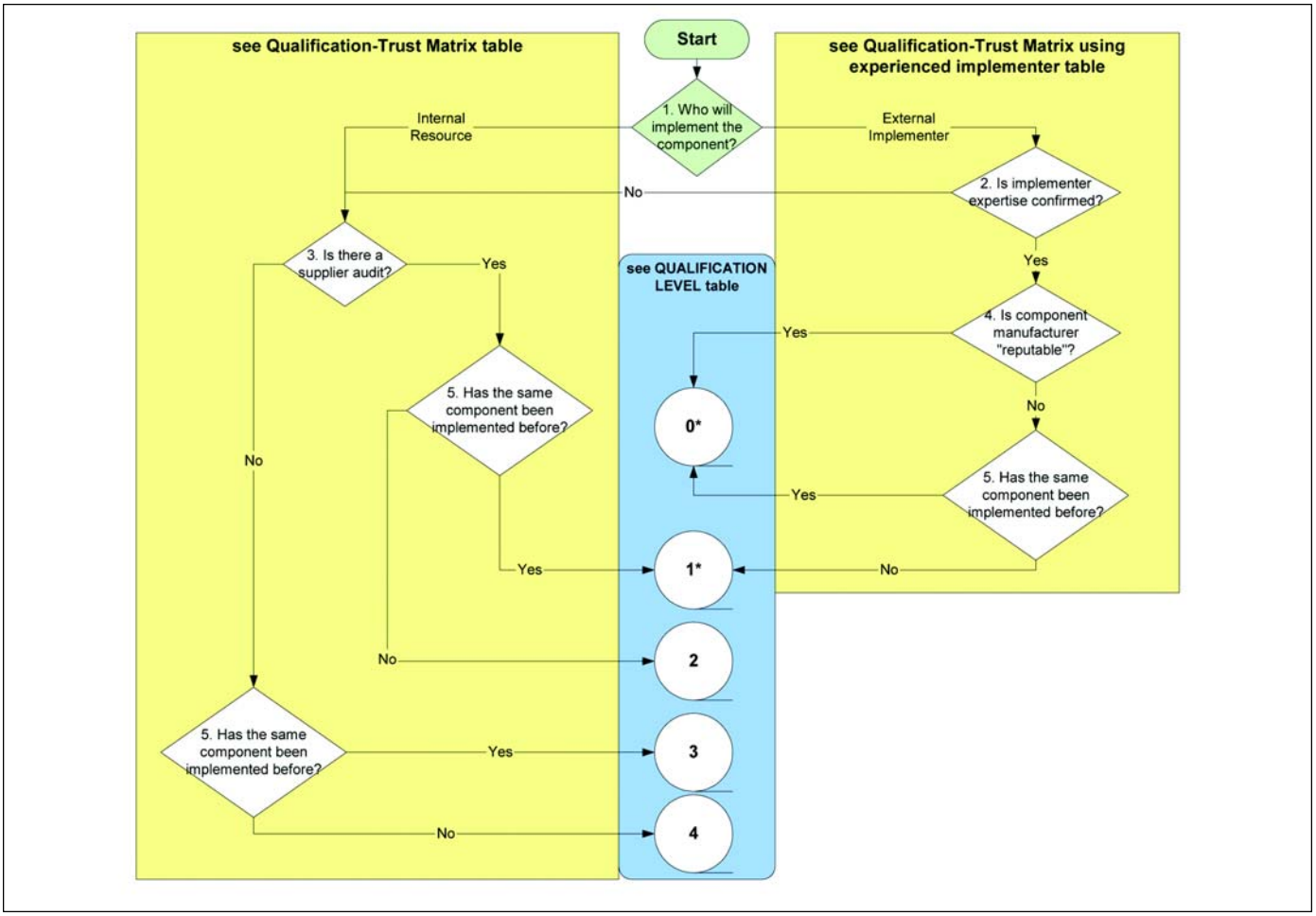

Figure 3. Qualification level decision tree.

Quality, and Implementer Expertise, as described in Figure 2. This may indicate the requirement for a formal risk assessment. However, it must be stated that we are not looking to put in place a big complex risk assessment methodology, but a risk-based framework that leverages (documented) good suppliers, quality products, etc.

If we consider the NIST SP 800-30 approach, we can allow for many generic risks as part of the design process, and therefore, it is not necessary to perform a separate risk assessment so long as design documents identify which design elements address various risk scenarios.

Figure 4 shows the process for determining the final set of activities required for qualifying an infrastructure component.

The final set of activities will be documented in a Qualification Plan (including required remediation of legacy infrastructure). This will detail the specific activities to be performed, including a rationale that justifies those activities and will identify the deliverables that will be produced as part of the qualification.

This plan could include the following activities dependant on the result of the process carried out:

1. Production of an As-Built Specification for the whole IT infrastructure
2. Production of a Traceability Matrix
3. Production of Installation Qualification/Operational Qualification (IQ/OQ) Protocols, including (but not limited to) the following:
   - Switches and Routers
   - Network Link (Cabling)
   - Network Management Applications (If Utilized)
   - Servers H/W and Operating Systems
   - Desktop Applications and Configuration
4. Review/Update of Standard Operating Procedures
5. Production of IQ/OQ Reports for the Executed Protocols
6. Production of a Qualification Summary Report

These deliverables are expanded below:

As-Built Specification

This document will be written in order to detail the 'as-built' functional and design specification for network infrastructure (in line with client standards). It will define how the network infrastructure is configured and functions for both hardware and software and its interaction with other systems. The document will typically contain the configuration items for each of the devices on the network, how they are interconnected, and which IT industry standards they comply with. Thus, it provides a reference document that could be

used to assist in the rebuilding of the infrastructure following a disaster if required (each device is represented as an attachment to the main document, which sets out the standards required for new equipment). Following qualification, this document will be maintained throughout the life of the system with any updates being fed into it via a formalized IT configuration management and change control process.

Traceability Matrix

As in all qualification exercises, there is a fundamental need to provide traceability from the requirements through to the testing. In the case of the infrastructure that already exists, traceability is provided from the system functionality through to the design (as detailed in the as-built specification). We also can include at this point, the business requirements that are expected of the infrastructure. All areas are verified by the testing that will be carried out during execution of the relevant IQ/OQ protocols. In addition to the obvious traceability provided between the IT infrastructure and GxP Critical Applications, this collection of information may be advantageous in providing an overview of the impact of failure in the case of dedicated components (i.e., which applications will fail if a server fails).

IQ/OQ Protocols

These will be written to include all of the infrastructure devices and could include:

- Switch/Router Protocols
- Server Protocols
- Network Management Application Protocols

Level	Details
0	The company will apply the Definition and Control activities described in Table B. The implementer will perform testing activities. (Note: the implementer may also provide some Control requirements.)
1	Refer to Table B.
2	Refer to Table B with the addition of documented data to show the general acceptance of the component within industry. If this is unavailable (e.g., innovative component) go to Level 4.
3	Activities defined in Table B with the addition of Supplier Audit. The result of Supplier Audit may require additional qualification activities as determined by risk assessment.
4	Activities defined in Table B with additional qualification activities as determined by risk assessment, e.g., redundancy testing of RAID configuration supporting GxP critical data.
*	Appropriate documented evidence (e.g., implementer audit) is required to prove the expertise and previous experience of implementer with component type.

Table C. Qualification level activities - refer to Figure 3.

- Desktop Configuration Protocols

In general, these can be written as generic protocols (per device type), which can be used across all of the devices being tested. They will typically contain attachments, which will cover the various types of devices and operating systems utilized.

Each of the protocols will have associated attachments containing test cases, which are used to capture information, and test functionality of the components. (In order to reduce testing at OQ, "type testing" could be utilized.) These test cases could typically include:

GAMP® Section	Title	ITIL Section	Title
7.11	Maintaining the Validated State		
7.11.1	Operational Plans and Procedures	Throughout	All
7.11.2	Training	4.4.11 (SS) 5.5.3 (SS)	Identifying Training Needs Possible Problem Areas
7.11.3	Problem Management and Resolution	6 (SS)	Problem Management
7.11.4	Service Level Agreements	4 (SD)	Service Level Management
7.11.5	System Management	7 (SD)	IT Service Continuity Management
7.11.6	Backup and Recovery	7.3.2 (SD) 8.5.4 (SD)	Requirements Analysis and Strategy Definition Designing for Recovery
7.11.7	Configuration Management	7 (SS)	Configuration Management
7.11.8	Operational Change Control	8 (SS) 9 (SS)	Change Management Release Management
7.11.9	Security Management	ALL (SM)	Best Practice for Security Management
7.11.10	Performance Monitoring	8 (SD)	Availability Management
7.11.11	Record Retention, Archiving, and Retrieval	7.3.3 (SD)	(Service Continuity Management) Implementation
7.11.12	Business Continuity Planning	7.3 (SD)	The Business Continuity Lifecycle
7.11.13	Periodic Review	7.3.4 (SD)	Stage 4 Operational Management
7.11.14	System Retirement		
Legend: (SS) Best Practice for Service Support (SD) Best Practice for Service Delivery			

Table D. Cross reference of ITIL to GAMP 4, section 7.11.

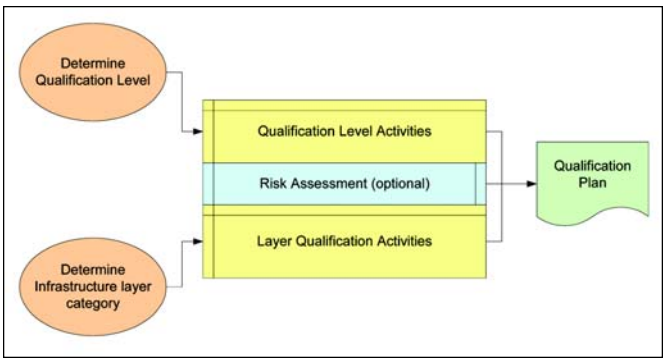

Figure 4. Overview of qualification activity determination.

- Configuration Items
- Physical and Logical Security Checks
- Utilities, Services and Support Applications
- Network Connectivity
- Documentation

Fiber and UTP/STP Cable Protocol

Within these protocols, test cases are used to verify the following:

- the cable possessed a valid Test Certificate (to TSB 67, ISO 11801 or another valid standard)
- all Network Infrastructure documentation affected by the project had been updated (including topology and site cabling schematics)
- the cables have been installed and labelled in accordance with the site standards

Standard Operating Procedures

As we are looking directly at the operational management of the whole IT infrastructure, there is need to create/review the existing SOPs against the framework for operational management set up in ITIL, and the framework for compliance specified in GAMP® 4.

Figure 5 represents the framework for operational management (Service Support and Service Delivery), taken from ITIL. These areas can map across to the sections specified in GAMP® 4 section 7.11 "Maintaining the Validated State:"[5]

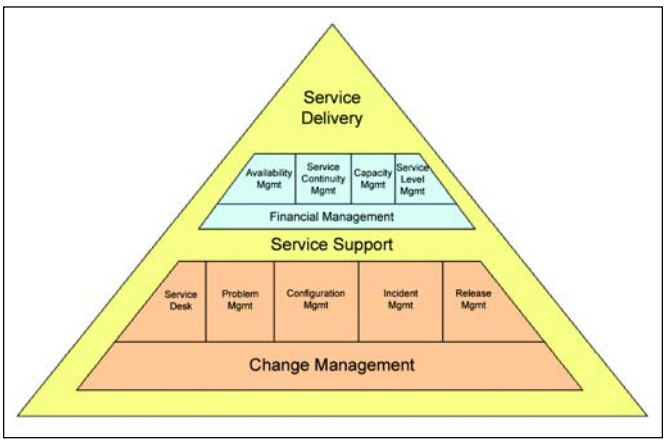

Figure 5. ITIL framework for operational management.

If we approach the subject of SOPs, with reference to both GAMP® and ITIL, combining their approaches, we can produce an approach that is both compliant and efficient when utilized in support of the IT infrastructure.

IQ/OQ Reports

An IQ/OQ report will be written against all of the protocols that were executed. It will verify and record that cabling, routers, switches, servers, desktops, and applications (where applicable), installed as part of the site network infrastructure, have been assembled, installed, and tested in accordance with design criteria and the manufacturers recommendations. These reports once written can be brought together in a cohesive package, containing:

- the original signed protocol
- the executed protocol attachments
- the recorded evidence (screen captures)
- the protocol report

Qualification Summary Report

The final step is to combine the documents together and wrap up the qualification exercise in a final summary report, which should detail the following:

- verification of the qualification deliverables
- verification of the protocols executed and the test data produced
- explanation of any exceptions/deviations recorded and how they were resolved
- verification of SOP creation and testing
- verification that all documents and electronic files have been stored in a secure location
- verification that processes have been put into place to ensure that ongoing compliance will be maintained

Conclusion

In conclusion, my experience is that IT infrastructure can be qualified and controlled in a pragmatic and cost effective manner. The approach to infrastructure qualification detailed above is one where:

- The infrastructure hierarchy is defined with respect to layers and components within these layers.
- A clear, enterprise-wide decision is taken on whether or not to segregate the infrastructure into GxP and non-GxP segments.

Minimum qualification requirements are defined for each layer, based upon a series of documented risk assessments

- Appropriate documentation is developed (processes, policies, procedures, work instructions, and checklists) to support the above decisions and the qualification activities.

- Risk assessment is used to identify where additional qualification/validation is required.

This approach has been demonstrated to be scalable in terms of organization size and infrastructure technology and to provide a method by which the cost of IT infrastructure qualification and on-going control can be reduced to an acceptable minimum.

Acronyms and Abbreviations

DDS - Detailed Design Specification

FRS - Functional Requirements Specification

ITIL - IT Infrastructure Library

LAN - Local Area Network

Multi-Mode Fiber - Optical fiber supporting propagation of multiple frequencies of light Multi-mode fibers have relatively thick core that reflects light at many angles. Multi-mode transmitters usually use LEDs as a light source and a photodiode detector to translate light signals into electrical signals.

Router - A device that connects two networks and allows packets to be transmitted and received between them.

Single Mode Fiber - Optical fiber with a narrow core that allows light to enter at a single angle only. This type of fiber has higher bandwidth than multi-mode fiber. Also known as monomode fiber.

STP - Shielded Twisted Pair. A four pair medium used in a variety of networks.

Specifications - Describes the requirements and design of a system.

Switch - A logical device which connects multiple segments of a network together and passes data on to the required recipient.

UTP - Unshielded Twisted Pair. A four pair medium used in a variety of networks.

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About the Author

David Stephenson joined the Life Sciences Division of Mi Services in 2004 where he is Head of IS Compliance. During his 15 years in the pharmaceutical industry, he has worked for Mi Services, ABB, and GSK in computer systems validation, network management and administration, and computer access and security. Now focused on infrastructure qualification, he is a member of the GAMP® Infrastructure Special Interest Group (SIG), whose Good Practice Guide: IT Infrastructure Control and Compliance was launched in August 2005. During 2003/2004, he has been leading the qualification effort for the IT network infrastructure at various pharmaceutical manufacturing sites in Europe, including the qualification of Cisco equipment (routers/switches, etc.), site servers, network management applications, physical layer connectivity (fiber and copper cabling), and the provision of procedural controls. He has presented at CSV conferences on the subjects of network qualification and the impact of SOPs on IT departments. Within ABB and Mi Services, he has been developing a common methodology for both retrospective and prospective IT network qualification, including the production of guidance and associated training packages. He is a member of ISPE and the Institute of Leadership and Management (MinstLM).

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This article presents benchmark data for the pharmaceutical industry and analyzes the barriers and opportunities in moving from the existing to best in industry performance in research and operations.

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From World Class Research to World Class Manufacturing: The Challenges

by Professor Roger S. Benson, FREng

Introduction

The pharmaceutical industry has a continuous record of growth, innovation and profitability. An innovative stream of new products drives this growth and the company share prices. Manufacturing is controlled by Good Manufacturing Practice (GMP) and the industry is regulated by the US Food and Drug Administration (FDA) and the national regulatory bodies such as the Medicines and Healthcare Regulatory Authorities (MHRHA) in the United Kingdom.

The established industry is faced with a number of pressures for change:

1. stock market demanding continuous growth and profitability
2. a reducing success rate developing new profitable molecules
3. healthcare pressures to reduce the costs of life saving medicines
4. increased access to life saving medicines in developing countries
5. competition from lower cost generic manufacturers

These pressures drive a need to improve the effectiveness of research, development, and manufacturing operations. The challenge is to achieve this in the highly regulated pharmaceutical industry.

This article provides and analyzes benchmark data for research, development, and manufacturing. It suggests that there is much to learn from other industries that are ahead of the pharmaceutical industry on the journey to world class performance.

Benchmarking

This is a mechanism used to evaluate operational performance against the best in the world.

Benchmarking does not imply that the manufacturing, research, or development process and practices have to be the best in the world at everything. However, it is important to know what the best in the world is and to have made

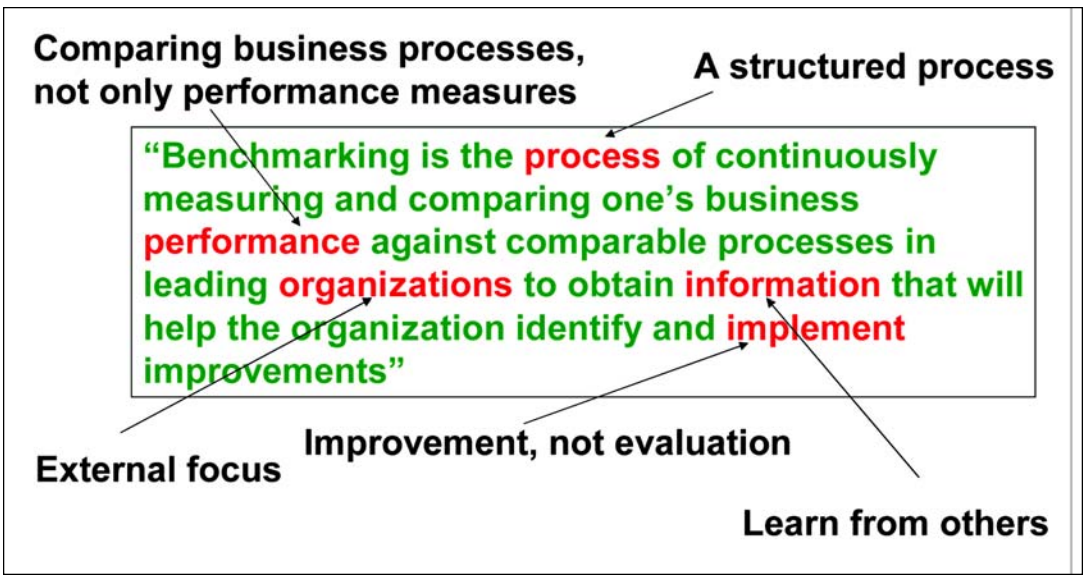

Figure 1. Benchmarking.

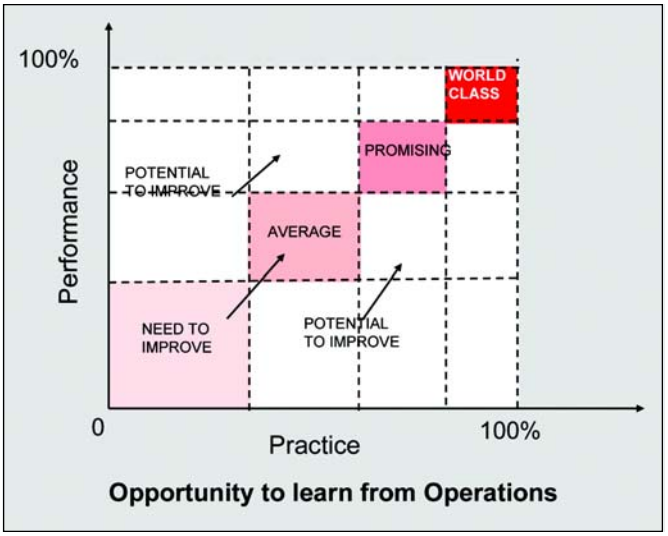

Figure 2. Practices drive performance.

a conscious decision to operate at a different level of performance for sound business reasons. In many ways, good research, development, and manufacturing are like the Decathlon in the Olympics. The champion does not need to win every event in order to win the Decathlon, but they are outstanding at the important events and above average in the other events.

It is important to note that benchmarking must be a structured process to ensure consistency of definition and validity of benchmarks. Benchmarking focuses on two aspects. The first is the Performance, which is what the operation delivers. These identify and quantify the opportunities to improve. The second are the Practices that deliver this performance and indicate where and how to improve. These are not covered in this article.

In the pharmaceutical industry, Good Manufacturing Practice (GMP) defines many of these practices. Extensive evidence supports the argument that Practices drive Performance.[1]

Without excellent practices, the performance expected will not be delivered.

Benchmarks for Pharmaceutical Manufacturing Operations

An earlier article in *Pharmaceutical Engineering* published benchmark data for manufacturing operations in the industry and these are briefly repeated below for continuity.[2]

The terms referred to in the benchmark study are briefly defined at the end of this article with full definitions.[1]

Table A presents real data for three typical operations. Figures in the first column are typical of the pharmaceutical industry and have been established by the author over several years from benchmarking and discussions within a range of pharmaceutical companies. The second column is an award-winning pharmaceutical company manufacturing over-the-counter drugs, prescription drugs, and injectables. It has in the past been a winner of the UK Best Factory Awards.[3] The world-class facility is a food plant supplying supermarkets and grocery stores. Food manufacturing is different from pharmaceutical, and its regulatory environment and specific rules of engagement are not as stringent as the pharmaceutical industry. However, it also is regulated under the principles of GMP. Consumer protection and product safety is no less a concern than it is for the pharmaceutical company. The figures represent a target of what is possible in the longer term. The debate is how practical it is for the pharmaceutical industry to achieve these targets.

Benefits of World Class Operations

At first sight the figures may appear to be just numbers, but it is when they are interpreted into the industry impact that the full opportunity is quantified.

Pharmaceutical industry annual reports declare stock turns between three and five, but already there is a pharmaceutical manufacturer in the UK achieving stock turns of 14 and increasing. If all of the world pharmaceutical industry with an estimated annual turnover $290 billion moved from the current average to that of the UK award-winning factory, the cash release would be in the order of $54.3 billion (Calculation 1). While these are one off releases of cash, they are extremely significant and would have dramatic effects on both short-term and long-term profitability of the companies. Stock turn is a powerful measure of the manufacturing performance. High stocks often are a buffer that covers for poor operations. Only excellence in manufacturing will deliver high stock turn. It is not something that is adjustable by financial manipulation.

Examining the OEE measure suggests typically equipment is only being used to 30% of its full potential while a winning figure is 74% and a world-class figure nearer 92%. This suggests that the industry could increase the output of the present assets by more than a factor of two with minimum capital investments (Calculation 2).

It is often argued that since the capital has been invested, this does not represent a saving. The benchmark suggests there is the potential to more than double the number of new molecules manufactured by the existing assets or the potential. A second argument is that this is not real potential as the extra product cannot be sold. The answer, unfortunately, is that up to half the capacity will nearly take out the excess manufacturing capacity, and there is already evidence of this happening.

Safety is an excellent measure of manufacturing performance. Experience of other industries demonstrates a direct correlation between excellent manufacturing practices and excellent safety. In the pharmaceutical industry, there is scope to improve the safety. It is good, but not outstanding. The other measures are supportive of the conclusions. Given the nature of the industry, one would expect a high OTIF and right first time. The CpK should be nearer four to six than the two to three measured. Similarly, for many formulation and packaging operations, one could expect the cycle time to be less than 24 hours rather than several days.

Following the launch of a new molecule, there is often a period of 10 to 15 years patent protection before the molecule is available for competition from generic manufacturers. In

many industries, such a protection window is used to hone the principles of lean manufacturing, such that at the end of the protection window, it is the most competitive manufacturing operation in the world. If that were the case in the pharmaceutical industry, competition from generic manufacturers would be less of an issue.

Benchmarking Research and Development

The effectiveness of new drug research and development is a key to the success and share price of the pharmaceutical industry. In this respect, the pharmaceutical industry is almost unique. A consequence is that the financial analysts regularly benchmark and report the effectiveness of the R&D processes. One example featured in the annual report by the Novartis Chairman Highlights in 2003 is the analysis published by Goldman Sachs.[4] The measure used is NPV/Capitalized R&D.

This is the NPV of the product pipeline divided by the capitalized value of the research investment. This is a real benchmark of the performance effectiveness of different pharmaceutical companies. The data indicates that this varies from a high of 2.1 to a low of 0.3 with and average of 0.9.

ABB has benchmarked New Product Development in both pharmaceuticals and other industries. While a smaller database than manufacturing, Table B provides real benchmarks for the research and development process.

The R&D Stage Gate process is used to manage the new molecule development process and the concept of OEE applies, though in this case it is the New Product Development Efficiency. This is a very demanding measure because it is the product of three numbers that are less than one.

The figures in the table are for typical pharmaceutical research, primarily in the UK. The world-class figures are for research and development, and are the best observed and recorded within and outside the pharmaceutical industry where that is appropriate. The Bottleneck Gate is the one which, on analysis, is the rate determining Gate.

Potential Benefits of World Class Research and Development Operations

While again these are only figures, it is the interpretation that brings out the real significance.

The most significant is the NPV/Capitalized R&D. Comparing the average with the world class suggests that some companies are more than twice as effective at successfully developing new molecules. If all companies could move to the practices and performance of the best this would lower the average cost of developing a new molecule from $802 million to <$344 million[5] (Calculation 3).

The other figures provide supporting evidence. Consider, for example, the ratio of nominations to launch. If industry could reduce this from 5,000 molecules to 2,000 molecules by more insight or scientific intuition, the benefit to the industry would be to increase the number of new drugs released by a factor of 2.5. That would increase the percent of sales from products that are less than five years old. It would represent a 2.5 fold increase in the effectiveness of the whole R&D process.

- NPE = RFT * Product rate * Availability
- RFT - % product that delivered RFT (no retesting etc)
- Product rate = $\frac{\text{Best ever time for gate}}{\text{Actual time to gate}}$
- Availability of critical resource = 100 - % time due to unavailability
- Typical values are
  - RFT – 85%
  - Product rate – 75%
  - Availability – 65%
  - NPE – 41.4%
- Note This is measured at the Bottleneck Gate - for a 5 stage Gate Process to release this would suggest an overall NPD efficiency of $(0.414)^5 = 1.2\%$!!

Figure 3. New Product Efficiency (NPE) - equivalent of OEE for R&D.

Similarly, if the new product efficiency could be increased from a typical 40% to 80% the development process time could be cut in half and the output doubled. This is the driver behind many of the current developments to automated evaluation and combinatorial chemistry.

It is recognized that drug discovery and science cannot be forced, and invention is a hard process. What can improve are the Practices adopted to support the drug discovery and product formulation processes that will ensure maximum speed and cost effectiveness to market.

While these are broad-brush figures, they are very significant figures, which would suggest that with the current world research budget of $43 billion, the number of successful new molecules developed could double or the total world research budget could be cut in half by adoption of best practices.

Delivering the Benefits

Other industries like food, electronics, automotive, and printing have extensive experience of delivering world class manufacturing, research, and development. The practices and tools are widely reported under the heading of Lean Manufacturing.[6] Some common messages are:

- It is a journey that takes time. For example, the practical limit in delivering OEE improvements is in the range of 4% to 8% per year.
- Constant leadership and support from the very top of the company is essential.
- The first step is to benchmark the existing processes, accept the results, and establish a consistent set of Key Performance Indicators that are used to drive the improvement journey.
- The improvement tools are known and much experience is readily available from other companies outside the pharmaceutical industry.

The investment in delivering these benefits is relatively

SOME OPERATIONS BENCHMARKS			
KPI	**Pharmaceutical Industry**	**A Winning Pharmaceutical Plant**	**A World Class Plant**
Stock turn	3 to 5	14	50
OTIF	60% to 80%	97.4%	99.6%
RFT	85% to 95%	96.0%	99.4%
CpK	1 to 2	3.5	3.2
OEE	30.0%	74.0%	92.0%
Cycle time hours	720	48	8
Hrs/LTA	1,000,000	2,000,000	10,000,000

Table A. Pharmaceutical plant benchmarks.

small compared with the costs of holding stock and developing new molecules.

Conclusions of the Benchmarking Evidence

The benchmarking figures suggest:

- Manufacturing has the potential to more than double the production of drugs from its existing assets by moving to world class manufacturing practices.

- Research has the potential to more than double the number of new drugs being released to the market.

Combining these two figures suggests, however tentatively, that the industry already has the assets necessary to manufacture the outputs from the increased productivity in the research environment.

The benefits of grasping this opportunity would be to significantly reduce:

- break even point of launch

- depreciation costs built into the selling price of the drugs

- counter the impact of generic competition

- make the drugs more widely available to the developing world

This would answer many of today's pharmaceutical industry challenges.

This is the real driver behind the FDA encouraging a move to Real Time Drug Release, delivery of which will require world-class manufacturing performance operating in conjunction with world-class research and development.

Other industries have already made the journey and the learning is equally applicable. It is possible for the Pharmaceutical Industry to "pinch with pride" from other operations from within both the pharmaceutical industry and elsewhere. Other industries realized:

"Standing still is the fastest way of going backwards."

Calculations

1. **Cash release from stock**
   Industry turnover $290 billion, average stock turn four, stock value $290/4=$75 billion. Winning pharmaceutical company stock turns 14. If all manufacturers achieved that performance, stock value $290/14=$20.7 billion. Potential saving = $75-$20.7 = $54.3billion

2. **Doubling the plant output**
   The average OEE in the pharmaceutical industry is measured at 30%. If the average OEE increased to 74%, the increase in output would be 74/30=2.46.

3. **Improving the effectiveness of the R&D process**
   Average NPV/Capitalized R&D = 0.9. The world-class figure is 2.1. Average cost of new molecule development to market $802 million. If the average increased to the world-class figure, this would fall to $802*0.9/2.1=$344 million.

Benchmark Definitions

Stock turn - this is the total turnover on the site at manufacturing price divided by all the stocks on the site on the same basis. Stocks include finished goods, work in progress, and purchased raw materials.

On Time in Full (OTIF) delivery - this is the percentage of orders that are satisfied on time in full with zero defects. Note that if there is one defect in an order, the OTIF is zero percent.

Right First Time (RFT) - this is the percentage of the products that at the point of manufacture are delivered right first time with no defects. Any recycling, blending, rework of documentation, or laboratory testing, or other adjustments is excluded from the right first time figure.

CpK - is a statistical process measure on the variability of the product. A Six Sigma figure corresponds to only four defects per million products while a Two Sigma figure corresponds to 308,000 defects per million products. This is measured on a logarithmic scale.

BENCHMARKING PHARMACEUTICAL RESEARCH/DEVELOPMENT		
	Typical Pharmaceutical Research	**World Class Pharmaceutical Research**
% sales from products < 5 years old	25%	60%
Number of active patents/ R&D employee	0.04	0.06
New Product Efficiency (NPE) @ bottleneck	40%	85%
Ratio nominations/launch	5000	2000
Absenteeism %	2%	< 1.0%
Hours/reportable accident	1,000,000	> 10,000,000

Table B. Pharmaceutical research benchmarks.

Overall Equipment Effectiveness (OEE) - this measures how effectively the manufacturing equipment is used. It is a product of the product rate multiplied by the quality rate multiplied by the plant availability. A figure of 100% implies the plant is running flat out every hour of the day making perfect product. A figure of 10% implies the plant could achieve 10 times the output that it currently achieves.

Life Cycle Time - this is the total time from commencing manufacture to delivering products to the customers, which in many cases is the factory warehouse.

Hours per reportable incident - this is the number of working hours achieved for all employees between reportable incidents. A reportable incident is one where the absence is greater than or equal to three days absence.

NPV/capitalized R&D is a benchmark used by Goldman Sachs to judge research effectiveness in the pharmaceuticals industry. This is the NPV of the product pipeline divided by the capitalized value of the research investment.

Percent of sales for products less than five years is a percentage of products sold today that did not exist in the product portfolio five years previously. It is a well-established metric for innovation, perhaps most widely associated with 3M.

Number of active patents per R&D employee is simply the number of patents that are active and being pursued divided by the number of R&D employees.

Ratio of nominations to launch is the number of molecules that entered the gate process divided by the number of molecules that are commercially launched.

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The Beginning of ISPE's 25 Years

by Don Cattaneo, Retired, Drug & Device Associates, ISPE Past President and Founding Member, and Cheryl Cattaneo, ISPE Founding Staff Member

Why Start ISPE?

Don: Prior to 1972, the FDA's main concern was "cross contamination" which pertained to oral dose. In 1972, Abbott Labs had a major recall of all their IV solutions, which were found not to be sterile. The FDA discovered that while all products were going through the sterilization process, they were not being sterilized. That began the process of determining how you could prove that the process was under control. It was out of that situation that another term, validation, became famous. The words "dead leg" became the watch words for mechanical engineers. The problem was, if you were not directly involved within the pharmaceutical industry, you didn't comprehend dead legs or validation. There was no knowledge base in the industry or the FDA for the industry to learn from the mistakes of others.

The industry's relationship with the FDA had been that the FDA was the enemy. The attitude was that the industry knew more than some Government hack. Even the Freedom of Information Act was not available. At that time, I was building a specialized IV plant for Pharmacia and it was the first sterilized product facility approved after the Abbott shutdown. Because there were no basic guidelines, the company went to the FDA before the plant was built with plans and specifications and got the FDA's input. This put them in the position of "part ownership" and certainly affected the approval cycle. (If you can't fight them, join them.)

In that era, the only thing to do was design and build everything in an "overkill" manner. The A&E firms we worked with really couldn't believe some of the requirements we specified. The industry people were guessing in many cases, but they tried to anticipate what the FDA was going to require. At that time, more emphasis was on how to satisfy the FDA in order to try to get the sterilized products process under control. Those demands varied a great deal with the inspector in your district.

A Forum for Engineers and the FDA

Don: By 1979, the industry was learning by trial and error as to what acceptable validation was. There was no place to go to get good information. Companies would not release information because they were afraid that it would be used against them by the FDA. The American Pharmaceutical Association (APhA) was more concerned about the local pharmacist rather than the industrial pharmacist. The PDA devoted most of their efforts toward theory, not physical application.

It was in that spirit that Paul Simmons and I felt there was a need for a forum for engineers and the FDA to discuss what was expected, what was possible, and what was acceptable. Paul and I called people we knew in the industry to see if they would head up the "National Society of Pharmaceutical Engineers." After the meeting at the Admiral Club in New York, the name was changed to the International Society of Pharmaceutical Engineers. It also was decided before the meeting to have a journal that was devoted to pharmaceutical engineers. The only magazine published at that time had a format of one article per issue and the rest was advertisements. We decided that the format of 60/40 would be used... 60% articles and 40% advertising. In the beginning, that was no problem because few would advertise in the journal.

Since the funding came from the two founders, we were limited to a few things we could do. The key was getting members to join. From August 1980 to August 1981, we had less than 200 members. The first annual meeting held in November 1980 had about 45 people attend, of which about 25 were FDA people who came for free. Money was a real problem!

Cheryl: The only avenue we had originally to increase membership was by getting mailing lists from some vendors, mailing out Society information, and then I would call these people. Literally one-on-one phone calls were made requesting these engineers and managers to join the Society. The meeting at the Admiral Club was attended by Chuck Newcomb, Paul Simmons, Jim O'Brien, Peter Merrett, Tom Henry, and staff, Diane Simmons, Dave Boyer, and me. The meeting's purpose was to get the industry people to commit to allowing us to use their names in promoting the Society, be sounding boards for technical advice, and information sources for hot issues in the industry.

The staff was prepared to "take off" with those commitments from the attendees. We began a full scale membership promotion, the first journal issue, and seminar outlines.

A New Society

Cheryl: The Society was an idea that Paul and Don had earlier in 1980. At that time, I was working at Astra Pharmaceutical in Worcester, Massachusetts. Paul had become a consultant there and he told me about this idea and invited me to join this project. On 1 July 1980 I moved to Tampa to become employed by ISPE. At that time, it was only Diane Simmons, Dave Boyer, and myself. To this day, I can't believe I moved that distance based on how little I knew about it.

Don: What really got the Society off the ground was the first seminar held in February 1981 in Tampa at the airport. It was the first time that the industry and the FDA shared the same platform. To get industry speakers, we had to state the views of the speaker were his/her own and did not necessarily represent their employer. Many of the speakers were vendors. We soon realized that we had to get the industry more

Continued on page 3.

A Look Over the Years

by Robert P. Best, ISPE President and CEO

Few things in life are more exciting than taking a good idea, nurturing it, and seeing it come to fruition. I have been blessed with such an opportunity as a member of the ISPE team for 21 of its 25 years. It has been a fast, thrilling ride as the Society has evolved from an organization struggling to survive and find an identity to one racing to keep pace with a growing number of requests and opportunities.

Back in 1980 the founders of ISPE recognized that an important segment of the industry was not being properly represented by existing organizations. They reasoned that as a global industry this same void inevitably existed in other parts of the world. So they decided to launch a professional society for "Pharmaceutical Engineers", initially in the United States, but they had the foresight to put the word "International" in the title for the years ahead. Today, with Members from 81 countries and Affiliates established in 26 of them, we can conclude that the founders were truly visionaries.

But I suspect that even they never imagined that ISPE would grow to 23,000 Members, or be invited to serve as a technical advisor to ICH for the US FDA, or be asked to facilitate a discussion between two governments exploring a Mutual Recognition Agreement. As an organization built from the bottom up, the founders could not have believed that senior industry management would one day knock on the door and ask ISPE to write technical documents *with* support of the FDA. In their wildest dreams they could not have foreseen a US Vice Presidential commendation for a document ISPE wrote *for* the FDA.

There have been several significant developments critical to ISPE's dramatic growth, but for me, three stand out. These include the establishment of the Chapters and Affiliates, the expansion into Europe, and the creation of the Baseline® Guides and GAMP®. The first two have provided more tangible Member benefits on a convenient, local level, and the latter thrust ISPE into the role of provider for the industry beyond being a provider for individuals in the industry. With that the Society was able to attract senior management, first with the Pharmaceutical Advisory Council, and more recently with the International Leadership Forum.

In the early years involvement with regulatory agencies was limited to the US FDA, and then only as speakers in *ISPE's* programs. Today ISPE works closely with regulators all over the world, including the EMEA, JMHLW, PIC/S, the WHO and many others. On a recent trip I had the honor of meeting with the Drug Controller General of India and the Secretary General of the Thailand FDA on successive days to discuss how ISPE could provide education to meet *their* needs.

Academia has been another recent focus for the Society. This began with one Student Chapter in 1991 at the New Jersey Institute of Technology and today includes 41 Chapters around the world. Efforts are underway to work with universities in the US, Europe, and Asia to develop a curriculum to prepare the best and brightest to become the innovators critically needed for an industry undergoing dramatic change.

The founders' vision and dedication has been transferred through a quarter century of people similarly passionate about ISPE. That has expanded from the original five-member board to a complex governance structure of board, committee, affiliate and chapter leadership, speakers and authors. And from the original four-member staff I inherited to over 60 in the Tampa headquarters and Brussels and Singapore regional offices. By now thousands of people have had a hand in the growth in numbers, activities, geography, and prestige ISPE has experienced in 25 years. And for an individual membership organization this growth has truly been commendable, exceptional, and enviable. I congratulate all the leaders for their commitment to an organization that has become an indispensable contributor to the life science community. Thank you for letting me be a part of it.

The Beginning of ISPE's 25 Years

Continued from page 1.

involved to be sure our credibility would be acceptable. At this time, the Society was run by a staff of two: Cheryl and Diane. The journal was run by Dave Boyer. Only Cheryl and I had ever worked in the pharmaceutical industry.

Breaking Down the Walls Between Industry and the FDA

Don: The main problem that the Society had was breaking down walls between the industry and the FDA. The FDA didn't trust the industry because they kept discovering products that were not being made correctly. The recalls were out of sight.

The industry's attitude was that they knew more than the FDA and that the FDA expected impossible or impractical and costly changes. We knew that if the Society was to survive, we had to get a dialogue going between the FDA and the industry. One of the most positive people in the FDA agreed to meet with Cheryl and I to set up FDA speakers for ISPE seminars. By getting FDA speakers at these seminars, the industry couldn't afford NOT to send their people to listen and learn what the FDA expected. The seminars proved to be the influx of cash the Society needed to stay alive.

Cheryl: These seminars also became a wonderful platform to recruit new members, speakers, board nominees, advertisers, etc. I went out of my way to utilize this time to "network" people there for each other and for us. I wanted there to be the friendly forum they said they needed. My goal was for us to be an indispensable source of information and support for them in their jobs. I often was given questions to ask speakers, the FDA, etc., that some engineer did not feel comfortable asking directly, especially at seminars.

The biggest struggle was money, money, money. We had to be very hands on for every little task. We labeled and bulk mailed our own journals, mailings, etc., with no equipment to help us. We worked lots of hours and weekends to meet our deadlines.

Getting off the Ground

Don: The second Board of Directors really took hold of the Society. They really believed in it and made it truly one that was run for the benefit of the industry. The Board members were asked to sign for a line of credit of $100,000. Only the Board members who lived out of state were asked since it was felt that, if the Society failed, the bank could not call in the line of credit easily. While the Society could have folded several times, it just seemed to get by. By the time we discovered that the Executive Director was not really business oriented, the debts had piled up. I believe Jim O'Brien and Dick Purdy came to Tampa and dismissed the Executive Director (Ron Hall). They hired a consultant (Cheryl) to run the Society and started the search for a new director. After an extensive interview cycle, the choice came down to an accountant or a public relations person from the Tampa Bay Bucs. Because of the financial problems, some thought we could use the accountant. Some felt we could always hire an accountant, but needed the public relations' experience to make the Society better known and influence people to join. Bob Best was hired, and the rest is history.

Cheryl: Frankly, I give lots of credit for ISPE's survival to the vendor members we had been fortunate enough to attract. I hesitate to name them because there were several and I would hate to leave anyone out; however, Walt Stadnisky at Millipore at that time; Vic DiChiara; Rich Malfa; Scott Geyer (Tri-Clover); Bob Gray (MECO); Chris Anderson; Dick Rooney, and a few other incredible people not only stood by us, but gave me SO much support. They were always available, always said yes to whatever I asked, and put their money where their mouths were. I can't say enough about what this had meant to the Society's success. They were everything!

There were many times that the staff did not get paid. Actually, my first two paychecks bounced at the bank. That was frightening. Many creditors were "pounding at the door."

All of the people that helped during the early days were unsure we would ever really get off the ground. They took a huge chance with their budgets, their time, and their contacts to make this happen. With everything else that competed for their attention, they were never anything but supportive, honest, and interested.

Early Numbers and Expansion

Don: When we started the Society in 1980 our goal was to have a membership of 500! We thought that perhaps 750 people might join the Society eventually. By naming the Society for the pharmaceutical industry, we cut off access to the medical device industry, which fought hard not to be controlled by pharmaceutical standards. After the first two years we came to the conclusion that if we counted on vendors joining, we could perhaps set a goal of 1,500 members.

Later on, a consultant was hired and calculated that the maximum number of members could be 8,000. It was when the Society decided to have chapters and the expansion really took hold.

Cheryl: I never believed we could have more than 2,000 members. I know how hard we worked at the beginning to get to 500 and how we celebrated each hundred achievement.

Doing Things Differently

Don: It is really hard to say what you would do differently. It would be much easier to start the Society today because the relationship of the industry is totally different. I believe the Society brought about that change. However, in the late 1970s and early 1980s there was no trust. The industry did not exchange information with each other. Consultants had a field

Continued on page 5.

The Future of ISPE -- Engineering Pharmaceutical Innovation

by Gert Moelgaard, Vice President, Process and Mechanical, NNE A/S, and ISPE Chairman of the Board 2005-2006

As ISPE celebrates the 25th anniversary of the Society, it is a good time to look both backward and forward at the challenges and opportunities we have been through and those we have ahead of us. We have achieved great results in the past and can be proud to represent the largest global Society for professionals in our field, soon approaching 25,000 members around the world and setting the standards in the many important areas that we are involved in worldwide.

1980 Challenges

ISPE started off humbly in 1980 with a simple purpose of providing education and networking opportunities for professionals in the pharmaceutical industry. By naming the Society "International Society of Pharmaceutical Engineers," the name, purpose, and values were set for something big. I do not think the ambitions were as big as the real result has been and I think it proves that to strive for ambitious, but realistic, goals is the best recipe for success in the long run. Our successes are spreading this spirit of ISPE throughout the world with more Affiliates and Chapters, with global and local events, with technical documents like the Baseline® Guides and GAMP® and many other activities. As a meeting place for members from industry, suppliers, academia, and regulators, we work at the very core for stimulating innovation and improving life for patients and other people worldwide.

ISPE's very first conference, titled "Upgrade to Meet cGMPs," became the motto for many years to follow. Back then, the US Good Manufacturing Practice regulation (from 1978) was fairly new and starting to influence pharmaceutical facilities and industrial practices. At the time, it was a real challenge for professionals in the industry – as well as for suppliers to the industry. For good reasons people needed a forum to meet and discuss current industry practices in the view of the new GMP requirements. It is hard to imagine today how difficult it was for daily practitioners in the industry to comply with the regulations. Especially as the little 'c' in cGMP – *current* Good Manufacturing Practices – gradually raised the bar for regulatory expectations, with a constant need for updates as regulatory inspections and new industry practices led into stricter and more advanced practices month by month and year by year.

In this environment, ISPE became the practitioners' Society. They were good at combining the regulation with good practice sharing throughout the industry and that made professionals from many pharmaceutical companies and suppliers seek the meeting place here. The sharing of practical solutions and practices among professionals and companies paved a cost-effective way of staying ahead of trouble and seeking better solutions.

2005 Challenges

In 2005 and forward, we are again facing big changes in industry's current practices and again they are being lead by regulatory changes. These changes may be just as challenging as in 2005, but they are more in line with practices of other mass-manufacturing industries. New regulations are starting to take shape with the risk-based approach to GMPs and the new focus on risk for the patients and on scientific product and process knowledge. But unlike in 1980, the present challenge is now international – or global - right from the start. It adds new opportunities and challenges that will be setting the new agenda for ISPE many years ahead.

We need to realize that many of the industry practices that have evolved in the past did NOT focus on real product and process understanding. Some of them have evolved into heavy, costly, and slowing practices of time- and money consuming activities that prevent good quality rather than ensuring it. Industry can get more quality to the patients for the same or less money by changing practices with inspiration from other industries that have better and more cost-effective quality practices with a long and good experience. This is a big opportunity and a big challenge for industry - and for ISPE - going forward.

Like in 1980 when the focus was on "Upgrade to meet cGMPs," we need to realize that most of the industry practitioners in the future will need to change many of their practices. They will need to focus more on science, methods, and tools that ensure quality as the products are being produced, rather than relying on Great Mounds of Paper to demonstrate compliance. Tools ensuring quality-by-design and ensuring a new kind of change control in our practices such as Process Analytical Technology (PAT), statistical process control, and controlled product variation are examples of skills of the future that will require training and re-education in industry.

And unlike in 1980, ISPE is now prepared to do it in close cooperation with academia, universities, regulators etc. from all over the world as we are now a global organization with a very broad membership and support.

Many New ISPE Initiatives Underway

"The pharmaceutical engineer of the future" will need to play a larger technical role in process design and development as well as in manufacturing. This will in turn require a science and skill set that will need to be developed around this entire area to prepare en-

The Future of ISPE...

gineers for the needs of the future pharmaceutical manufacturing business. Furthermore, a significant part of the new products in the pipelines are biopharmaceutical, so we are starting to see a major paradigm shift.

ISPE wants to remain the practitioners' Society in the future and as THE leading meeting place to seek training, solutions, and experiences. Therefore, we need to capture, educate, and share knowledge based on these principles. This will be an important part of ISPE's guiding principles of the future.

Today's ISPE is in good shape to cope with the changes with more than 10 years of close cooperation with regulators, starting with the FDA cooperation on Scale-Up and Post-Approval Changes (SUPAC). This type of teamwork has become the foundation of a long and good relationship. Now we work closely with the FDA and other regulators in a global perspective to educate, set standards, and make the change happen. A recent example was last year when the US FDA took the global regulatory lead on PAT. Here ISPE was a committed partner to bring out the message globally through a number of joint global events.

Furthermore, we are working to establish a new certification program of Chartered Pharmaceutical Professional – ChPP. We are establishing a new peer-reviewed industry-scientific journal that supports a protected scientific body-of-knowledge. We are revamping our training courses and seminars to provide the right knowledge. We have started a set of global Communities of Practices (COPs) in selected areas of industry practices of global importance, bringing together ISPE's strength of being global and local at the same time. And we are working together with selected industry organizations such as ASTM, AAPS, and IFPAT-MA to make sure that we do remain the leading Society for our members in the challenges ahead.

ISPE's core purpose is to develop innovative professionals to achieve technical and operational excellence in the Pharmaceutical Industry. With our broad membership and strong support from industry, suppliers, regulators, and academia worldwide, we are committed to make it happen now – and in the future.

Come to ISPE's Annual Meeting 2005 in Scottsdale, Arizona, USA

We will celebrate our 25th anniversary at the 2005 Annual Meeting in Scottsdale, Arizona 6-10 November. I encourage you to be there because there is a lot to learn and a very good reason to celebrate 25 years of success and growth. You as a member of ISPE have brought us to where we are. We are now a global membership organization soon approaching 25,000 members and we are the number one meeting place for members that are professionals in and around the pharmaceutical industry.

The Beginning of ISPE's 25 Years

Continued from page 3.

day because they knew with some limitations what different companies were doing and could indirectly use that knowledge. Also, those consultants had a better idea of what the FDA was looking at. It took at least five years for the industry to recognize the value of ISPE. If something should have been done differently, it is probably the name of the Society. The name turned off the medical device industry and the Bureau of Biologics. It took a while to get that group into the fold.

Cheryl: I don't know what could have been done differently. I will say that the struggles at the beginning and the necessary hands-on approach meant I got to know some of these members very well. We worked hard and played hard together and they became friends through and through. We went through job changes, cutbacks, marital problems, family deaths, injuries and illnesses, family births, marriages, divorces, and member deaths with them. I still mourn some key people who are no longer with us as though they were family members. I guess they were.

The Future of ISPE

Don: Being retired, it is difficult for me to envision the future of ISPE. It is astounding to me that the Society has grown the way it has. Not surprising... but astounding. Because of the leadership and the great support of the members, I believe there are still untapped members in the medical device area. If the Society could find a way to assist that industry, it could open the flood gates. Since many of the medical device company supplies come from developing nations, it could expand the coverage into countries where ISPE's presence is limited.

A Partnership made in Heaven

The Pharmaceutical Engineers work with the FDA

by Wes Wheeler, President, NA Region Global Commercial Development, Valeant Pharmaceuticals, and Past Chairman Baseline® Guides Steering Committee

How do you design a best in class factory for the lowest cost? Pharmaceutical engineers have been puzzled by this for years. Why?... because the regulations, although clear, are difficult to convert into design documents. The broad and varied interpretations of the FDA's Good Manufacturing Practices (GMPs) have frustrated engineers who strive for precision and detail. Without precise guidance, we found ourselves designing new facilities to exceed the standards of the last one built. We found ourselves sending our young designers to conferences to get hints from FDA speakers and we did our best to read between the lines to get the latest and greatest clues. We hired consultants to tell us what it would take to be the best and avoid disaster when we wanted to launch without an approved facility. Nobody wanted to fail the Pre-Approval Inspection (PAI)... there was too much at stake for the company.

In the 1980s and 1990s, we as an industry drove the costs of pharmaceutical facilities to record highs. We designed for the worst case, the maximum quality range, the most conservative inspector, and the most cautious and risk-averse validation consultant. We took no chances and we paid for it. And nobody was willing to change the status quo.

At least not until 1994 when ISPE took a chance. With the support of their respective companies and the ISPE, a few pharmaceutical executives led by Tim Tyson (then at GSK) approached the FDA with a proposal to create a partnership. The idea was to create more illustrative and specific guidance to engineers which would satisfy the FDA's quest for GMP compliance while providing engineers with some flexibility to design what they thought was best. The FDA were receptive and for the first time assigned their own people to help lead the way. I was asked by ISPE to lead the initiative, which ultimately led to an activity which would transform the industry, and the pharmaceutical engineers around the world who design our facilities.

It was a daunting challenge, but we assembled a team which consisted of engineers from GSK, Merck, Lilly, Roche, and nine other companies. FDA staffers Joe Phillips and Paul D'Eramo were assigned to the team by the Commissioner's office. Our first meetings were difficult, but we all knew we were blazing new ground, and if we were successful, we could change our industry. We took the job very seriously.

We began by drafting our charter. It was groundbreaking work at almost every turn. Lawyers got involved. Pharmaceutical executives bantered. Consultants wanted in. We decided that we couldn't create 'Guidelines', as FDA denotes a special meaning to the term. We settled on 'Baseline® Guides' as a name. Ultimately, ISPE and the FDA would approve the charter, and in June of 1996 they gave their legal approval and their logo to the document, an industry first.

We set out to draft 12 Baseline® Guides covering all types of pharmaceutical faciltities. There were many priorities: water, oral solid dosage, sterile facilities, commissioning (as opposed to validation) and even warehousing. The GAMP® Guide had already been written, so we put this at the end of the priority list. We ultimately chose Bulk Pharmaceutical Chemicals (BPC) as our first Guide, primarily because it was an area with few controversies, and an area that FDA was still struggling with. It was also an area where broad interpretations existed across the world. Cross contamination and appropriate water were key issues. Air flow and physical barrier in closed systems were also debated. The FDA listened and heard the arguments, and ultimately agreed with a 'baseline' that we could all work with. We cut our teeth on BPC, tested the relationship with the FDA, and felt confident that we could accomplish an early win for the partnership. Dozens of meetings, 18 months, and several re-drafts later, we had a document. The industry and the FDA had agreed to a new guidance. We immediately began work on the 'Sterile Manufacturing Facilities' and the 'Water and Steam Systems' documents. New teams were recruited and in November of 1996, I formally handed my role as Chairman back to ISPE.

In the years that followed, ISPE published six Baseline® Guides and have even begun revising some of the earlier Guides, including Bulk Pharmaceutical Chemicals. I understand that nearly 18,000 Guides have been sold throughout the world and are frequently referenced by, and hopefully challenged by, the next generation of pharmaceutical engineers. The Guides are the subject of training sessions at ISPE meetings, and as we first hoped, the Guides are being used as a baseline for the design of new pharmaceutical facilities across the world.

It was 10 years ago that I was asked to chair the new Baseline® Guides Committee which ultimately led to such a successful journey for ISPE. Although I have moved on to new challenges on the commercial side, I have never forgotten the important work we did together with ISPE and the FDA. I salute Bob Best, the ISPE Executive Council and the original Baseline® Guides team for their vision, support, and transforming work.

SUPAC Equipment Addendum: Eight Years in Use, Eight Years Strong

by Russ Somma, PhD, SommaTech, Inc., a division of IPS, and Past Chairman ISPE SUPAC Committee

Introduction

Eight years ago ISPE in cooperation with the FDA rolled out what has become to be regarded as the most significant guidance for industry in many years. The "Guideline for Industry: Manufacturing Equipment Addendum for SUPAC," guidance was a major breakthrough as far as FDA regulation is concerned. The partnership with the FDA was strong and the shared vision with ISPE brought this landmark guidance into every day use. The subsequent cost savings to industry is incalculable. But the most laudable aspect of the equipment addendum is its staying power as it is still routinely referenced eight years later.

History and Our Mission

At the FDA's invitation, ISPE collaborated with the Office for Regulatory Affairs (ORA) and the Center for Drug Evaluation and Research (CDER) to develop a list of "similar equipment." The list was needed for the implementation of CDER's Scale-Up and Post Approval Changes (SUPAC). Each SUPAC guide would cover a selected dosage form. The Guides envisioned included immediate release solid dosage forms, modified release solid dosage forms, and semi-solid topical dosage forms. Each Guide required an associated equipment addendum.

SUPAC defines manufacturing changes, directs how CDER is notified, and specifies the data to accompany change submissions. The "similar equipment list" or Equipment Addendum (EA) classifies comparable equipment by design and operating principle. The implementation of SUPAC with the associated equipment addenda have simplified CDER review of submissions. This simplification has proven to provide a significant cost saving effect for industry stakeholders.

The FDA came to ISPE because it represented a worldwide network of 10,000 engineers with broad based experience with manufacturing equipment. The FDA and ISPE have an excellent relationship having crafted together and delivering on several key tasks. An example of which is the Baseline® Guides for industry.

Many things have changed since that time including issuance of the "Changes to Approved NDA and ANDA," Industry Guidance in 1999. However, the utility of the equipment addendum continues to be valid with its main purpose of describing same design and operating principles for pharmaceutical processing equipment.

Chronologically these documents from conception to ultimate acceptance by the FDA and roll out to industry may be summarized:

- SUPAC EA Immediate Release (IR) Team Formed 10/96
- SUPAC EA Immediate Release (IR) Guidance issued 10/97
- SUPAC EA Modified Release (MR) completed 11/97
- SUPAC EA IR and MR documents merged 11/97
- SUPAC EA IR/MR Guidance issued 4/98
- SUPAC EA Team and FDA Meeting 6/98 for Final Roll Out
  - Introduction section updated for industry
  - Formal change control established to:
    - § Maintain equipment list current
    - § Track technology changes
    - § Assure list undergoes expert peer review periodically
  - Set up training for industry and FDA end users
- SUPAC EA Semi-Solid completed 6/98

The SUPAC Equipment Addendum Committee created a mission statement which embraced these efforts as well as providing for the mandatory maintenance of the EA which was foreseen.

"To encourage free and open communication with regard to the use, design, and operating principles for Pharmaceutical Processing Equipment within the Pharmaceutical Industry; to assure clarity and uniformity when dealing with process descriptions and regulatory changes; to make these data available to the industry by fulfilling the role of clearing house as well as providing expert peer review when documenting equipment classifications while maintaining the custodial duties of equipment comparability documentation."

Recognition

The genesis of the equipment addendum documents covers the selfless efforts of more than 60 ISPE professionals including engineers, pharmaceutical technologists, and ISPE staff.

For these efforts, at that time Vice President Gore's Committee for National Performance Review (NPR) presented the Vice President's *Hammer Award* to FDA's Office of Regulatory Affairs, Center for Drug Evaluation and Research, and ISPE. The Hammer Award is given to federal employees and their partners who advance the NPR's goals of cutting red tape, improving customer service, and building a better and more cost effective government.

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GAMP Guidance – Practical and Evolving Guidance for Industry

by Gail Evans, ISPE Technical Documents Advisor and Sion Wyn, Director, Conformity Ltd. and ISPE Technical Consultant

Introduction

A significant part of ISPE's commitment to the advancement of the educational and technical efficiency of its members has been met through the development of high quality, practical, and timely technical documents.

ISPE Baseline® documents have established and defined a cost effective approach to facility engineering, while still meeting regulatory expectations. Similarly, GAMP® Guidance has assisted both industry and regulators by defining a common framework for discussion and progress in the area of computer system validation and compliance.

GAMP 4 - *The GAMP Guide for Validation of Automated Systems* - is the most widely used and referenced international Guide for the validation of regulated computer systems in the life-science industries. GAMP guidance is developed with input from many of the world's major pharmaceutical and healthcare companies. It is widely referenced in FDA and PIC/S documents, and UK MHRA is represented on the GAMP Europe Steering Committee.

Good Automated Manufacturing Practice (GAMP) guidance aims to achieve validated and compliant automated systems meeting all current regulatory life science expectations, by building upon existing industry good practice in an efficient and effective manner.

The GAMP 4 Guide is intended for use by both *users* and *suppliers* of *automated systems*. The scope includes standard, configurable, and customizable products, as well as custom (bespoke) applications. The following terms are used throughout:

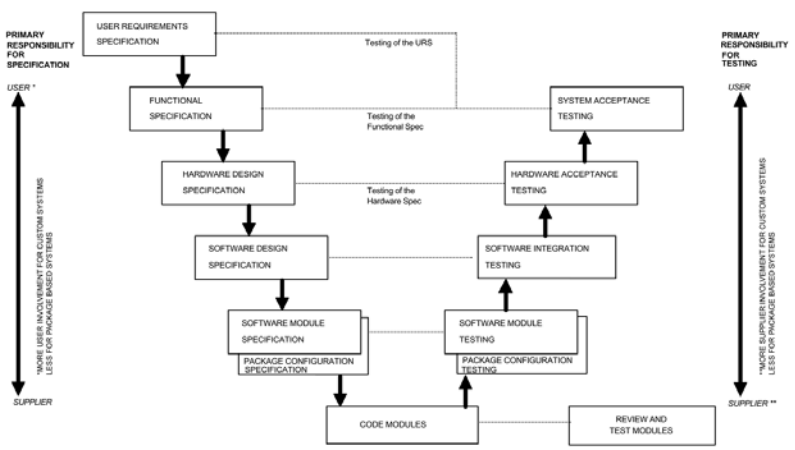
User
The customer or user organization contracting a supplier to provide a product. It is, therefore, not intended to apply only to individuals who *use* the system, and is synonymous with *customer*.

Supplier
Any organization or individual contracted directly by the user to supply a product.

Automated System
A broad range of systems including, but not limited to, automated manufacturing equipment, automated laboratory equipment, process control, manufacturing execution, laboratory information management, manufacturing resource planning, clinical trials data management, and document management systems.

The automated system consists of the hardware, software, and network components, together with the controlled functions and associated documentation. Automated systems are sometimes referred to as computerized systems.

GxP Regulated Automated Systems
Automated systems that may have an impact on product quality, safety, or efficacy are subject to GxP regulations. The user must ensure that such systems comply with the appropriate regulations.



Background

In the late eighties and early nineties, the validation of automated systems in pharmaceutical manufacturing assumed a much greater importance than had previously been the case. Although regulatory guidelines concerning the use of such automated systems had been available for some time, these systems had been subjected to less regulatory scrutiny than some other areas, and the interpretation of the regulatory guidance was less mature than in more conventional areas.

The focus on automated systems in pharmaceutical manufacturing increased due to their wider use and greater complexity. With this came the need to improve understanding and interpretation of the regulations. Better communication was required, not only within the pharmaceutical industry, but also with its suppliers and regulators.

An industry group was set up to promote that understanding. This group is now known as the GAMP Forum, which is now a very active Community of Practice within ISPE, with wide and diverse worldwide participation.

As interest and participation has grown, the GAMP organization also has developed and matured. At the highest level, policy and strategy is defined by a GAMP Council, which oversees regional Steering Committees covering Europe, the Americas, and Japan. Local groups, such as GAMP Nordic, and GAMP D-A-CH (covering German-speaking areas) are also very active. Special Interest Groups (SIGs) provide forums for discussion of detailed technical issues, possibly leading to published guidance. There is also an active Supplier Group focusing on the needs and interests of sup-

GAMP Guidance...

pliers. For further information on the GAMP Forum, see the ISPE Web site.

Guidance

On formation, one of the priorities of the GAMP Forum was to establish guidelines for suppliers of automated systems. A subgroup was established at the first meeting to draft such guidelines. The group's objectives were to devise a draft set of guidelines for suppliers of automated systems to the pharmaceutical industry, taking account of the requirements of international regulatory bodies, and making use of existing internationally recognized standards where appropriate. The first draft of the guidelines was made available for comment from the suppliers of automated systems to the industry and other interested parties in March 1994.

The comments received were very supportive. A number of suggestions to improve and extend the Guide were considered and resulted in a significant revision. The second draft was launched in 1995 and was endorsed by the Association of the British Pharmaceutical Industry and by the Pharmaceutical Quality Group of the Institute of Quality Assurance. An electronic version of the document was also made available. A second edition of the Guide - GAMP 96 - incorporating comments and additions from a number of companies was published in 1996.

A third edition, published in 1998, contained revised and enhanced guidance for suppliers, in addition to new, significant, and separate guidance for the *users* of automated systems. This version also saw the introduction of a companion volume containing good practice examples.

The current - considerably enhanced and restructured – GAMP 4 Guide, was launched in December 2001, and included much new or significantly revised material, including guidance on system operation, maintenance, and control aspects. Another significant addition is specific guidance describing a risk assessment process that can be used to scale the validation, to target validation effort on areas that most require it, and to identify GxP risks, and to manage those risks in the most appropriate way.

Further companion volumes of GAMP Good Practice Guides, covering topics including the validation of process control systems, a risk-based approach to compliant electronic records and signatures, and the validation of laboratory computerized systems have followed. Further Good Practice Guides are under development.

The benefits to both users and suppliers of following the GAMP approach include:

- increased understanding of the subject, and introduction of a common language and terminology
- reduction of the cost and time taken to achieve compliant systems
- improved compliance with regulatory expectations
- clarification of the division of responsibility between user and supplier

As well as compliance, the approach provides cost benefits, by assisting the development of systems that are fit for purpose, meet user and business requirements, and have acceptable operation and maintenance costs.